Clinical Trial Protocol: PT003007-02

Title:	A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multicenter Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects With Moderate to Very Severe COPD, Compared With Placebo
Study Number:	PT003007-02
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:	Multicenter
Sponsor:	[redacted]
Sponsor Contact:	[redacted]

	Version Number	Date
Original Protocol:	Version 1.0	[redacted]
Amendment 1	Version 2.0	[redacted]
Amendment 2	Version 3.0	[redacted]

SUMMARY OF CHANGES TO AMENDED PROTOCOL VERSION 2.0, DATED [redacted]

After receiving advice from the United States (US) Food and Drug Administration (FDA), the amended study protocol, PT003007-02 (Version 3.0), includes the following edits:

- The US primary endpoint was changed to the evaluation of change from baseline in morning pre-dose trough forced expiratory volume in 1 second (FEV_1) at a landmark timepoint of Week 24. That is, the change from baseline in morning pre-dose trough FEV_1, was changed from "over Week 12-24" to "at Week 24". These changes are reflected in the Synopsis, Section 3.1, and Section 9.2.1.
- In order to provide 90% power to demonstrate differences on the new US primary endpoint of change from baseline in morning pre-dose trough FEV_1 at Week 24, the sample size of the clinical trial has been increased to 1614 subjects. This change is reflected in the Synopsis, Section 4.1, and Section 9.9.
- The US secondary endpoints, peak FEV_1 and St. George's Respiratory Questionnaire (SGRQ), were changed to landmark timepoints at Week 24. That is, peak change from baseline in FEV_1 within 2 hours was changed from "over 24 weeks" to "at Week 24". Change from baseline in SGRQ total score was changed from "over 24 weeks" to "at Week 24". These changes are reflected in the Synopsis, Section 3.1, and Section 9.2.1.
- The primary and secondary objectives were also adjusted to remove references to time frames or order to prevent any confusion in the Synopsis and in Section 2.
- In Section 9.3.3.3, 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 the FDA. Additional changes to model covariates were also made to be consistent with the Statistical Analysis Plan (SAP).
- The scheme for the control of Type I error was adjusted to allow for a strict control of the assessment of onset of action (Section 9.3.2.4 and Section 9.3.4.1). Similar changes were also made accordingly for European (EU) and Hybrid approaches (Sections 9.3.4.2 and 9.3.4.3). The approach for control of Type I error for the US was also modified to include the new primary and secondary efficacy endpoints requested by FDA.
- Additional changes were made for consistency with the SAP. These include:
  - Throughout Section 9.2.1.1, the abbreviation, mixed-model repeated measures (MMRM), was changed to repeated measures (RM), where appropriate, for consistency with the SAP.
  - The existing text of Section 9.3.1 was sub-sectioned into Sections 9.3.1.1 and 9.3.1.2 in order to include statistical analyses of both co-primary endpoints for the EU and Hybrid approaches in the Primary Efficacy Analysis Section. To this end, analysis text for "Transition Dyspnea Index (TDI) score over 24 weeks" was moved from

Section 9.3.2.1 to Section 9.3.1.2. Minor edits in Sections 9.3.1.1 and 9.3.1.2 were implemented for consistency with the SAP text.

- In Section 9.3.3.4, the text for analysis of time to treatment failure was edited for consistency with the SAP. Treatment failure due to COPD exacerbation is now defined as occurring for a moderate or severe COPD exacerbation rather than an exacerbation of any severity. In Section 9.4, the description of the Medical Dictionary of Regulatory Activities (MedDRA) version to be used for final reporting was updated for consistency with the SAP and will be the version current at the time of database lock for the 28-week extension study.

- In Section 9.13, additional sensitivity analyses based on cumulative responder curves have been incorporated.

The following changes were made to harmonize the protocol content with the content of the SAP:

- Content added to Section 9.12: The Holter Monitoring Population is defined as all subjects in the Safety Population who had at least 18 hours of acceptable quality Holter monitoring data at both Visit 3 (Holter Baseline) and Visit 6 (Week 4). Exclusions from this population may be identified by Pearl Therapeutics prior to database lock and unblinding.

Other minor protocol inconsistencies and typographical errors were also addressed throughout the document. None of the changes compromise subject safety or the intent of the original study design.

SYNOPSIS

Sponsor:
Pearl Therapeutics, Inc.

Names of Finished Products:
Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; PT003, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler (GFF MDI)

Formoterol Fumarate Inhalation Aerosol; PT005, Formoterol Fumarate Metered Dose Inhaler (FF MDI)

Glycopyrronium Inhalation Aerosol; PT001, Glycopyrronium Metered Dose Inhaler (GP MDI)

Placebo (matching) for GFF MDI, FF MDI, and GP MDI

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

Study Title:
A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multicenter Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects With Moderate to Very Severe COPD, Compared With Placebo

Study Number: PT003007-02

Study Phase: III

Overall Study Objective:

The overall objective of this study is to assess the efficacy and safety of treatment with Glycopyrronium and Formoterol Fumarate metered dose inhaler (MDI) (GFF MDI, 14.4/9.6 µg ex-actuator, BID), Formoterol Fumarate MDI (FF MDI, 9.6 µg ex-actuator, BID), and Glycopyrronium MDI (GP MDI, 14.4 µg ex-actuator, twice-daily [BID]) compared with each other and with Placebo MDI in subjects with moderate to very severe chronic obstructive pulmonary disease (COPD).

Primary Objectives:

The primary objective of this study is to compare the efficacy of treatment with GFF MDI, FF MDI, and GP MDI to Placebo MDI and to compare the efficacy of GFF MDI to its components on lung function using trough forced expiratory volume in 1 second (FEV_1) in

subjects with moderate to very severe COPD.

Secondary Objectives:

- To compare the effects of GFF MDI, GP MDI, FF MDI, and Placebo MDI on dyspnea using the Transition Dyspnea Index (TDI) focal score
- To compare the effects of GFF MDI, GP MDI, FF MDI and Placebo MDI on health-related quality of life (HRQoL) using the change in St. George Respiratory Questionnaire (SGRQ) score
- To compare the effects of GFF MDI, GP MDI, FF MDI, and Placebo MDI on symptoms using the change in rescue Ventolin Hydrofluoroalkane (HFA) use as an indirect measure of symptom control
- To determine the time to onset of action on Visit 4 (Day 1)

Other Efficacy Objectives:

- To evaluate the effects of GFF MDI, GP MDI, FF MDI, and Placebo MDI on pulmonary function test parameters (PFTs).
- To assess the effects of GFF MDI, GP MDI, FF MDI, and Placebo MDI on COPD exacerbations
- To evaluate the effect of treatments on nighttime awakenings, morning and evening rescue Ventolin HFA use, breathlessness, cough, and sputum production as assessed by subjects' electronic diary (eDiary) entries

Safety Objective:

To assess the safety of GFF MDI, FF MDI, and GP MDI relative to Placebo MDI based on adverse events (AEs), vital sign measurements, electrocardiograms (ECGs), and clinical laboratory evaluations

12-Hour Pulmonary Function Test Sub-study Objective:

To evaluate the effect of GFF MDI, GP MDI, FF MDI, and Placebo MDI on PFTs over 12 hours at Visit 4 (Day 1) and Visit 8 (Week 12)

24-Hour Holter Monitoring Sub-study Objective:

To evaluate the safety of GFF MDI, GP MDI, FF MDI, and Placebo MDI as evaluated by Holter monitoring based on 24-hour assessments obtained at Visit 6 (Week 4) relative to baseline obtained at Visit 3

Dose Indicator Assessment Objective:

To evaluate the accuracy, reliability and functionality of the dose indicator in subjects treated with GFF MDI, GP MDI, FF MDI or Placebo MDI from Visit 4 (Day 1) through Visit 6 (Week 4)

Healthcare Resource Utilization Objective:

To assess overall and COPD-specific healthcare resource utilization (HCRU) between treatment groups over 24 weeks

Study Design:

This is a multicenter, randomized, double-blind, parallel group, chronic dosing (24 weeks), placebo-controlled study to assess the efficacy and safety of GFF MDI (14.4/9.6 µg ex-actuator, BID), GP MDI (14.4 µg ex-actuator, BID), FF MDI (9.6 µg ex-actuator, BID) compared with Placebo MDI in subjects with moderate to very severe COPD.

This multicenter study will be conducted at approximately 140 sites, contributing approximately 10 to 20 subjects per site. Across these sites, it is planned that approximately 1614 subjects with moderate to very severe COPD will be randomized into the study to provide approximately 1300 subjects to complete the study.

Subjects will be randomized in a 7:6:6:3 scheme (GFF MDI, GP MDI, FF MDI, and Placebo MDI). Approximately 514 subjects will be enrolled into the GFF MDI treatment group, 440 subjects into each of the GP MDI and FF MDI treatment groups and approximately 220 subjects will be enrolled in the Placebo MDI treatment group. Randomization will be stratified by reversibility to Ventolin HFA (albuterol), disease severity, and participation in the 12-hour PFT sub-study.

12-Hour PFT Sub-study: Serial PFTs will be conducted over 12 hours in a subset of approximately 100 subjects randomized to each active treatment arm and approximately 50 subjects randomized to Placebo MDI at Visit 4 (Day 1) and Visit 8 (Week 12).

24-Hour Holter Monitoring Sub-study: Holter Monitoring will be conducted over 24 hours in a subset of approximately 150 subjects randomized to each active treatment arm and approximately 75 subjects randomized to Placebo MDI at Visit 3 (Holter Baseline) and Visit 6 (Week 4).

Dose Indicator Assessment: The accuracy, reliability, and functionality of the dose indicator will be evaluated in all subjects randomized to blinded study treatment (GFF MDI, GP MDI, FF MDI, and Placebo MDI) from Visit 4 (Day 1) through Visit 6 (Week 4).

Study Duration:

The entire study period is scheduled to take a maximum of 32 weeks for each individual subject. The study is anticipated to run for approximately 16 months and is not expected to exceed 24 months.

Study Population:

Approximately 1614 subjects with moderate to very severe COPD will be enrolled to provide approximately 1300 subjects to complete the study.

Test Product, Dose, and Mode of Administration:

Investigational materials will be provided by Pearl Therapeutics as summarized.

Product Name and Dosage	Product Strength	Dose Form/Fill Count	Administration
Study Medications			
GFF MDI (PT003) 14.4/9.6 µg ex-actuator	GFF MDI 7.2/4.8 µg per actuation	1 MDI 120 inhalations	Taken as two inhalations BID
FF MDI (PT005) 9.6 µg ex-actuator	FF MDI 4.8 µg per actuation	1 MDI 120 inhalations	Taken as two inhalations BID
GP MDI (PT001) 14.4 µg ex-actuator	GP MDI 7.2 µg per actuation	1 MDI 120 inhalations	Taken as two inhalations BID
Open-label Products			
Ventolin (albuterol sulfate) HFA inhalation aerosol 90 µg ex-actuator [a]	Ventolin (albuterol sulfate) HFA inhalation aerosol will be the US supplied product Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	1 MDI 60 or 200 actuations	Taken as needed Supplies are open-label
Atrovent (ipratropium bromide) HFA inhalation aerosol 34 µg ex-actuator [b]	Atrovent (ipratropium bromide) HFA will be the US supplied product Each inhalation contains 17 µg ex-actuator per actuation	1 MDI 200 actuations	Taken as two inhalations QID during Screening Supplies are open-label
Placebo			
Placebo MDI	Formulation does not contain active ingredient	1 MDI 120 inhalations	Taken as two inhalations BID

Abbreviations: BID=twice daily; COPD=chronic obstructive pulmonary disease; FF MDI=Formoterol Fumarate Inhalation Aerosol; GFF MDI=Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; GP MDI=Glycopyrronium Inhalation Aerosol; HFA=Hydrofluoroalkane; MDI=Metered Dose Inhaler; QID=four times daily; US=United States

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

Note: Glycopyrronium 14.4 µg in GFF MDI and GP MDI is equivalent to 18 µg of glycopyrronium bromide.

[a] Reversibility testing at Visit 2 and rescue medication during the study.

[b] Reversibility testing at Visit 3 and COPD maintenance therapy during Screening Period.

Duration of Treatment:

Each subject will receive study treatment for 24 weeks. The entire study is scheduled to take a maximum of 32 weeks for each individual subject from the time of screening through Follow-up (refer to Figure 1).

Efficacy Assessments:

All efficacy assessments are relative to pre-dose baseline obtained at or prior to Visit 4. Lung function measurements and symptom-based endpoints will be evaluated. The primary endpoint differs by approach but is always based on morning pre-dose trough FEV_1. However, in some regions co-primary endpoints are required for registration purposes. The three different registration approaches will be called: US, EU, and Hybrid.

The US approach is for countries or regions such as the United States (US) where co-primary endpoints are not required. The EU approach is for registration purposes in countries or regions such as Europe where co-primary endpoints are required. The Hybrid approach is for countries or regions where co-primary endpoints are only required for comparisons to Placebo MDI and not for the comparison of GFF MDI to its components. The delineation of multiplicity controls for the primary and secondary measures are separated by approach and detailed in Section 9.3.4.

All inferential results will be based on analyses using the Intent to Treat (ITT) Population (refer to Section 9.12).

Primary Efficacy Endpoints:

Primary Endpoint (US):

- The primary endpoint will be the change from baseline in morning pre-dose trough FEV_1 at Week 24.

Co-Primary Endpoints (EU and Hybrid):

- The first co-primary endpoint will be the change from baseline in morning pre-dose trough FEV_1 over 24 weeks of treatment
- The second co-primary endpoint will be the TDI focal score over 24 weeks

Secondary Efficacy Endpoints:

Secondary Endpoints (US):

- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks
- Peak change from baseline in FEV_1 within 2 hours post-dosing at Week 24
- Change from baseline in SGRQ total score at Week 24
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Time to onset of action on Day 1

Secondary Endpoints (EU and Hybrid):

- Peak change from baseline in FEV_1 within 2 hours post-dosing over 24 weeks
- Change from baseline in SGRQ total score over 24 weeks
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Time to onset of action on Day 1

Other Efficacy Endpoints:

Day 1 Assessments (Within 2 Hours Post-dose):

- Change from baseline at each post-dose timepoint in FEV_1 as well as FEV_1 area under the curve from 0 to 2 hours (FEV_1 AUC_{0-2}) and peak change from baseline in FEV_1
- Proportion of subjects achieving an improvement from baseline in FEV_1 using different thresholds (eg, ≥10%, ≥12%, ≥200 mL, and ≥12% and ≥200 mL)

Assessments Over 24 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 24 weeks, over Week 12 to Week 24, and at each post-randomization visit (including Week 24):
  - 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 three 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 morning total and individual symptom scores, and the

mean evening total and individual symptom scores over 24 weeks, over Weeks 12-24, and over each 4-week interval of the 24 week treatment period

- Changes from baseline at each post-randomization visit for SGRQ total score
- TDI focal score at each post-randomization visit
- Individual components of the TDI: functional impairment, magnitude of task, and magnitude of effort over 24 weeks and at each post-randomization visit
- Percentage of subjects achieving a MCID threshold of ≥1 unit on average in TDI focal score
- Change in individual domain scores of SGRQ: Symptoms, Activity, and Impacts over 24 weeks and at each post-randomization visit (including Week 24)
- Percentage of subjects achieving an MCID threshold of ≥4 units on average in SGRQ total score

<u>12-Hour PFT Sub-study:</u>

Primary Endpoint:

- FEV_1 area under the curve from 0 to 12 hours (FEV_1 AUC_{0-12}) at Week 12

Additional Endpoints Assessed on Day 1 and Week 12:

- Serial spirometry parameters including FEV_1 area under the curve from 0 to 6 hours (FEV_1 AUC_{0-6}) and from 6 to 12 hours (FEV_1 AUC_{6-12}), and peak change in FEV_1
- FEV_1 AUC_{0-12} on Day 1
- FVC, PEFR, and FEF_{25-75} will be evaluated using AUC_{0-12}, AUC_{0-2}, and peak change from baseline
- Change from baseline in FEV_1, FVC, FEF_{25-75}, and PEFR at each post-dose time point through 12 hours post-dose including the change from baseline in 12-hour post-dose trough

Safety Endpoints:

The safety endpoints for this study include:

- AEs
- 12-Lead ECG: Change from baseline in heart rate, PR interval, QRS axis, QRS interval, QT interval, and QTcF (Fridericia Corrected QT) interval
- Clinical Laboratory Testing
- Vital Sign Measurements

24-Hour Holter Monitoring Sub-study Endpoints (Assessed at Week 4)

Primary Endpoint:

The primary Holter monitoring sub-study endpoint is:

- Change from baseline in mean heart rate averaged over 24 hours

Secondary Endpoints:

Secondary 24-hour Holter monitoring sub-study endpoints are:

- Change from baseline in mean night-time [22:00 to 06:00) and day-time [06:00 to 22:00) heart rate
- Change from baseline in the maximum 24-hour heart rate
- Change from baseline in the minimum 24-hour heart rate
- Change from baseline in the frequency of ventricular ectopic events (including a single premature ventricular contraction [PVC])
- Change from baseline in the frequency of ventricular couplets (defined as two PVCs preceded or followed by regular beats)
- Change from baseline in the frequency of ventricular runs (defined as three or more PVCs preceded or followed by regular beats)
- Incidence of sustained ventricular tachycardia (VT) [defined as PVCs lasting >30 seconds]
- Change from baseline in the frequency of supraventricular ectopic events
- Change from baseline in the frequency of supraventricular couplets
- Change from baseline in the frequency of supraventricular runs
- Incidence of atrial fibrillation with rapid ventricular response (>100 beats per minute [bpm])

Other Endpoints:

Other Holter endpoints will include the following:

- Proportion of subjects with maximum heart rate >180, >160-180, >140-160, >120-140, >100-120, and 100 or less
- Proportion of subjects with minimum heart rate >60, >50-60, >40-50, and ≤40
- Proportion of subjects in each category of change from baseline in the number of PVCs per hour (no change, increase of >0-<60, 60-<120, and ≥120, and decrease of >0-<60, 60-<120, and ≥120)

Dose Indicator Assessment Endpoints

The primary endpoint will be the comparison of the number of doses used as displayed by the dose indicator with the number of doses used as determined by information from the electronic Case Report Form (eCRF) and the subject diary for the first MDI used after randomization.

Health Care Resource Utilization Endpoints:

The number of days missed from work, and COPD-related and non-COPD related telephone calls and visits to health care providers, Emergency Room (ER) visits, and hospitalizations including days in hospital, days in Intensive Care Units (ICU), days in Coronary Care Units (CCU), and subject intubations will be captured and compared between treatments.

Statistical Methods:

Primary Efficacy Analysis:

The change from baseline in morning pre-dose trough FEV_1 will be analyzed using a repeated measures (RM) linear model. The model will include baseline FEV_1 and reversibility to Ventolin HFA as continuous covariates and visit, treatment, treatment by visit, smoking status at baseline, and inhaled corticosteroids (ICS) use at baseline as categorical covariates. Baseline is defined as the average of the non-missing -60 minute and -30 minute values obtained prior to dosing at Visit 4. An unstructured correlation model will be used to model additional autocorrelation within subject. If this model fit fails to converge, a first order autoregressive [AR (1)] structure will be used to model correlation between timepoints from the same subject; for this model subject will be considered a random effect. Contrasts will be used to obtain estimates of the treatment differences at Week 24 and over the entire 24-week treatment period. Two-sided p-values and point estimates with two-sided 95% confidence intervals (CIs) will be produced for each treatment difference. The primary analysis associated with all approaches will be conducted using the ITT Population.

Additional supportive analyses of morning pre-dose trough FEV_1 will include the change from baseline at Week 24 and over the entire 24-week treatment period in the Per Protocol (PP) Population, treatment differences over Weeks 12-24 and at individual timepoints estimated by the RM model, and the analysis of weighted average (WAVE). WAVE will be calculated as the weighted average change from baseline over 24 weeks (and also over Weeks 12-24) using the exposure time represented by each clinic visit as the weights. It will be analyzed using analysis of covariance (ANCOVA). The ANCOVA will evaluate treatment differences and include baseline and reversibility to Ventolin HFA as continuous covariates and smoking status at baseline and ICS use at baseline as categorical covariates.

Sensitivity analyses will also be conducted to evaluate the robustness of the primary analyses to the nature of the missing data.

Sample Size:

It is estimated that a sample size of 1614 subjects (514 subjects in the GFF MDI arm,

440 subjects in each of the GP MDI, and FF MDI treatment arms, and 220 subjects in the Placebo MDI arm) will provide approximately 91% power with Type I error controlled at a two-sided alpha level of 0.05 to detect differences for all five primary comparisons if the true differences from Placebo MDI are 90 mL for FF MDI, 100 mL for GP MDI, and 150 mL for GFF MDI resulting in corresponding differences between GFF MDI and FF MDI and GP MDI of 60 mL and 50 mL, respectively, in morning pre-dose trough FEV_1 at Week 24 and approximately 99% power for morning pre-dose trough FEV_1 over 24 weeks. Assumptions regarding variability for the primary endpoint are based on Pearl Therapeutics' experience with Phase IIb clinical studies and on published data for within patient variation (D'Urzo, 2001, van Noord , 2005; Maesen, 1995) and between patient variation (Dahl, 2001, Calverley, 2003). A composite value SD of 200 mL has been assumed. A within subject correlation structure has been assumed combining a block diagonal structure induced by using subject as a random effect with an AR (1) structure with ρ=0.5. Differential dropout rates have been assumed with increased dropout due to lack of efficacy ranging up to 25% in the Placebo MDI arm. Under these assumptions, based on this sample size, the study will have approximately 99% power to detect differences between FF MDI and Placebo MDI and between GP MDI and Placebo MDI in the change from baseline in morning pre-dose trough FEV_1 at Week 24 or over 24 weeks using a two-sided alpha level of 0.05.

For the TDI focal score, the true differences from Placebo MDI are assumed to be 0.7 for FF MDI and GP MDI and 1.2 for GFF MDI. A standard deviation (SD) of 2.4 at each visit is assumed for the self-administered computerized (SAC) version based on Mahler 2007 and Mahler, 2009. The planned sample size under similar assumptions about dropout and serial correlation will provide approximately 99% power to detect differences in TDI between FF MDI or GP MDI and Placebo MDI and approximately 98% power to detect differences for all five primary comparisons required for GFF MDI to be declared efficacious including GFF MDI compared to FF MDI, GP MDI, and Placebo MDI in addition to FF MDI and GP MDI compared to Placebo MDI. If the SD is 2.8, the power is approximately 98% for FF MDI and for GP MDI and approximately 91% for GFF MDI.

Data Monitoring and Adjudication Committees:

Data Safety Monitoring Committee:

An independent, external Data Monitoring Committee (DMC) will be set up to review all serious AEs (SAEs) (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.
Date of Original Approved Protocol: [redacted]
Date of Approval of First Amended Protocol: [redacted]
Date of Approval of Second Amended Protocol: [redacted]

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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
AUC_{x-y}	Area Under the Curve from Time x to Time y
AV	Atrioventricular block
BDI	Baseline Dyspnea Index
BID	bis in die, Twice Daily
BiPAP	Bilevel Positive Airway Pressure
BMP	Basic Metabolic Panel
BP	Blood Pressure
Bpm	Beats per minute
BTPS	Body Temperature and Pressure Saturated
CAT	COPD Assessment Test
CCU	Coronary Care Unit
CCV	Cardio- and Cerebro-vascular
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CRT	Cardiac Resynchronization Therapy
CRT_D	Cardiac Resynchronization Therapy-Defibrillator
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events

DMC	Data Monitoring Committee
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
Eg	Exempli gratia, for example
ER	Emergency Room
ERS	European Respiratory Society
EU	European Union
EV	Back Extrapolation Volume
ex-actuator	Dose Delivered From The Actuator (ie, mouthpiece) Of The MDI
FDA	Food and Drug Administration
FEF_{25-75}	Forced Expiratory Flow between 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	Hydrofluoroalkane
HR	Heart Rate
HRQoL	Health-related Quality of Life
IB	Investigator's Brochure
ICD	Implantable Cardioverter-Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid

ICU	Intensive Care Unit
Ie	Id est, that is
IEC	Independent Ethics Committee
IPF	Interstitial Pulmonary Fibrosis
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IWRS	Interactive Web Response System
L	Liter
LABA	Long-acting Beta Agonist
LAMA	Long-acting Muscarinic Antagonist
LTOT	Long Term Oxygen Therapy
MAR	Missing At Random
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
MMRC	Modified Medical Research Council
MMRM	Mixed Model Repeated Measures
Msec (ms)	Millisecond
NHANES III	Third National Health and Nutrition Examination Survey
NIPPV	Non-invasive Positive Pressure Ventilation Device
NMAR	Not Missing At Random
OTC	Over the counter
PEFR	Peak Expiratory Flow Rate
PFT	Pulmonary Function Test

PIN	Personal identification number
PP	Per Protocol
PRN	pro re nata, As Needed
QD	quaque die, Once Daily
QID	quater in die; Four Times Daily
QTcF	QT corrected using Fridericia's formula ($QT/(RR^{1/3})$)
SABA	Short-acting Beta Agonist
SAC	Self-administered computerized
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic blood pressure
SGRQ	St. George Respiratory Questionnaire
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitors
TDI	Transition Dyspnea Index
TEAE	Treatment Emergent Adverse Event
TNF α	Anti-tumor Necrosis Factor α
TURP	Trans-urethral Resection of Prostate
US	United States
VT	Ventricular Tachycardia
WAVE	Weighted average

TRADEMARK INFORMATION

Trademarks Not Owned By Pearl Therapeutics

Aerolizer
Atrovent
Breezhaler
Combivent
Elkira
Foradil
Genuair
Handihaler
Pressair
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, 2003; 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 Halbert 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, 2013).

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, 2008) 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 metered-dose inhaler [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. The descriptions of Pearl clinical studies which follow remain in this prior expression. 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® Breezhaler® Inhalation Powder, glycopyrronium bromide) was recently approved throughout the European Union (EU), Australia, Canada, and Japan 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 Breezhaler 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 1361 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 Breezhaler, 2012]. In addition to the published data with Seebri Breezhaler (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, as follows:

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 2500 subjects demonstrated that formoterol fumarate is effective and well tolerated in patients with COPD (Dahl, 2001; Rossi, 2002; Albers, 2002; Campbell, 2005; Campbell, 2007).

Pearl Therapeutics conducted three studies to confirm dose selection and safety for FF MDI. These include studies: PT0050801, PT0031002, and PT003005. Results demonstrated dose proportionality of FF MDI 9.6 µg and bioequivalence to Foradil Aerolizer (Foradil).
In terms of safety, results showed no substantial differences between the FF MDI treatment groups to placebo or to Foradil 12 µg, and there were no important trends noted for FF MDI at any dose.

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 multicenter studies in subjects with COPD conducted in the US, Australia, and New Zealand. The studies in subjects with COPD included three Phase IIb studies of a 1-week duration and one cardiovascular safety study of a 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, more than 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, as follows:

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 µg compared to its components and open-label Foradil. In this study,

on Day 1 and Day 14 of dosing, data obtained during 24-hour Holter monitoring were comparable across all treatments and comparable to 24-hour Holter monitoring data obtained during the screening period on Atrovent Hydrofluoroalkane (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 area under the curve from 0 to 12 hours (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 these 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 adverse event (AE) profile similar to its components and approved products for the management of COPD (ie, Spiriva, Atrovent, and Foradil). A more detailed description of the studies design and results can be obtained in the Investigator Brochure (IB).

1.1 Study Rationale

The purpose of this study is to provide pivotal efficacy and safety data for GP MDI, FF MDI, and GFF MDI in subjects with moderate to very severe COPD. Data obtained from this study, together with a similarly designed 6-month pivotal study (Study PT003006) and a 6-month safety extension study (Study PT003008), are intended to be used to support the registration of GFF MDI, GP MDI, and FF MDI worldwide. As described above, the doses selected for evaluation in this study are based primarily on the findings from three previous clinical studies with GP MDI (Studies PT0010801, PT001002, and PT001003), two clinical studies with FF MDI (Studies PT0050801 and PT005003), and four studies with GFF MDI (Studies PT0031002, PT003003, PT003004, and PT003005).

2 STUDY OBJECTIVES

The overall objective of this study is to assess the efficacy and safety of treatment with Glycopyrronium and Formoterol Fumarate MDI (GFF MDI, 14.4/9.6 μg ex-actuator, BID), Formoterol Fumarate MDI (FF MDI, 9.6 μg ex-actuator, BID), and Glycopyrronium MDI (GP MDI, 14.4 μg ex-actuator, BID) compared with each other and Placebo MDI in subjects with moderate to very severe COPD.

2.1 Primary Objective

The primary objective of this study is to compare the efficacy of treatment with GFF MDI, FF MDI, and GP MDI to Placebo MDI and to compare the efficacy of GFF MDI to its components on lung function using trough FEV_1 in subjects with moderate to very severe COPD.

2.2 Secondary Objectives

- To compare the effects of GFF MDI, GP MDI, FF MDI, and Placebo MDI on dyspnea using the Transition Dyspnea Index (TDI) focal score
- To compare the effects of GFF MDI, GP MDI, FF MDI, and Placebo MDI on quality of life using the change in St. George Respiratory Questionnaire (SGRQ) score
- To compare the effects of GFF MDI, GP MDI, FF MDI, and Placebo MDI on symptoms using the change in rescue Ventolin HFA use as an indirect measure of symptom control
- To determine the time to onset of action on Visit 4 (Day 1)

2.3 Other Efficacy Objectives

- To evaluate the effects of GFF MDI, GP MDI, FF MDI, and Placebo MDI on pulmonary function test (PFT) parameters
- To assess the effects of GFF MDI, GP MDI, FF MDI, and Placebo MDI on COPD exacerbations
- To evaluate the effect of treatments on nighttime awakenings, morning and evening rescue Ventolin HFA use, breathlessness, cough, and sputum production as assessed by subjects' electronic diary (eDiary) entries

2.4 Safety Objectives

- To assess the safety of GFF MDI, FF MDI, and GP MDI relative to Placebo MDI based on AEs, vital sign measurements, electrocardiograms (ECGs), and clinical laboratory evaluations

2.5 Sub-Study Objectives

2.5.1 12-Hour Pulmonary Function Test Objective

- To evaluate the effect of GFF MDI, GP MDI, FF MDI, and Placebo MDI on PFT parameters over 12 hours at Visit 4 (Day 1) and Visit 8 (Week 12)

2.5.2 24-Hour Holter Monitoring Objective

- To evaluate the safety of GFF MDI, GP MDI, FF MDI, and Placebo MDI as evaluated by Holter Monitoring based on 24-hour assessments obtained at Visit 6 (Week 4) relative to baseline obtained at Visit 3

2.6 Dose Indicator Assessment Objective

- To evaluate the accuracy, reliability and functionality of the dose indicator in subjects treated with GFF MDI, GP MDI, FF MDI or Placebo MDI from Visit 4 (Day 1) through Visit 6 (Week 4)

2.7 Healthcare Resource Utilization Objective

- To assess overall and COPD-specific healthcare resource utilization (HCRU) between treatment groups

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

All efficacy assessments are relative to pre-dose baseline obtained at Visit 4. Lung function measurements and symptom-based endpoints will be evaluated. The primary endpoint differs by approach but is always based on morning pre-dose trough FEV_1. However, in some regions co-primary endpoints are required for registration purposes. The three different registration approaches will be called US, EU, and Hybrid.

The US approach is for countries or regions such as the United States where co-primary endpoints are not required. The EU approach is for registration purposes in countries or regions such as Europe where co-primary endpoints are required. The Hybrid approach is for countries or regions where co-primary endpoints are only required for comparisons to Placebo MDI and not for the comparison of GFF MDI to its components. The delineation of multiplicity controls for the primary and secondary measures are separated by approach and detailed in Section 9.3.4.

All inferential results will be based on analyses using the Intent-to-Treat (ITT) Population (refer to Section 9.12).

3.1.1 Primary Efficacy Endpoints

Primary Endpoint (US):

- The primary endpoint will be the change from baseline in morning pre-dose trough FEV_1 at Week 24.

Co-Primary Endpoints (EU and Hybrid):

- The first co-primary endpoint will be the change from baseline in morning pre-dose trough FEV_1 over 24 weeks of treatment
- The second co-primary endpoint will be the TDI focal score over 24 weeks

3.1.2 Secondary Efficacy Endpoints

Secondary Endpoints (US):

- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks
- Peak change from baseline in FEV_1 within 2 hours post-dosing at Week 24
- Change from baseline in SGRQ total score at Week 24
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Time to onset of action on Day 1

Secondary Endpoints (EU and Hybrid):

- Peak change from baseline in FEV_1 within 2 hours post-dosing over 24 weeks
- Change from baseline in SGRQ total score over 24 weeks
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Time to onset of action on Day 1

3.1.3 Other Efficacy Endpoints

Day 1 Assessments (Within 2 Hours Post-dose):

- Change from baseline at each post-dose timepoint in FEV_1 as well as FEV_1 area under the curve from 0 to 2 hours (FEV_1 AUC_{0-2}) and peak change from baseline in FEV_1
- Proportion of subjects achieving an improvement from baseline in FEV_1 using different thresholds (eg, ≥10%, ≥12%, ≥200 mL, and ≥12% and ≥200 mL)

Assessments Over 24 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 24 weeks, over Week 12 to Week 24, and at each post-randomization visit (including Week 24):
  - Change from baseline in morning pre-dose trough for FEV_1, 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 three 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 morning total and individual symptom scores, and the mean evening total and individual symptom scores over 24 weeks, over Weeks 12-24, and over each 4-week interval of the 24 week treatment period
- Changes from baseline at each post-randomization visit for SGRQ total score

- TDI focal score at each post-randomization visit
- Individual components of the TDI: functional impairment, magnitude of task, and magnitude of effort over 24 weeks and at each post-randomization visit
- Percentage of subjects achieving a MCID threshold of ≥1 unit on average in TDI
- Change in individual domain scores of SGRQ: Symptoms, Activity, and Impacts over 24 weeks and at each post-randomization visit (including Week 24)
- Percentage of subjects achieving an MCID threshold of ≥4 units on average in SGRQ total score

3.2 12-Hour PFT Sub-study Endpoints

Primary Endpoint:

- FEV_1 AUC_{0-12} at Week 12

Additional assessments on Day 1 and Week 12:

- Serial spirometry parameters including FEV_1 area under the curve from 0 to 6 hours (FEV_1 AUC_{0-6}) and from 6 to 12 hours (FEV_1 AUC_{6-12}), and peak change in FEV_1
- FEV_1 AUC_{0-12} on Day 1
- FVC, PEFR, and FEF_{25-75} will be evaluated using AUC_{0-12}, AUC_{0-2}, and peak change from baseline
- Change from baseline in FEV_1, FVC, FEF_{25-75}, and PEFR at each post-dose time point through 12 hours post-dose including the change from baseline in 12-hour post-dose trough

3.3 Safety Endpoints

The safety endpoints for this study include:

- AEs
- 12-Lead ECG: Change from baseline heart rate, PR interval, QRS axis, QRS interval, QT interval and QTcF (Fridericia Corrected QT) interval
- Clinical laboratory testing
- Vital sign measurements

3.4 24-Hour Holter Monitoring Sub-Study Endpoints (Assessed at Week 4)

Primary Endpoint:

The primary Holter monitoring sub-study endpoint is:

- Change from baseline in mean heart rate averaged over 24 hours

Secondary Endpoints:

Secondary 24-hour Holter monitoring sub-study endpoints are:

- Change from baseline in mean nighttime (22:00 to 06:00) and daytime (06:00 to 22:00) heart rate
- Change from baseline in the maximum 24-hour heart rate
- Change from baseline in the minimum 24-hour heart rate
- Change from baseline in the frequency of ventricular ectopic events (including a single premature ventricular contraction [PVC])
- Change from baseline in the frequency of ventricular couplets (defined as two PVCs preceded or followed by regular beats)
- Change from baseline in the frequency of ventricular runs (defined as three or more PVCs preceded or followed by regular beats)
- Incidence of sustained ventricular tachycardia (VT) [defined as PVCs lasting >30 seconds]
- Change from baseline in the frequency of supraventricular ectopic events
- Change from baseline in the frequency of supraventricular couplets
- Change from baseline in the frequency of supraventricular runs
- Incidence of atrial fibrillation with rapid ventricular response (>100 beats per minute [bpm])

Other Endpoints:

Other Holter endpoints will include the following:

- Proportion of subjects with maximum heart rate >180, >160-180, >140-160, >120-140, >100-120, and 100 bpm or less
- Proportion of subjects with minimum heart rate >60, >50-60, >40-50, and ≤40 bpm
- Proportion of subjects in each category of change from baseline in the number of PVCs per hour (no change, increase of >0-<60, 60-<120, and ≥120, and decrease of >0-<60, 60-<120, and ≥120)

3.5 Dose Indicator Assessment Endpoints

The primary endpoint will be the comparison of the number of doses used as displayed by the dose indicator with the number of doses used as determined by information from the electronic Case Report Form (eCRF) and the subject diary for the first MDI used after randomization.

3.6 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 subject intubations will be captured and compared between treatment groups.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, parallel group, chronic dosing (24 weeks), placebo-controlled study to assess the efficacy and safety of GFF MDI (14.4/9.6 µg ex-actuator, BID), GP MDI (14.4 µg ex-actuator, BID), FF MDI (9.6 µg ex-actuator, BID) compared with Placebo MDI in subjects with moderate to very severe COPD.

This multicenter study will be conducted at approximately 140 sites, contributing approximately 10 to 20 subjects per site. Across these sites, it is planned that 1614 subjects with moderate to very severe COPD will be randomized into the study to provide approximately 1300 subjects to complete the study (refer to Study Flow Diagram Figure 1). Subjects will be randomized in a 7:6:6:3 scheme (GFF MDI, GP MDI, FF MDI, and Placebo MDI. Approximately 514 subjects will be enrolled into the GFF MDI treatment group, 440 subjects into each of the GP MDI, and FF MDI treatment groups; and approximately 220 subjects will be enrolled in the Placebo MDI treatment group. Randomization will be stratified by reversibility to Ventolin® HFA, disease severity, and participation in the 12-hour PFT sub-study. The entire study period is scheduled to take a maximum of 32 weeks for each individual subject (refer to Figure 1). The study is anticipated to run for approximately 18 months and is not anticipated to exceed 24 months.

This study includes 2 sub-studies, a 12-hour PFT sub-study and a 24-Hour Holter monitoring sub-study. A subset of approximately 100 subjects randomized to each active treatment arm and approximately 50 subjects randomized to Placebo MDI will be required to participate in the 12-hour PFT sub-study involving collection of PFTs over 12 hours at Visit 4 (Day 1, Randomization) and Visit 8 (Week 12).

The 24-Hour Holter Monitoring sub-study will be conducted over 24 hours in a subset of approximately 150 subjects randomized to each active treatment arm and approximately 75 subjects randomized to Placebo MDI at Visit 3 (Holter Baseline) and Visit 6 (Week 4).

A subset of sites will be identified and designated for participation in the 12-hour PFT and 24-Hour Holter monitoring sub-studies. Individual subjects will be allowed to participate in both sub-studies. Subjects must provide written informed consent prior to participation in the sub-studies.

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

At Visit 1 (Screening), all subjects are to sign an informed consent form prior to the conduct of any screening assessments. The Investigator will obtain a medical history including specific cardiovascular history, COPD exacerbations within the last year, clinical laboratory tests, physical examination, and any required documentation in order to determine eligibility for participation (ie, inclusion/exclusion criteria). Subjects must meet spirometry criteria for COPD (FEV_1 <80% predicted and FEV_1/FVC ratio <0.7) at Visit 1 to qualify for study enrollment. Re-screening is not allowed for subjects who do not meet the spirometry criteria at Visit 1. Providing the subject meets the eligibility criteria, the Investigator or designee

will review current COPD medications and, if necessary, will make arrangements to adjust the prohibited COPD therapy to protocol-allowable COPD therapy described, as follows:

Subjects who meet all entry criteria but are using certain prohibited COPD medications (eg, oral β_2 agonists, LABAs), cromoglycate or nedocromil inhalers, leukotriene antagonists (eg, zafirlukast, montelukast, zileuton), glycopyrronium bromide (eg, Seebri® Breezhaler® , [redacted]), aclidinium (eg, Tudorza® Pressair™ [redacted], Eklira® Genuair [redacted]) or tiotropium (Spiriva® Handihaler [redacted]) will discontinue these medications for the duration of the trial. During the screening period, subjects will be switched to sponsor-provided Atrovent® HFA (ipratropium bromide inhalation aerosol) [redacted] administered four times daily (QID) and sponsor-provided rescue Ventolin HFA (albuterol sulfate inhalation aerosol) [redacted] or locally available and comparable product(s), as needed, to control symptoms.

Subjects taking a fixed-dose combination treatment with an inhaled corticosteroid plus a LABA must discontinue the combined medication and instead be prescribed an inhaled corticosteroid monotherapy at an equivalent dose and regimen for the duration of the study, and be switched to sponsor-provided Atrovent HFA MDI administered QID and sponsor-provided rescue Ventolin HFA MDI as needed to control symptoms (refer to Section 5.4).

Subjects will be issued and trained on an eDiary use at Visit 1 (Screening) and will be instructed to collect practice data during the screening period (between Visit 1 and Visit 4).

During the screening period, between Visits 1 and 4, subjects will use sponsor-provided Atrovent HFA MDI QID and use sponsor-provided rescue Ventolin HFA MDI, as needed, to control symptoms. Subjects previously using an inhaled corticosteroid (ICS) and/or phosphodiesterase inhibitor may continue using the medications at the same dose as previously described.

In order to allow for an adequate washout of previous maintenance medications, subjects will undergo a washout period of at least one week (at least two weeks if taking Spiriva or other LAMAs), but not greater than 26 days in duration prior to returning to the clinic for Visit 2. Reversibility of FEV_1 to a SABA and to a short-acting anticholinergic will be tested on two separate test days.

At Visit 2, reversibility to Ventolin HFA (SABA) will be evaluated (refer to Section 7.1.1.1). The spirometry data obtained at Visit 2 will be used as an inclusion criterion (Section 5.1). In addition, at Visit 2, dyspnea will be evaluated through the Modified Medical Research Council (MMRC) Dyspnea Scale, and the burden of disease will be assessed through the COPD Assessment Test (CAT). Subject eDiary compliance will be reviewed, and the subject will be retrained, when appropriate (refer to Section 7.1.2).

At Visit 3, reversibility to Atrovent HFA (short-acting anticholinergic) will be evaluated (refer to Section 7.1.1.1). The spirometry data obtained at this visit will not be used as an entry criterion, but will be used to characterize the population. Subject eDiary compliance will be reviewed, and the subject will be retrained, when appropriate.

At Visit 3, following post bronchodilator spirometry assessments, a Holter monitor will be applied and subjects will undergo 24-hour Holter monitoring to provide a baseline (refer to Section 7.2.5).

On the following day, when the subject returns to the clinic for Holter monitor removal, the quality of the recordings will be assessed at the site. If the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours), the Holter monitor will be reconnected for another 24 hours using a new Holter monitor hook-up kit. The subject will be instructed to continue his/her medications as per study protocol. The subject will return the following day for removal of the Holter monitor. If the Holter monitoring quality remains unacceptable on the second attempt, no further attempts will be made and the subject will be permitted to enroll in the study but will be excluded from the Holter monitor sub-study. If clinically significant findings are noted on any of the Holter monitor recordings as defined in Section 5.7.1, the subject will be considered a screen failure and will not be eligible to enroll in the study.

Once an acceptable (ie, acceptable tracings for a minimum of 18 hours) baseline Holter monitor test is obtained, subjects can proceed to Visit 4 (Randomization) provided no clinically significant findings (as defined in Section 5.7.1) are reported by [redacted] following review of the Holter monitor recordings.

At Visit 4 (Randomization Visit; Treatment Day 1), subjects will return to the clinic before 10:00 AM. Subject eDiary compliance will be reviewed, and subjects who are unable to meet the compliance requirement (>70% subject completion of diary assessments) in the last 7 days preceding the Randomization Visit or who are unable to meet the reproducibility criteria will be considered a screen failure (refer to Section 7.1.2). Subjects who continue to meet entry inclusion/exclusion criteria, including the FEV_1 reproducibility criteria (the baseline FEV_1 at Visit 4 must be within ±20% or 200 mL of mean of the pre-dose FEV_1 values obtained at the two preceding visits (refer to Section 7.1.1.2), and who remain eligible for participation in the study, will be randomized into one of the treatment arms. At Visit 4, all sponsor-provided Atrovent HFA and Ventolin HFA provided during the screening period will be discontinued and collected by site personnel for accountability.

If a subject is assigned to GFF MDI, GP MDI, FF MDI or Placebo MDI, it will not be possible to differentiate between these treatments since they will be identical in all aspects.

Randomization will be centralized through the use of an Interactive Web Response System (IWRS). The randomization will be stratified by disease severity (moderate vs. severe or very severe), reversibility (yes or no), and participation in the 12-hour PFT sub-study (yes or no) to ensure even distribution of treatment arms within each stratum.

Subjects will be trained on how to read the dose indicator. Refer to Appendix 10 for instructions on how to read the dose indicator.

After the randomization visit, subjects will be examined at Visit 5 (Week 2), Visit 6 (Week 4), Visit 7 (Week 8), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20) and Visit 11a (Week 24). In total, each completed subject will attend 11 scheduled visits in this study. For the assessments scheduled at each of these visits, refer to the assessment schedule in Table 9.

Subjects will be required to take their study medication twice a day. Subjects 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).

Mean pre-dose morning PFTs will be assessed at every visit. Post-dose PFTs will be assessed at all visits except Visit 6 and Visit 9 (refer to Section 7.1 for details).

Subjects participating in the 12-hour PFT sub-study will undergo 12-hour serial PFT assessments at Visit 4 (Day 1) and Visit 8 (Week 12). On these two test days, additional serial spirometry will be obtained at 4, 6, 8, 10, 11.5 and 12 hours post-dose (refer to Section 7.1 for details).

Subjects participating in the 24-Hour Holter Monitoring sub-study will undergo Holter collection assessments at Visit 6 (Week 4) (refer to Section 7.2.5). A Holter monitor will be placed following collection of spirometry pre-dose assessment but prior to in-clinic dosing. Subjects will take their morning dose of study medication at the clinic. Subjects will undergo all protocol-defined post-dose assessments. Subjects will be instructed to return to the clinic the following day for removal of the Holter monitor.

When the subject returns to the clinic the following day, the quality of the Holter monitor recordings will be assessed at the site. If the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours) on the first attempt, a second attempt will be made for another 24 hours using a new Holter monitor hook-up kit.
The subject will be instructed to continue his/her medications as per study protocol.
The subject will return the following day for removal of the second Holter monitor.
No further attempts are allowed if the second attempt is unacceptable.

Subjects can proceed to Visit 7 (Week 8) provided no clinically significant findings (as defined in Section 5.7.1) are reported by [redacted] following review of the Holter monitor recordings.

SGRQ will be assessed in all subjects at Visit 4 (Day 1), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), and Visit 11a (Week 24). Baseline Dyspnea Index (BDI) will be assessed in all subjects at Visit 4 (Day 1) and TDI at Visit 6 (Week 4), Visit 7 (Week 8), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20) and Visit 11a (Week 24). When BDI/TDI and SGRQ are obtained at the same visit, the BDI/TDI will be collected first followed immediately by the SGRQ. Whenever possible, it is recommended that the BDI/TDI and SGRQ be completed by the subject prior to any other visit procedures.

4.1.1 General Considerations for Treatment Visits 4 through Visit 11a:

- 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 phosphodiesterase-4 inhibitors) 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 (eg, reproducibility and eDiary compliance).

- Subjects must not ingest xanthine (caffeine)-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.
    - Subjects will be required to return to the clinic at approximately the same time as Visit 2 for all treatment visits (± 2 hours) but not to exceed 10:00 AM and will be required to remain at the clinic until completion of all protocol-defined assessments.
    - 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.
- 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 should be reminded to take their last dose the evening 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 study drug (GFF MDI, GP MDI, FF MDI or Placebo 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.

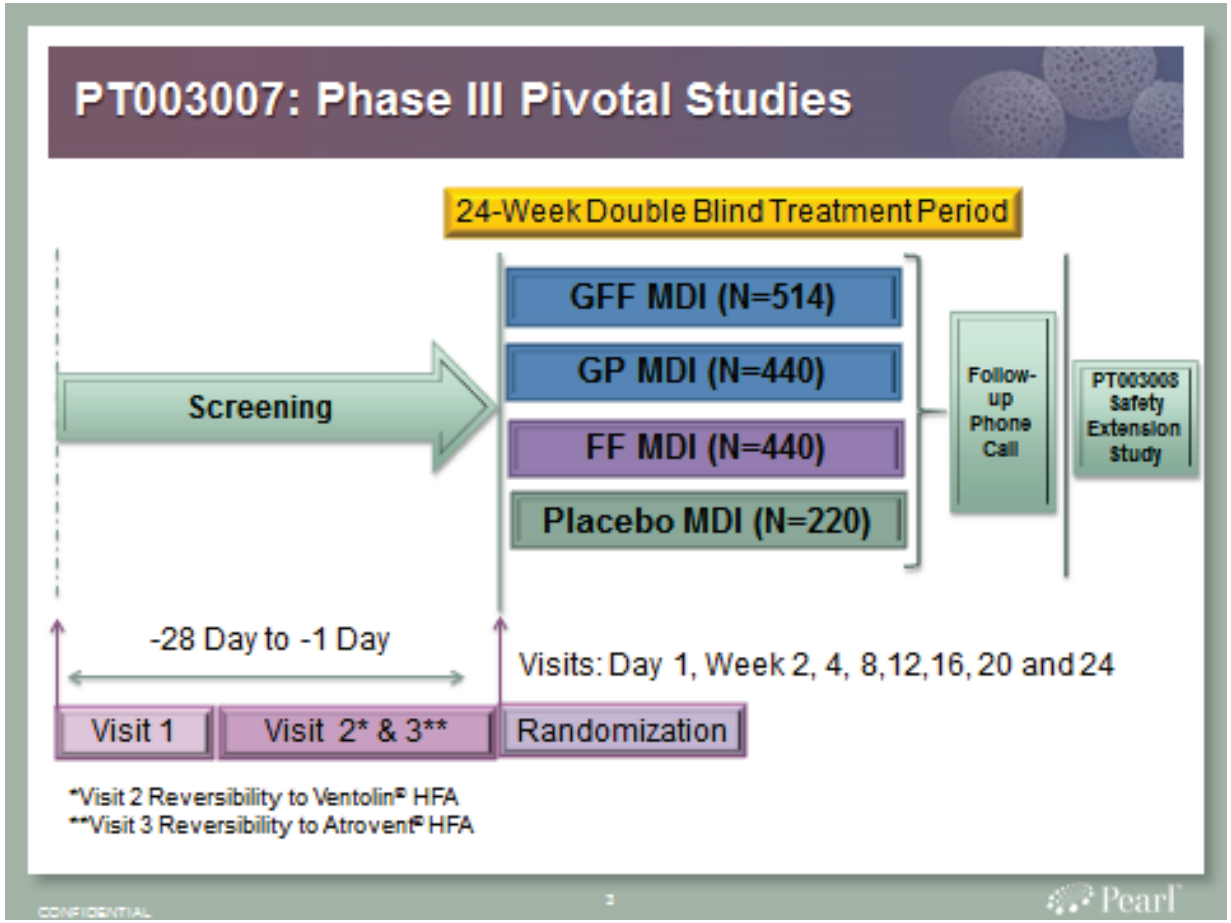
- Protocol-adjusted ICS therapy as defined at Visit 1 (Screening) if any, should be continued and remain stable for the duration of the trial (refer to Section 5.4).
- Post-randomization, all visits will be scheduled relative to Visit 4 (Day 1). Thus Visits 5, 6, 7, 8, 9, 10 and 11a will be scheduled 2, 4, 8, 12, 16, 20 and 24 Weeks ± 2 days of Visit 4 respectively. Sites should make every effort to maintain subjects within the scheduled visit window. If a visit falls outside the expected visit window the subsequent visit should still be scheduled as planned relative to Visit 4.

Subjects completing Visit 11a will be invited to participate in a safety extension study (Study PT003008) to evaluate the long-term safety of GFF MDI, GP MDI, and FF MDI for an additional 28 weeks. All subjects who volunteer to participate in the extension study will complete Visit 11a (Final Study Visit) and Visit 11b (Safety Extension Study Entry Visit) (refer to the protocol for Study PT003008 for additional details).

Subjects who do not participate in the safety extension study (Study PT003008) will complete all Visit 11a (Final Study Visit) assessments and will be scheduled for a post-study follow-up telephone call at least 14 days from Visit 11a.

A Study Flow Diagram is displayed in Figure 1.

Figure 1. Study Flow Diagram



4.2 Rationale of Study Design

This study will assess the long-term (24 weeks) bronchodilator efficacy, safety and tolerability of GFF MDI 14.4/9.6 µg, GP MDI 14.4 µg, and FF MDI 9.6 µg administered twice daily compared to Placebo MDI. This study will also allow for comparison of the efficacy and safety of GFF MDI 14.4/9.6 µg to its components (GP MDI 14.4 µg and FF MDI 9.6 µg) to assess the relative contribution of each component to the combination and to confirm that the combination is safe and effective for patients with moderate to very severe COPD.

Due to the duration of the trial, a randomized, double-blind, parallel-group design was adopted in order to minimize bias in treatment allocation and to allow unbiased comparisons of treatment groups.

4.3 Rationale of Dose/Regimen, Duration of Treatment, and Placebo Arm

The selection of the GFF MDI (14.4/9.6 µg BID) dose in this study was based on data from the findings of three previous dose-ranging studies with GP MDI (Studies PT0010801, PT001002, and PT001003), two dose-ranging clinical studies with FF MDI (Studies PT0050801 and PT005003), and four studies with GFF MDI (Studies PT0031002, PT003003, PT003004, and PT003005).

These programs identified the optimal doses as 9.6 µg BID for FF MDI and 14.4 µg BID for GP MDI. The aforementioned studies also showed that GP 14.4 µg when added to FF 9.6 µg provides a reasonable benefit across all parameters. GFF MDI 14.4/9.6 µg was safe and well- tolerated with an AE profile similar to its components and other approved products for the management of COPD (ie, Spiriva, Atrovent, and Foradil® Aerolizer®).

The study will evaluate the effects of GFF MDI, GP MDI, FF MDI, and Placebo MDI on lung function, including subject reported outcomes such as symptoms, and health status over 24 weeks. While studies of shorter duration (eg, 8-12 weeks) may be sufficient for the assessment of bronchodilators, Pearl Therapeutics has decided to characterize efficacy and safety of the aforementioned drugs for at least 24 weeks to allow for global registration of GFF MDI, GP MDI, and FF MDI.

In order to place the efficacy and safety of GFF MDI (14.4/9.6 µg) into context, FF MDI (9.6 µg), and GP MDI (14.4 µg) are included in the study. It is important to note that subjects will receive the treatment assigned by randomization in addition to the subject's established maintenance COPD therapy, such as daily inhaled corticosteroids or phosphodiesterase inhibitors (eg, roflumilast). In addition, subjects will be allowed to use sponsor-provided Ventolin HFA as rescue medication when required.

A Placebo MDI arm will also be included in the trial. The Placebo MDI arm does not imply that this cohort is untreated. Subjects will be permitted to receive maintenance inhaled steroids (ICS), and/or phosphodiesterase inhibitors if they were on a stable dose of these

medications prior to enrolling in the study, and Ventolin HFA MDI will be provided as rescue medication. No currently approved treatment prevents death or irreversible morbidity by influencing the course of disease.

With respect to exacerbations, changing an ICS/LABA to an ICS and as needed (PRN) Ventolin HFA MDI or changing Spiriva, Tudorza or Seebri to PRN Ventolin HFA is unlikely to cause significant short-term harm. There are three further safeguards to ensure subject safety in this study. First, roflumilast, a recently approved drug to prevent COPD exacerbations, is a permissible medication throughout the course of the study provided the subject was on a stable dose prior to enrollment. Second, subjects experiencing two moderate exacerbations or one severe exacerbation will be discontinued from the trial. An independent data monitoring committee (DMC) will review significant safety findings on a periodic basis and can suggest modification or termination of the study based on the safety implications of the data.

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

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

1. Give their signed written informed consent to participate.
2. Are at least 40 years of age and no older than 80 at Visit 1.
3. A female is eligible to enter and participate in the study if she is of:
   - Non-child bearing potential (ie, physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal); or
   - Child bearing potential, has a negative serum pregnancy test at Visit 1, and agrees to one of the following acceptable contraceptive methods used consistently and correctly as outlined below (ie, in accordance with the approved product label and the instructions of the physician for the duration of the study – from Visit 1 (Screening) until 14 days after Visit 11a:
     - Complete abstinence from intercourse or
     - Implants of levonorgestrel inserted for at least 1 month prior to the study drug administration but not beyond the third successive year following insertion; or
     - Injectable progestogen administered for at least 1 month prior to study drug administration; or
     - Oral contraceptive (combined or progestogen only) administered for at least one monthly cycle prior to study drug administration; or
     - Double barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository); or
     - An intrauterine device (IUD), inserted by a qualified physician, with published data showing that the highest expected failure rate is less than 1% per year; or
     - Estrogenic vaginal ring; or
     - Percutaneous contraceptive patches.
4. COPD Diagnosis: Subjects with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) (Celli, 2004) characterized by:
   - Airflow limitation that is not fully reversible. Progressive airflow limitation associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.
5. Tobacco Use: Current or former smokers with a history of at least 10 pack-years of cigarette smoking. [Number of pack-years = (number of cigarettes per day / 20) x number of years smoked (eg, 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years represent 10 pack-years)].
6. Severity of Disease: Subjects with an established clinical history of COPD and severity defined as:

- At Visit 1, FEV_1/FVC ratio of <0.70.
- At Visit 2, and 3, pre- and post-bronchodilator FEV_1/FVC ratio of <0.70.
- At Visit 1, FEV_1 must be <80% predicted normal value calculated using the Third National Health and Nutrition Examination Survey (NHANES III) reference equations.
- At Visit 2, post-bronchodilator FEV_1 must be <80% predicted normal value, calculated using NHANES III reference equations, and the measured FEV_1 must also be ≥750 mL if FEV_1 <30% of predicted normal value.
- At Visit 4, pre-bronchodilator FEV_1/FVC ratio of <0.70.
- At Visit 4, the average of the -60 minute and -30 minute pre-dose FEV_1 assessments must be <80% predicted normal value calculated using NHANES III reference equations.

7. Subject is willing and, in the opinion of the Investigator, able to adjust current COPD therapy as required by the protocol.
8. Screening clinical laboratory tests must be acceptable to the Investigator.
9. Screening ECG must be acceptable to the Investigator.
10. Chest X-ray or computed tomography (CT) scan of the chest/lungs within 6 months prior to Visit 1 must be acceptable to the Investigator. Subjects who have a chest X-ray (or CT scan) that reveals clinically significant abnormalities not believed to be due to the presence of COPD should not be included. A chest X-ray must be conducted if the most recent chest X-ray or CT scan is more than 6 months old at the time of Visit 1.
11. Compliance: Subjects must be willing to remain at the study center as required per protocol to complete all visit assessments.

5.2 Exclusion Criteria

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

1. Significant diseases other than COPD, ie, disease or condition which, in the opinion of the Investigator, may put the subject at risk because of participation in the study or may influence either the results of the study or the subject's ability to participate in the study
2. Pregnancy: Women who are pregnant or lactating.
3. Respiratory
    a) Asthma: Subjects, who in the opinion of the Investigator, have a current diagnosis of asthma.
    b) Alpha-1 Antitrypsin Deficiency: Subjects who have alpha-1 antitrypsin deficiency as the cause of COPD.
    c) Other Respiratory Disorders: Subjects who have other active pulmonary disease such as active tuberculosis, lung cancer, bronchiectasis (High Resolution CT evidence of bronchiectasis that causes repeated acute exacerbations), sarcoidosis, idiopathic interstitial pulmonary fibrosis (IPF), primary pulmonary hypertension, or uncontrolled sleep apnea (ie, in the opinion of the Investigator severity of the

disorder would impact the conduct of the study). **Note:** Allergic rhinitis is not exclusionary.

d) Lung Volume Reduction: Subjects who have undergone lung volume reduction surgery, lobectomy or bronchoscopic lung volume reduction (endobronchial blockers, airway bypass, endobronchial valves, thermal vapor ablation, biological sealants, and airway implants) within 1 year of Visit 1.

e) Hospitalization: Subjects who have been hospitalized due to poorly controlled COPD within 3 months prior to Visit 1 (Screening) or during the Screening Period (Visit 1 to Visit 4).

f) Poorly Controlled COPD: Subjects who have poorly controlled COPD, defined as acute worsening of COPD that requires treatment with oral corticosteroids or antibiotics within 6 weeks prior to Visit 1 (Screening) or during the Screening Period (Visit 1 to Visit 4). Note: Subjects who are steroid dependent and maintained on an equivalent of 5 mg prednisone per day or 10 mg every other day for at least 3 months prior to Visit 1 are eligible for enrollment providing the dose of oral steroids remains stable during the screening period (Visit 1 through Visit 4).

g) Lower Respiratory Tract Infection: Subjects who had lower respiratory tract infections that required antibiotics within 6 weeks prior to Visit 1 (Screening) or during the Screening Period (Visit 1 to Visit 4).

h) Spirometry Performance:

   a. Acceptability: Subjects who cannot perform acceptable spirometry, ie, meet ATS/ERS acceptability criteria.

   b. Repeatability: Subjects who cannot perform technically acceptable spirometry with at least three acceptable flow-volume curves with two or more meeting ATS repeatability criteria for FEV_1during at least one of the pre-bronchodilator assessments at Visit 2 (-60 minute or -30 minute) and at the post-bronchodilator assessment at Visit 2.

   c. Reproducibility: Subjects who cannot meet protocol-specified reproducible criteria. Reproducibility is defined as the average of the -60 minute and -30 minutes pre-dose FEV_1 assessments at Visit 4 being within ±20% or 200 mL of the mean of the pre-bronchodilator FEV_1 assessments obtained at the two preceding visits (average of pre-dose FEV_1 assessments obtained at Visit 2 and Visit 3).

i) Oxygen: Subjects receiving long-term-oxygen therapy (LTOT) or nocturnal oxygen therapy required for greater than 12 hours a day. **Note:** As needed (PRN) oxygen use is not exclusionary.

j) Subject use of any non-invasive positive pressure ventilation device (NIPPV). **Note:** Subjects using continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) for Sleep Apnea Syndrome are allowed in the study.

k) Change in smoking status (ie, start or stop smoking,) or initiation of a smoking cessation program within 6 weeks of Visit 1 and throughout the Screening Period (Visit 1 to Visit 4).

l) Pulmonary Rehabilitation: Subjects who have participated in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1 (Screening) or who will enter the acute phase of a pulmonary rehabilitation program during the study. Subjects who are in the maintenance phase of a pulmonary rehabilitation program are not to be excluded.

m) Subjects who have initiated or altered the dose regimen of intranasal corticosteroids, intranasal antihistamines, or a combination thereof within 7 days prior to Visit 1 or during the Screening Period (Visit 1 to Visit 4).

4. Cardiac disease

a) Subjects who have unstable ischemic heart disease, left ventricular failure, or documented myocardial infarction within 12 months of enrollment. Subjects with a recent history of acute coronary syndrome, or who have undergone percutaneous coronary intervention or coronary artery bypass graft within the past 3 months are to be excluded.

b) Subjects with congestive heart failure (CHF NYHA Class III/IV)

c) Clinically significant abnormal ECG: A clinically significant abnormal ECG is defined as (but not limited to) any of the following:

1. Clinically significant conduction abnormalities [eg, left bundle branch block, Wolff-Parkinson-White syndrome or evidence of second degree (Mobitz Type II) or third degree atrioventricular (AV) block].
2. Clinically significant arrhythmias (eg, atrial fibrillation with irregular ventricular response, atrial flutter, ventricular tachycardia). **Note:** atrial fibrillation that has been clinically stable for at least 6 months is appropriately treated with anticoagulation and controlled with a rate control strategy (ie, selective beta blocker, calcium channel blocker, digoxin or ablation therapy) for at least 6 months is allowed for inclusion. In such subjects, atrial fibrillation must be present at pre-randomization visits, with a resting ventricular rate <100 beats per minute (bpm). At screening, the atrial fibrillation must be confirmed by central reading.
3. A mean corrected QT interval using Fridericia's correction factor (QTcF) value at screening >450 ms for males and >470 ms for females or an ECG that is not suitable for QT measurements (eg, poorly defined termination of the T wave) at Visit 1 that remains elevated on repeat testing prior to Visit 2.
4. Ventricular rate <45 bpm.
5. Pathological Q waves of ≤1 year compared to the Screening Visit.
6. ST- T wave abnormalities deemed to be clinically significant by the Investigator. **Note:** Subjects with non-specific ST-T wave abnormalities that are not deemed clinically significant (per Investigator) are allowed.

7. Any other ECG abnormalities not listed above that in the opinion of the are clinically significant.

d) Clinically Uncontrolled Hypertension: Subjects who have clinically significant uncontrolled hypertension.

5. Neurological
   a) Subjects with seizures requiring anticonvulsants within 12 months prior to Visit 1 (Screening). Note: Subjects treated with anticonvulsant medication for 12 months or more with no seizure events are eligible.
   b) Subjects taking selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) whose dose has not been stable for at least four weeks prior to Visit 1 or is altered at any point during the Screening Period (Visit 1 to Visit 4), or exceeds the maximum recommended dose.
6. Renal
   a) Subjects with symptomatic prostatic hypertrophy that is clinically significant in the opinion of the Investigator. Subjects with a trans-urethral resection of prostate (TURP) or full resection of the prostate within 6 months prior to Visit 1 are excluded from the study.
   b) Subjects with bladder neck obstruction or urinary retention that is clinically significant in the opinion of the Investigator.
   c) Subjects with a calculated creatinine clearance ≤50 mL/minute using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula (Levey 2009) at Visit 1 and on repeat testing prior to Visit 2.

      Note: Subjects with overactive bladder syndrome treated with oral anticholinergics who have been on treatment for at least 1 month are allowed in the trial.
7. Endocrine
   a) Subjects, who in the opinion of the Investigator, have uncontrolled hypo-or hyperthyroidism, hypokalemia or hyperadrenergic state.
   b) Subjects, who in the opinion of the Investigator, have uncontrolled Type I or II diabetes.
8. Liver: Subjects with abnormal liver function tests defined as AST, ALT, or total bilirubin ≥1.5 times upper limit of normal at Visit 1 and on repeat testing prior to Visit 2.
9. Cancer: Subjects who have cancer that has not been in complete remission for at least five years. **Note:** Subjects with squamous cell carcinoma of the skin, basal cell carcinoma of the skin, or localized prostate cancer are eligible, if in the opinion of the Investigator, the condition has been adequately worked up, is clinically controlled and the subject's participation in the study would not represent a safety concern.
10. Glaucoma: Subjects with a diagnosis of glaucoma, who, in the opinion of the Investigator, have not been adequately treated. All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective beta-blockers (eg, betaxolol, carteolol, levobunolol, metipranolol, and timolol).

11. Drug Allergy: Subjects who have a history of hypersensitivity to β2-agonists, glycopyrronium or other muscarinic anticholinergics, lactose/milk protein or any component of the MDI.
12. Substance Abuse: Subjects, who in the opinion of the Investigator, significantly abuse alcohol or drugs (refer to Exclusion Criterion 1).
13. Medication prior to spirometry: Subjects who are medically unable to withhold their short-acting bronchodilators for the 6-hour period required prior to spirometry testing at each study visit will be excluded.
14. Prohibited Medications: Subjects who, in the opinion of the Investigator, would be unable to abstain from protocol-defined prohibited medications during the screening period and treatment phases of this study (refer to Section 5.4).
15. Vaccinations: Subjects who received a live attenuated vaccination within 30 days prior to Visit 1 (Screening) or during the Screening Period (between Visit 1 to Visit 4). **Note:** Inactivated influenza vaccination, pneumococcal vaccination or any other inactivated vaccine is acceptable provided it is not administered within 48 hours prior to Visit 1 (Screening) or Visit 4 (randomization).
16. Non-compliance: Subjects unable to comply with study procedures including non-compliance with diary completion (ie, <70% subject completion of diary assessments in the last 7 days preceding Visit 4).
17. Affiliations with Investigator site: Study Investigators, sub-Investigators, study coordinators, employees of a participating Investigator or immediate family members of the aforementioned are excluded from participation in this study.
18. Questionable Validity of Consent: Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol), or other conditions that will limit the validity of informed consent to participate in the study.
19. Subjects using prohibited medications (refer to Table 4).
20. Investigational Drugs or Devices: Treatment with investigational study drug or device in another clinical trial within the last 30 days or five half-lives prior to Visit 1 (Screening), whichever is longer. **Note:** Subject participation in observational studies (ie, studies that do not require change to medication or an additional intervention) is not exclusionary.
21. Hand-to-Breath Coordination: Subjects who requires the use of a spacer device to compensate for poor hand-to-breath coordination with a MDI. **Note:** Use of a nebulizer to deliver COPD medications is prohibited throughout the trial.
22. Previous Participation: Subjects who were previously enrolled in any trial conducted or sponsored by Pearl Therapeutics, Inc.

5.2.1 24-Holter Monitoring Sub-Study Exclusion Criteria

Subjects with a pacemaker or implantable cardioverter-defibrillator (ICD)/cardiac resynchronization therapy (CRT)/cardiac resynchronization therapy-defibrillator (CRT_D) devices will not be allowed into the Holter sub-study.

Clinically significant abnormal findings during the baseline Holter monitor recording defined as (but not limited to) any of the following:

1. Average HR ≤40 bpm for any 1 hour.
2. Second-degree AV block (Type 2) or third-degree AV block.
3. Sinus pause of:
   - >2.5 seconds duration during daytime
   - >3.0 seconds duration during nighttime
4. Any episode of ventricular flutter and/or ventricular fibrillation.
5. Any episode of non-sustained ventricular tachycardia (VT) with symptoms of hypotension or syncope or asymptomatic non-sustained VT >15 ventricular premature beats (VPB's) in a row.
6. Sustained VT (>30 seconds in duration)
7. Five or more episodes of non-sustained VT/ 24 hours
8. Greater than 500 VPB/hr

5.3 Subject Identification

All subjects who undergo screening will be assigned a unique screening identification number at the Screening Visit (Visit 1). Only subjects continuing to meet entry inclusion/exclusion criteria at Visit 4 will be assigned a unique subject randomization number.

5.4 Prior, Concomitant, and Prohibited Medications

All prescription and over-the-counter (OTC) medications taken by the subject within 30 days before Visit 1 (Screening) will be recorded on the prior/concomitant medications eCRF. Any additions, deletions, or changes in the dose of these medications while in the study should be entered on the eCRF. Any current ongoing medications, including OTC drugs and herbal supplements, will be allowed provided they are not prohibited by the protocol (refer to Section 5.4.1) 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 eCRF with indication, dose, dose regimen, 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 be discontinued at Visit 1 (Screening) and are not permitted during the Screening Period. The minimum washout period between Visit 1 and Visit 2 is shown in Table 1.

Table 1. COPD Medications: Required Washout Periods, Pre Visit 2

Required Washout Period Prior to Visit 2:	
Class of medication	**Minimum washout period prior to Visit 2**
Long-acting anticholinergics	14 days
Short-acting anticholinergics	6 hours
Fixed-combinations of long-acting β_2 agonists and inhaled corticosteroids	7 days. At Visit 1 (Screening) these medications must be switched to the nearest equivalent dose of inhaled corticosteroid monotherapy
Fixed-combinations of short-acting β_2 agonists and short-acting anticholinergics	6 hours
Long acting β_2 agonists	48 hours; indacaterol, 7 days
Short-acting β_2 agonists (including study rescue Ventolin HFA)	6 hours
Theophylline (Total daily dose $\leq$400 mg/day)*	7 days

*Theophylline is allowed if the total daily dose is $\leq$400 mg. Subjects taking roflumilast are allowed provided they have been on stable dose of therapy for at least 2 months prior to randomization.

Subjects that have received depot corticosteroids including, intra-articular or intraocular corticosteroids require a 3 month washout prior to Visit 1. Subjects that have received oral, intravenous or intramuscular corticosteroids for any reason require a 6 week washout prior to Visit 1. Any subject that requires use of systemic corticosteroids during the screening period (Visit 1 to Visit 4) will be screen failed.

Note:

- Subjects who are steroid dependent and maintained on an equivalent of $\leq$5 mg oral prednisone per day or $\leq$10 mg oral prednisone every other day for at least 3 months prior to Visit 1 are eligible providing the dose of oral steroids remains stable during the screening period (Visit 1-Visit 4).
- During the Treatment Period (Visit 4 to Visit 11a), subjects may be treated with corticosteroids if required.

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

- Subjects taking COPD medications (listed previously) at Visit 1 (Screening) will discontinue these medications for the duration of the trial and be switched to sponsor-provided Atrovent HFA MDI administered QID and sponsor-provided Ventolin HFA to

be administered up to four times per day as needed for control of symptoms during the Screening Period.

- Subjects receiving a maintenance dose of an ICS as part of a fixed dose combination therapy containing fluticasone and salmeterol, mometasone and formoterol, budesonide and formoterol or fluticasone and formoterol must have been on the ICS component for at least 4 weeks prior to Visit 1 (Screening) and maintained on a stable dose for at least 4 weeks prior to Visit 1 (Screening). These subjects will be switched to the corresponding dose of fluticasone, mometasone or budesonide administered as a single agent BID, with sponsor-provided Atrovent HFA MDI administered QID, and sponsor-provided Ventolin HFA to be administered up to four times per day as needed for control of symptoms during the Screening Period.
- Subjects receiving a maintenance dose of an ICS that is not administered as a fixed-dose combination together with a LABA will be permitted to continue the ICS provided they have been maintained on a stable dose for at least 4 weeks prior to Visit 1 (Screening).
- All subjects treated with either a LABA (salmeterol, formoterol, indacaterol) or currently marketed long- acting anti-muscarinic agent (LAMA) (tiotropium, aclidinium, glycopyrronium bromide, [eg, Seebri]) administered alone or as a loose combination will have these medications discontinued and replaced with sponsor-provided Atrovent HFA MDI administered QID, and sponsor-provided Ventolin HFA to be administered up to four times per day as needed for control of symptoms during the Screening Period.

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

Table 2. Other Respiratory/Nasal Medications: Required Washout Periods

Required Washout Periods Prior to Visit 2:	
Class of medication	**Minimum cessation period prior to Visit 2**
Leukotriene antagonists (eg, zafirlukast, montelukast, and zilueton)	7 days
Cromoglycate	7 days
Nedocromil	7 days
Ketotifen *	7 days

*Ketotifen eye drops are allowed

5.4.2 Other Prohibited Medications

The following medications should be used under the stated conditions during this study (Table 3). Each concomitant drug must be individually assessed against all exclusion criteria. If in doubt, the Investigator should contact the Pearl Therapeutics Medical Monitor before randomizing a subject or allowing a new medication to be started:

Table 3. Non-COPD Medications Allowed Under Certain Condition

Medications allowed under certain conditions	Condition
Selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs)	Treatment regimen has been stable for at least four weeks prior to Visit 1 and not altered during the Screening Period and does not exceed the maximum recommended dose
Intranasal corticosteroids, intranasal antihistamines or combination thereof	Administered at constant dose and dosing regimen for at least 7 days prior to Visit 1 (Screening) and during the Screening Period

Subjects requiring the following medications are prohibited from this study (Table 4). Subjects who recently discontinued use of these medications may be considered for study enrollment providing they have met the minimum washout period prior to Visit 1 (Screening). 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 4. Prohibited Medications

Prohibited Medications	Minimum cessation period prior to Visit 1 (Screening)
Any drug with potential to significantly prolong the QT interval	14 days or 5 half-lives, whichever is longer
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Non-selective beta-blocking agents	7 days
Cardiac antiarrhythmics Class Ia, III	7 days; amiodarone, 3 months
Anticonvulsants for seizure disorder	Allowed if stable dose for 12 months and free of seizures for 1 year
Anticonvulsants for other indications	Allowed if stable dose for at least 3 months and the Investigator confirms there have been no seizures within the past 12 months.
Tricyclic antidepressants	14 days
Monoamine oxidase inhibitors	14 days
Anti-tumor necrosis factor α (TNF α) antibodies (eg, infliximab and any other members of this class of drugs)	30 days or 5 half-lives, whichever is longer
Monoclonal antibodies	30 days or 5 half-lives, whichever is longer
Antipsychotic drugs [a]	30 days
Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors and cimetidine	30 days
Systemic anticholinergics [b]	7 days

[a] Antipsychotic agents used for other indications may be allowed after consultation with the Medical Monitor of the trial.

[b] If systemic anticholinergics are used for treatment of overactive bladder and the treatment has been constant for at least 1 month, they are allowed.

Note: Benzodiazepines are not exclusionary.

5.5 Other Restrictions, Illicit Drugs or Drugs of Abuse

5.5.1 Illicit Drugs and/or Drugs of Abuse

Illicit drugs or drugs of abuse will not be allowed from the start of Screening (Visit 1) to the end of Visit 11a 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.

5.5.2 Dietary Restrictions

Subjects are encouraged to refrain from consuming grapefruits or grapefruit juice throughout the study. Subjects must not ingest xanthine (ie, caffeine)-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 (ie, 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 (ie, whether a subject's status has changed from smoker to non-smoker or vice versa). Any change in smoking status during the Screening Period (Visit 1 to Visit 4) will result in a screen failure. Smoking status changes during the 24 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: For this study, the use of electronic cigarettes will be treated in the same manner as 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 randomized, regardless of the cause, should undergo the assessments outlined in Section 8.7 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 >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 >160 mmHg.
- Decrease in creatinine clearance to a value below 30 mL/minute 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 >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 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, is 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 4.
- Initiation of maintenance therapy with a marketed LABA (eg, salmeterol, formoterol, indacaterol) administered alone or in combination with an ICS or a marketed LAMA (eg, tiotropium, aclidinium, or glycopyrronium bromide [Seebri]).

If a female subject 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 7.2.8).

5.7.1 24- Hour Holter Monitoring Sub-study Criteria for Discontinuation:

Subjects with a pacemaker or implantable cardioverter-defibrillator (ICD), or cardiac resynchronization therapy (CRT), cardiac resynchronization therapy-defibrillator (CRT_D) devices will not be allowed into the Holter sub-study.

Clinically significant abnormal findings during the Holter recording defined as (but not limited to) any of the following:

1. Average HR ≤40 bpm for any 1 hour
2. Second-degree AV block (Type 2) or third-degree AV block
3. Sinus pause of:
   - >2.5 seconds duration during daytime
   - >3.0 seconds duration during nighttime
4. Any episode of ventricular flutter and/or ventricular fibrillation
5. Any episode of non-sustained ventricular tachycardia (VT) with symptoms of hypotension or syncope or asymptomatic non-sustained VT >15 ventricular premature beats (VPB's) in a row
6. Sustained VT (more than 30 seconds in duration)
7. Five or more episodes of non-sustained VT/24 hours
8. Greater than 500 VPB/hr

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 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 personal identification number (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 5.

Table 5. Study Product Packaging Descriptions

Product Name and Dosage	Product Strength	Dose Form/Fill Count	Administration
Study Medications			
GFF MDI (PT003) 14.4/9.6 µg ex-actuator	GFF MDI 7.2/4.8 µg per actuation	1 MDI 120 inhalations	Taken as two inhalations BID
FF MDI (PT005) 9.6 µg ex-actuator	FF MDI 4.8 µg per actuation	1 MDI 120 inhalations	Taken as two inhalations BID
GP MDI (PT001) 14.4 µg ex-actuator	GP MDI 7.2 µg per actuation	1 MDI 120 inhalations	Taken as two inhalations BID
Open-label Products			
Ventolin (albuterol sulfate) HFA inhalation aerosol 90 µg ex-actuator [a]	Ventolin (albuterol sulfate) HFA inhalation aerosol will be the US supplied product Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	1 MDI 60 or 200 actuations	Taken as needed Supplies are open-label
Atrovent (ipratropium bromide) HFA inhalation aerosol 34 µg ex-actuator [b]	Atrovent (ipratropium bromide) HFA will be the US supplied product Each inhalation contains 17 µg ex-actuator per actuation	1 MDI 200 actuations	Taken as two inhalations QID during Screening Supplies are open-label
Placebo			
Placebo MDI	Formulation does not contain active ingredient	1 MDI 120 inhalations	Taken as two inhalations BID

Abbreviations: BID=twice daily; COPD=chronic obstructive pulmonary disease; FF MDI=Formoterol Fumarate Inhalation Aerosol; GFF MDI=Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; GP MDI=Glycopyrronium Inhalation Aerosol; HFA=Hydrofluoroalkane; MDI=Metered Dose Inhaler; QID=four times daily; US=United States

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

Note: Glycopyrronium 14.4 µg in GFF MDI and GP MDI is equivalent to 18 µg of glycopyrronium bromide.

[a] Reversibility testing at Visit 2 and rescue medication during the study.

[b] Reversibility testing at Visit 3 and COPD maintenance therapy during Screening Period.

Open-label Atrovent HFA MDIs 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. Atrovent HFA and Ventolin HFA supplies will be supplied as open-label MDIs.

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 Atrovent HFA and 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 (Atrovent HFA 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
Atrovent HFA	1 MDI
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.

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.

Atrovent HFA supplies: Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. For optimal results, the canister should be at room temperature before use. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw the inhaler into a fire or incinerator.

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, FF MDI, and Placebo MDI

Individual GFF MDI, GP MDI, FF MDI, and Placebo 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 must 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. Refer to Appendix 4 for instructions on the administration of GFF MDI, GP MDI, FF MDI, and Placebo MDI. Cleaning instructions are provided in Appendix 4.

6.7.2 Atrovent HFA (Ipratropium Bromide)

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

Atrovent HFA is a solution aerosol that does not require shaking. However, as with any other MDI, some coordination is required between actuating the canister and inhaling the medication. Atrovent HFA should be primed per manufacturer's instructions prior to dispensing to subject (ie, "prime" or actuate Atrovent HFA before using for the first time by releasing 2 test sprays into the air away from the face). In cases where the inhaler has not

been used for more than 3 days, prime the inhaler again by releasing 2 test sprays into the air away from the face. Subjects should avoid spraying Atrovent HFA into their eyes.

Subjects will be dispensed the Atrovent HFA for COPD maintenance therapy during screening period (between Visit 1 and 4) per the manufacturer's instruction, 2 puffs with each administration four times a day, approximately 6 hours apart. The MDI should be stored at room temperature by the subject, avoiding temperature extremes and storage in direct sunlight. Refer to Appendix 5 for the manufacturer's instructions on the administration of Atrovent HFA.

6.7.3 Ventolin HFA (Albuterol Sulfate)

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. Refer to 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 (ie, 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 be randomized/continue with the study. Any deviation from this must be discussed with the Clinical Monitor.

For each subject, all used study drug materials will be collected. 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 9. Detailed schedules for pre- and post-dose procedures to be performed on visit days are provided in Table 10 and Table 11.

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 (refer to Appendix 1).

The volume accuracy of the spirometer is to be checked daily using a 3 L syringe across 3 flow ranges (ie, 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% (ie, 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 will be conducted at Visit 1. At Visit 2 and Visit 3, Spirometry will be conducted 60 minutes and 30 minutes prior to bronchodilator administration and at 30 minutes post-bronchodilator (refer to Section 7.1.1.1). **Note:** Spirometry must meet both acceptability and repeatability criteria (refer to Exclusion Criterion 3 h).

Spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration at Visit 4 through Visit 11a. The mean of the -60 minutes and -30 minutes pre-dose

spirometry assessments conducted at Visit 4 will be used to establish baseline FEV_1, FVC $FEF_{25-75,}$ and PEFR.

At Visit 4 (Day 1), spirometry will be obtained at 5, 15 and 30 minutes, and 1 and 2 hours post-dosing of study drug. **Note:** The 5-minute post-dose spirometry assessment will be obtained at Visit 4 (Day 1) only.

At Visit 5 (Week 2), Visit 7 (Week 8), Visit 8 (Week 12), Visit 10 (Week 20) and Visit 11a (Week 24) spirometry will be obtained at 15 and 30 minutes, and 1 and 2 hours post-dosing of study drug. Post-dose spirometry assessments will not be conducted at Visit 6 (Week 4) and Visit 9 (Week 16).

For subjects participating in the 12-hour PFT sub-study, at Visit 4 (Day 1) and Visit 8 (Week 12) additional spirometry assessments will be obtained at 4, 6, 8, 10, 11.5 and 12 hours post-dosing.

7.1.1.1 Characterization of Reversibility

Reversibility to Ventolin HFA (SABA) will be evaluated at Visit 2. Reversibility to Atrovent HFA (short-acting anticholinergic) will be evaluated at Visit 3.

The procedure will be, as follows:

- Reversibility testing to Ventolin HFA (Visit 2 Only):
  - Perform pre-bronchodilator PFTs (-60 minutes and -30 minutes) prior to administration of Ventolin HFA (albuterol).
  - Administer 4 puffs of Ventolin HFA (albuterol).
  - Perform post-bronchodilator PFT 30 minutes after the administration of Ventolin HFA.

- Reversibility testing to Atrovent HFA (Visit 3 Only):
  - Perform pre-bronchodilator PFTs (-60 minutes and --30 minutes) prior to administration of Atrovent HFA.
  - Administer 4 puffs of Atrovent HFA.
  - Perform post-bronchodilator PFT 30 minutes after the administration of Atrovent HFA.

Reversibility will be a comparison of the average best FEV_1 effort obtained at -60 minutes and -30 minutes pre-bronchodilator to the best FEV_1 effort obtained at 30 minutes post-bronchodilator. A subject is determined to be reversible to Ventolin HFA or Atrovent HFA if the improvement in FEV_1 approximately 30 minutes following administration of 4 puffs of Ventolin HFA or Atrovent HFA, respectively, is $\geq$12% and $\geq$200 mL. Reversibility to Ventolin HFA (obtained at Visit 2) will be used as a stratification

variable at randomization to ensure an even distribution of reversibility across the treatment arms. Reversibility to Atrovent HFA will be used to characterize the population.

7.1.1.2 Reproducibility Criteria

Since all comparisons will be made to the baseline (mean of 60 and 30 minutes prior to dosing) values obtained at Visit 4, it is important to ensure that the baseline FEV_1 is stable and reflective of the subjects COPD severity prior to being randomized into the study. As such, the baseline FEV_1 at Visit 4 must be within ±20% or 200 mL of the mean of the pre-dose FEV_1 obtained at the two preceding visits (average of pre-dose FEV_1 obtained at Visit 2 and Visit 3). At Visit 4, if the pre-dose FEV_1 average is outside of the ±20% or 200 mL range, but the -30 minute assessment is within ±22% or 220 mL, then another assessment may be conducted 30 minutes later. If the last two assessments meet the reproducibility requirements (ie, within ±20% or 200 mL), the initial 60 minute pre-dose assessment will not be used and the last two assessments will be used to establish the eligibility criteria. If the test day FEV_1 is not within ± 20% or 200 mL, the subject will not be randomized.

7.1.2 Subject Electronic Diary Data Collection

Subjects will be provided with an eDiary to be completed twice daily to record time of study medication administration, morning and evening symptoms, and the use of rescue albuterol (Ventolin HFA). The dose indicator reading will be recorded twice daily from Visit 4 to Visit 6 and once daily thereafter. Before issuing the eDiary to the subject, site personnel will be responsible for programming the eDiary and training the subject on the eDiary use.

Subjects will be issued and trained on an eDiary use at Visit 1 (Screening) and instructed to collect data during the Screening Period (between Visit 1 to Visit 4).

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 completion, 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.

  Subjects who are unable to meet the compliance requirement (>70% subject completion of diary assessments) in the last 7 days preceding the Randomization Visit (Visit 4) will be considered a screen failure.

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

During the Screening Period and for the duration of the Treatment Period, each subject will record his/her symptoms in the study-provided eDiary, twice daily (morning and evening).

The subject will record his/her use of rescue Ventolin HFA twice daily, morning and evening. In addition, the subject will record study medication usage.

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 eDiary. 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 eDiary 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, FF MDI and Placebo MDI are fitted with a dose indicator to track use of the MDI.

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

Prior to dosing at each Treatment Period Visit (Visit 4 to Visit 11a) or at a Premature Discontinuation Visit, 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 the 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 (ie, >20 puff difference), the site staff will review the major discrepancy with the subject and document reason for the major discrepancy in the appropriate study source and eCRF. 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: COPD Assessment Test (CAT), Modified Medical Research Council Dyspnea Scale (MMRC), SGRQ, and BDI and TDI. Whenever possible, it is recommended that the BDI/TDI and SGRQ are obtained at the same visit; the BDI/TDI will be collected first followed immediately by the SGRQ.

7.1.6.1 COPD Assessment Test

The COPD Assessment Test (CAT) (http://www.catestonline.org/) is a self-administered questionnaire designed to assess the condition of subjects and overall impact of COPD. It has been proven that the CAT has good repeatability and discriminative properties which suggest that it is sensitive to treatment effects at a group level. Since the CAT is designed to assess the impact of COPD on the subject by measuring overall impairment, it has moderate correlations with other instruments, such as the MMRC Dyspnea Scale, SGRQ, and the 6-minute walk test.

Subjects will complete the CAT (refer to Appendix 7) at Visit 2.

The CAT score will describe the burden and symptomatic impact of COPD in subjects enrolled in the trial and will not be used to determine subject eligibility to participate in the study.

7.1.6.2 Modified Medical Research Council Dyspnea Scale

The Modified Medical Research Council (MMRC) Dyspnea Scale uses a simple grading system to assess a subject's level of dyspnea, shortness of breath (Table 7).

Table 7. MMRC Dyspnea Scale

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing.

The MMRC scale is a five-point scale published in 1959 that considers certain activities, such as walking or climbing stairs, which provoke breathlessness (Fletcher 1959).
In one minute, the subject selects a grade on the MMRC scale that most closely matches his/her severity of dyspnea. The MMRC scale is considered a discriminative instrument that can categorize subjects with COPD in terms of their disability. The MMRC scale is not

satisfactory as an evaluative instrument to measure changes in dyspnea, and its broad grades are generally unresponsive to interventions such as pharmacotherapy.

Subjects will complete the MMRC scale at Visit 2, as a description of the symptomatic burden in study subjects. The MMRC scale will not be used to determine subject eligibility to participate in the study.

7.1.6.3 Baseline and Transition Dyspnea Indices

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 BDI and 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). 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 9 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 domain and are summed to determine the BDI focal score (0 to 12) (ie, 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 (- to +9) (ie, 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.

The BDI will be completed by the subject at Visit 4 (Day 1, prior to study drug administration). The TDI will be completed by the subject at Visit 6 (Week 4), Visit 7 (Week 8), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20) and Visit 11a (Week 24) or Premature Discontinuation Visit.

Whenever possible, it is recommended that the BDI/TDI and SGRQ be obtained at the same visit; BDI/TDI first, followed by the SGRQ. It is preferable to have subjects complete the BDI/TDI prior to study drug administration and before administration of SGRQ Questionnaire.

7.1.6.4 St. George Respiratory Questionnaire

The SGRQ will be used to provide the health status/health-related Quality of Life (HRQoL) measurements in this study (refer to Appendix 8). For the purposes of this study when BDI/TDI and SGRQ are obtained at the same visit, the BDI/TDI questionnaire will be collected first followed by the SGRQ. The appropriate language version 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 domain 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 (refer to Appendix 8) will be completed by the subject at Visit 4 (Day 1, prior to study drug administration), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), and Visit 11a (Week 24) 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 eCRF 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, including specific cardiovascular history details, will be collected at Visit 1 (Screening) and updated during the Screening Period (Visit 1 to Visit 4). The number of COPD exacerbations requiring oral steroids and/or oral antibiotics, or hospitalization within 12 months of Visit 1 (Screening) will be collected. A complete physical examination will be performed at Visit 1 (Screening) and at Visit 11a (Final Visit) or Premature Discontinuation Visit. A complete physical examination will include evaluation of 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 1 (Screening) and Visit 11a (Final Visit) only. Height will be recorded at Visit 1 (Screening) only.

7.2.2 Vital Sign Measurements

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

A single set of vital signs will be obtained at Visit 1 (Screening) and the Premature Discontinuation Visit.

Vital signs will be obtained at Visit 2 and Visit 3 within 60 minutes pre-bronchodilator and at 30 minutes post-bronchodilator.

At Visit 4 (Randomization Visit) only, pre-dose vital signs will be obtained twice at least 5 minutes apart within 1 hour prior to dosing. **Note:** Only one pre-dose temperature measurement is required unless a repeat measurement is clinically indicated. Post-dose vital signs will be obtained 30 minutes and 2 hours post study drug dosing.

At all visits post randomization (after Visit 4):

- Pre-dose vital signs will be obtained once within 1 hour prior to 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 all visits except at Visit 6 (Week 4) and Visit 9 (Week 16).

For subjects participating in the 12-hour spirometry at Visit 4 (Day 1) and Visit 8 (Week 12) additional post-dose vital signs will be obtained at 12 hours post study drug dosing.

Temperature will be obtained at Visit 1 (Screening) and at pre-dose at all visits and will not be repeated post-dose at subsequent time points unless clinically indicated.

7.2.3 12-Lead Electrocardiogram

An ECG will be obtained at the Visit 1 (Screening) and Premature Discontinuation Visit.

ECGs will be obtained at Visit 2 and Visit 3 within 60 minutes pre-bronchodilator and at 30 minutes post-bronchodilator.

At Visit 4 only, pre-dose ECGs will be obtained twice at least five minutes apart within 1 hour prior to dosing.

Pre-dose ECG will be obtained once within one hour prior to dosing at Visit 5 (Week 2), Visit 6 (Week 4), Visit 8 (Week 12), and Visit 11a (Week 24).

A post-dose ECG will be obtained at 30 minutes and two hours post study drug dosing at Visit 4 (Day 1), Visit 5 (Week 2), Visit 8 (Week 12), and Visit 11a (Week 24).

For subjects participating in the 12-hour spirometry sub-studies only, a post-dose ECG will be obtained at 12 hours after study drug dosing at Visit 4 (Day 1) and Visit 8 (Week 12).

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. All clinical laboratory tests will be obtained at Visit 1 (Screening) and prior to dosing at Visit 4 (Day 1), Visit 6 (Week 4), Visit 8 (Week 12) and Visit 11a (Week 24) 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 at Visit 1 (Screening) and prior to dosing at Visit 4 (Day 1), Visit 6 (Week 4), Visit 8 (Week 12) and Visit 11a (Week 24) 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 at Visit 1 (Screening) and prior to dosing at Visit 4 (Day 1), Visit 6 (Week 4), Visit 8 (Week 12) and Visit 11a (Week 24) or Premature Discontinuation Visit.

The Central Laboratory will supply procedures for the preparation and collection of these samples (Table 8).

Table 8. 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 1 (Screening) and Final Visit (Visit 11a) only and Urine HCG at Visit 8 (Week12)

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 Visit 1 (Screening) and prior to dosing at Visit 4 (Day 1), Visit 6 (Week 4), Visit 8 (Week 12) and Visit 11a (Week 24) 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 Visit 1 (Screening) and Visit 11a (Week 24 or Premature Discontinuation Visit. A urine pregnancy test will be performed on-site at Visit 8 (Week 12). 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 Holter Monitoring: 24-Hour Continuous Electrocardiography

The following information applies only to subjects participating in the 24-Hour Holter Monitoring Sub-study.

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

Continuous 12-lead ECGs (Holter assessment) will be obtained at Visit 3 (baseline) and Visit 6 (Week 4). The Visit 3 and Visit 6 Holter monitor recordings are to be initiated in the morning at approximately the same time (+/- 2 hours).

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

The Visit 3 (Screening) Holter monitoring will be initiated subsequent to the post-dose spirometry assessments. The Holter recording obtained at Visit 3 will be used to determine the subject's eligibility for participation in the 24-Hour Holter Monitor sub-study and will serve as the baseline for all comparisons. If the initial Holter monitor assessment at Visit 3 is unacceptable, the Holter monitor will be reconnected for another 24 hours using a new Holter monitor hook-up kit. The subject will be instructed to continue his/her medications as per study protocol. The subject will return the following day for removal of the Holter monitor. If the Holter monitoring quality remains unacceptable on the second attempt, no further attempts will be made and the subject will be permitted to enroll in the study but will be excluded from the Holter monitor sub-study. If clinically significant findings are noted on any of the Holter monitor recordings as defined in Section 5.2.1, the subject will be considered a screen failure and will not be eligible to enroll in the study.

At Visit 6 (Week 4) Holter monitoring will be initiated following the pre-dose spirometry assessments but 15-30 minutes prior to the administration of the morning dose of study medication. Subjects will take their morning dose of study medication at the clinic. Subjects will undergo all protocol-defined post-dose assessments. Subjects will be instructed to return to the clinic the following day for removal of the Holter monitor.

When the subject returns to the clinic the following day, the quality of the Holter monitor recordings will be assessed at the site. If the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours) on the first attempt, a second attempt will be made for another 24 hours using a new Holter monitor hook-up kit. The subject will be instructed to continue his/her medications as per study protocol. The subject will return the following day for removal of the second Holter Monitor. No further attempts are allowed if the second attempt is unacceptable.

Subjects can proceed to Visit 7 (Week 8) provided no clinically significant findings (as defined in Section 5.7.1) are reported by [redacted] following review of the Holter monitor recordings.

Data for analysis will include:

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

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

7.2.6 Adverse Events

7.2.6.1 Performing Adverse Events Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's case report form and on the AE Reporting Form. If the AE is "alarming," the Investigator must report the AE immediately to Pearl Therapeutics. In addition, certain AEs (as described in Section 7.2.6.8) are classified as "serious" and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as a serious AE (SAE) to Pearl Therapeutics or its designee.

In the case of SAEs, after discussing the details of the AE, the Investigator and the Medical Monitor may discontinue the subject prematurely.

7.2.6.2 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 AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (eg, 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 results in the procedure is considered an AE (eg, bleeding esophageal varices, dental caries).
- Overdose of either study drug or concurrent medication without any clinical signs or symptoms.
- Non-clinically significant abnormal laboratory values. (If accompanied by signs/symptoms, the signs or symptoms are considered an AE).

7.2.6.3 Pre-Randomization Adverse Events

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

7.2.6.4 Severity

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

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

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

Severe: Associated with inability of 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.

7.2.6.5 Relationship

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

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

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

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

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

7.2.6.6 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.

7.2.6.7 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 (eg, elevated BUN and creatinine in the setting of an AE of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). In such cases, the laboratory abnormality itself (eg, 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 (eg, an abnormality that results in study drug dose reduction, suspension, or discontinuation)
- A laboratory abnormality that results in any therapeutic intervention (ie, concomitant medication or therapy)
- Other laboratory abnormality judged by the Investigator to be of any particular clinical concern (eg, significant fall in hemoglobin not requiring transfusion)

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

7.2.6.8 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 AE
- In patient 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 jeopardize the subject 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 subject 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 AE is considered “life-threatening’ if, in the view of the Investigator or Sponsor, its occurrence places the subject 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.

An unexpected AE means any AE for which the specificity or severity 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' 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 SAE. 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 (eg, SAE Report Form). After the initial report, as necessary, the Investigator must provide any additional information on a SAE to the Medical Monitor within two working days after he/she receives that information. This follow-up information will be a detailed written report that may include copies of hospital records, case reports, and autopsy reports, and other pertinent documents.

Post-study SAEs following the last dose of study drug must be reported to Pearl Therapeutics as described in Section 7.2.6.11.

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

7.2.6.9 Supplemental Investigations of SAEs

The Investigator and supporting personnel responsible for subject 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 subject dies during participation in the study and a post-mortem examination is performed, a copy of the autopsy report must be submitted to Pearl Therapeutics.

7.2.6.10 Post-Study Follow-Up of Adverse Events

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

Adverse events ongoing at the Follow-up/Final Visit will be followed for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes or resolves. If resolved, a resolution date should be documented on the case report form or reported to Pearl Therapeutics if the case report forms have been locked. 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. Activities at Follow-up may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals as is practical.

7.2.6.11 Notification of Post-Study Serious Adverse Events

Investigators are not obligated to actively follow subjects after the completion of the study. However, if the Investigation 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 an SAE.

7.2.6.12 IRB/IEC Notification of Serious Adverse Events

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

7.2.6.13 Health Authority Safety Reports

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

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

7.2.7 Overdose

An overdose is defined as a dose greater than the high dose level evaluated in this study as described in Section 6.2 (Product Descriptions) that 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, AEs, 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 Investigator's brochure for GP MDI.

7.2.8 Pregnancy

To ensure subject safety, each pregnancy in a female subject from Visit 1 (Screening) until study completion 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 Safety Department. 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.

7.2.9 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.

7.2.10 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 (SAEs) (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 Visit 5 (Week 2), Visit 6 (Week 4), Visit 7 (Week 8), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), and Visit 11a (Week 24).

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 for the study is presented in Table 9. Table 10 presents details about activities conducted pre and post dose at Visits 4 through 11a. Table 11 displays pre- and post dose activity details at Visits 4 and 8 (12-hour PFT sub-study), and Table 12 presents details specific to 24-hour Holter monitor procedures at Visits 3 and 6.

Table 9. Schedule of Events

Procedures	Screening Period			Treatment Period									Follow-Up
	Visit 1	Visit 2	Visit 3	Visit 4 Day 1	Visit 5 Week 2	Visit 6 Week 4	Visit 7 Week 8	Visit 8 Week 12	Visit 9 Week 16	Visit 10 Week 20	Visit 11a Week 24	Discon[§] Visit	14 days Post-Dose
Study Day/Week[a]	Day -28 to -9	Day -21 to -2	Day -19 to -1	Day 1	Wk 2 ±2Days[a]	Wk 4 ±2Days[a]	Wk 8 ±2Days[a]	Wk 12 ±2Days[a]	Wk 16 ±2Days[a]	Wk 20 ±2Days[a]	Wk 24 ±2Days[a]		
Obtain Informed Consent	X												
Review Incl/Excl Criteria	X	X	X	X									
Verify Continued Eligibility					X	X	X	X	X	X	X		
Reversibility[b]		X	X										
Demographics & Medical/Surgical History	X	X	X	X									
Smoking Status	X	X	X	X	X	X	X	X	X	X	X		
COPD Assessment Test (CAT)[c]		X											
MMRC[c]		X											
Prior/Concomitant Medications[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry[e]	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination[f]	X										X	X	
Vital Signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[h]	X	X	X	X	X	X		X			X	X	
Pregnancy Test[i]	X							X			X	X	
Clinical Laboratory Testing[i]	X			X		X		X			X	X	
Chest X-ray[j]	X												
Adjust COPD Medications[k]	X										X	X	
COPD Exacerbations and Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Inhalation Device Training[l]	X												
Study Drug Dispensing/Collection	X[m]			X		X	X	X	X	X	X	X	
Study Drug Administration[n]				X	X	X	X	X	X	X	X		
BDI/TDI[o]				X		X	X	X	X	X	X	X	

Procedures	Screening Period			Treatment Period									Follow-Up
	Visit 1	Visit 2	Visit 3	Visit 4 Day 1	Visit 5 Week 2	Visit 6 Week 4	Visit 7 Week 8	Visit 8 Week 12	Visit 9 Week 16	Visit 10 Week 20	Visit 11a Week 24	Discon[§] Visit	14 days Post-Dose
SGRQ[o]				X				X	X	X	X	X	
Electronic Diary Training[p]	X												
Review of Electronic Diary[q]		X	X	X	X	X	X	X	X	X	X	X	
24- Hour Holter Monitoring[r]			X			X							
Review/Record Dose Indicator Reading[s]				X	X	X	X	X	X	X	X	X	
HCRU[t]					X	X	X	X	X	X	X	X	
Telephone Contact[u]		X	X	X	X	X	X	X	X	X	X		X

a. Scheduling Visits: The maximum Screening Period is 28 days; the earliest a subject can be randomized from Visit 1 Date is 9 Days (7 days for LABA washout plus 1 day between Visit 2 and 3 plus 1 day between Visit 3 and Visit 4) or 16 days if subject is washing off of tiotropium; Site should make every effort to maintain subjects within the scheduled visit window. Subjects who fall outside the visit window will be placed in the appropriate visit window at the next scheduled visit.

b. Subjects will be tested for reversibility to albuterol (Ventolin HFA) at Visit 2 and reversibility to Atrovent HFA at Visit 3; Refer to Section 7.1.1.1 for additional details

c. CAT and MMRC will be used to characterize the subject population only and not to be used to determine eligibility to participate in the study

d. At all visits beyond Visit 1 (Screening), note time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, visit should be rescheduled).

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

f. Includes evaluation weight at Visit 1 (Screening) and Visit 11a (Final Visit) and height at Visit 1 (Screening) only.

g. 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 1 (screening) and Visit 11a (Final Visit) only.

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

i. 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 1 (Screening) and Visit 11a (Week 24) and a urine pregnancy test will be done at Visit 8 (Week 12).

j. Obtain a new Chest X-ray if Chest X-ray or CT performed within the 6 months prior to Visit 1 (Screening) is not available.

k. At Visit 1 (Screening), stop prohibited COPD medications and change COPD medications as specified in Section 5.4 (ie, Sponsor-provided Atrovent HFA with or without ICS). At the end of Visit 11a, return subject to pre-study or other appropriate inhaled maintenance COPD medications if the subject will not be participating in the safety extension study (Study PT003008).

l. Sites may use sponsor-provided Atrovent HFA or Ventolin HFA to train subjects on the use of MDIs

m. Sponsor-provided Atrovent HFA or Ventolin HFA is dispensed only after a subject is determined to be eligible to proceed to Visit 2 (ie, only if a subject meets COPD definition following spirometry assessments at screening).

n. 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.

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

p. Issue and train subjects on eDiary use only after a subject is determined to qualify to proceed to Visit 2

q. Refer to Section 7.1.2 for details of electronic diary review.
r. Refer to Section 7.2.5 for details of 24-Hour Holter monitor assessments. Applies to 24-Hour Holter monitoring sub-study subjects only.
s. Refer to Section 7.1.5 for details and instructions on recording dose indicator readings.
t. Refer to Section 7.3 for details on HCRU collection.
u. 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 (eg, 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 8.7).

Note: When data collection time-points are concurrent, it is recommended that variables be collected in the following order: BDI/TDI, SGRQ, vital signs, ECG, clinical laboratory assessments, and spirometry.

Table 10. Timed Assessments during Treatment Period (Visits 4-11)

	Pre-dosing		Post-dosing				
Clinical Variable[a]	**-1 hour**	**-30 minutes**	**5 minutes**	**15 minutes**	**30 minutes**	**1 hour**	**2 hours**
BDI/TDI[b]	X[†]						
SGRQ[b]	X[†]						
Review of Electronic Diary Data	X[†]						
Vital Signs[c]	X				X		X
12- Lead ECG[d]	X[d]				X		X
Clinical Laboratory Testing[e]	X[†]						
Spirometry (FEV_1, FVC, PEFR) [f]	X[g]	X[g]	X[h]	X	X	X	X
Study Drug Collection[i]	X[†]						
Record Dose Indicator Reading[j]		X[†]					
Study Drug Dispensing[k]							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 (ie, FEV_1, FVC, and PEFR assessments need to be conducted within ± 15 minutes of specified time prior to study drug administration; ± 5 minutes of specified time for the first 60 minutes post study drug administration; ± 15 minutes of specified time point for assessments obtained thereafter)

b. When BDI/TDI and SGRQ are obtained at the same visit BDI/TDI will be collected first followed immediately by SGRQ. These questionnaires must be completed by the subject prior to any other visit procedures. BDI/TDI will be obtained at all visits except Visit 5 (Week 2). SGRQ will be obtained at Visit 4 (Day 1), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 11a (Week 24) or Premature Discontinuation Visit

c. At Visit 4 only, pre-dose vital signs will be collected twice at least five minutes apart. Vital signs will be obtained within one hour pre-dosing and at 30 minutes post study drug administration at all treatment visits. At all visits post randomization except Visit 6 (Week 4) and Visit 9 (Week 16) only, vital signs will be obtained at 2 hours post study drug dosing. Temperature will be obtained pre-dose; no further temperature assessments are required unless clinically indicated.

d. At Visit 4 only, pre-dose ECG will be collected twice at least five minutes apart. An ECG will be obtained pre-dose and at 30 minutes and 2 hours post-dose at Visit 4 (Day 1), Visit 5 (Week 2) , Visit 8 (Week 12), and Visit 11a (Week 24). At Visit 6 (Week 4), only a pre-dose ECG will be obtained.

e. Clinical laboratory tests (hematology, chemistry and urinalysis) will be obtained prior to dosing at Visit 4 (Day 1), Visit 6 (Week 4), Visit 8 (Week 12) and Visit 11a (Week 24) only. Serum pregnancy test will be performed at Visit 11a (Week 24) and a urine pregnancy test will be done at Visit 8 (Week 12).

f. Post-dose spirometry assessment will be obtained at all visits except Visit 6 (Week 4) and Visit 9 (Week 16).

g. To be randomized, all subjects must meet reproducibility criteria. Refer to Section 7.1.1.2 for additional details.

h. The 5-minute post-dose spirometry assessment will be obtained at Visit 4 (Treatment Day 1) only.

i. 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.

j. 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

k. Dispense study drug for at 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: When data collection time-points are concurrent, it is recommended that variables be collected in the following order: BDI/TDI, SGRQ, vital signs, ECG, clinical laboratory assessments, and spirometry.

Table 11. Timed Assessments at Visit 4 (Day 1) and Visit 8 (Week 12) for 12-Hour PFT Sub-study

	Pre-dosing		Post-dosing												
Clinical Variable[a]	**-1 hr**	**-30 min**	**2 min**	**5 min**	**15 min**	**20 min**	**30 min**	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**11.5 hr**	**12 hr**
BDI/TDI[b]	X†														
SGRQ[b]	X†														
Review of Electronic Diary Data	X†														
Vital Signs[c]	X						X		X						X
12- Lead ECG[d]	X						X		X						X
Clinical Laboratory Testing[e]	X†														
Spirometry (FEV_1, FVC, PEFR)[f]	X[g]	X[g]		X[h]	X		X	X	X	X	X	X	X	X	X
Study Drug Collection[i]	X†														
Record Dose Indicator Reading[j]		X													
Study Drug Dispensing[k]															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 (ie, FEV_1, FVC, and PEFR assessments need to be conducted within ± 15 minutes of specified time prior to study drug administration; ± 5 minutes of specified time for the first 60 minutes post study drug administration; ± 15 minutes of specified time point for assessments obtained thereafter)

b. When BDI/TDI and SGRQ are obtained at the same visit BDI/TDI will be collected first followed immediately by SGRQ. These questionnaires must be completed by the subject prior to any other visit procedures. BDI/TDI will be obtained at all visits except Visit 5 (Week 2). SGRQ will be obtained at Visit 4 (Day 1), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20) , and Visit 11a (Week 24) or Premature Discontinuation Visit

c. At Visit 4 only, pre-dose vital signs will be collected twice at least five minutes apart. Temperature will be obtained pre-dose; no further temperature assessments required unless clinically indicated.

d. At Visit 4 only, pre-dose ECG will be collected twice at least five minutes apart.

e. Clinical laboratory tests (hematology, chemistry and urinalysis) will be obtained prior to dosing at Visit 4 (Day 1) and Visit 8 (Week 12). A urine pregnancy test will be done at Visit 8 (Week 12).

f. Post-dose spirometry assessment will be obtained at all visits except Visit 6 (Week 4) and Visit 9 (Week 16).

g. To be randomized, all subjects must meet reproducibility criteria. Refer to Section 7.1.1.2 for additional details.

h. The 5-minute post-dose spirometry assessment will be obtained at Visit 4 (Treatment Day 1) only.

i. 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.

j. 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

k. Dispense study drug 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: When data collection time-points are concurrent, it is recommended that variables be collected in the following order: BDI/TDI, SGRQ, vital signs, ECG, clinical laboratory assessments, and spirometry.

Table 12. Schedule of Events at Visit 3 (Screening Period) and Visit 6 (Week 4) for 24-Hour Holter Monitoring Sub-study

Procedures	Screening Period			Treatment Period		
	Visit 3	Visit 3b	Visit 3c	Visit 6	Visit 6b	Visit 6c
24-Hour Holter Monitoring (1st Attempt)	X[a]			X[b]		
Removal of 24-Hour Holter Monitor (1st Attempt)[c]		X			X	
24-Hour Holter Monitoring (2nd Attempt)[d]		X[d]			X[d]	
Removal of 24-Hour Holter Monitor (2nd Attempt)[e]			X[e]			X[e]

a. Attach Holter monitoring device and initiate 24-hour Holter Monitor recording following the post-dose spirometry assessments.

b. Attach Holter monitoring device and initiate 24-hour Holter Monitor recording following the pre-dose spirometry assessments but 15-30 minutes prior to the administration of the morning dose of study medication.

c. Site personnel will determine the acceptability of Holter monitor recording.

d. If the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours) on the first attempt, a second attempt will be made for another 24 hours using a new Holter monitor hook-up kit.

e. No further attempts will be allowed if the second attempt is unacceptable.

Note: Subjects can proceed to Visit 4 (Randomization) or Visit 7 (Week 8) provided no clinically significant findings (as defined in Section 5.2.1 and Section 5.7.1) are reported by [redacted] following review of the Holter monitor recordings.

8.1 Visit 1

- Obtain informed consent.
- Register subject in IWRS to obtain subject screening number.
- Obtain demographic data, including age, race, smoking history, medical/surgical history (including cardiovascular risk factors and history), and age of onset of COPD.
- Review inclusion/exclusion criteria.
- Obtain medication history, including COPD medications.
- Conduct a serum pregnancy test for all female subjects unless it is documented in the medical history that the subject has been irreversibly surgically sterilized (hysterectomy, oophorectomy, or bilateral tubal ligation) or they are at least 2 years post-menopausal.
- Conduct a complete physical examination (general appearance, skin, head, eyes, ears, nose, throat, neck [including thyroid], lymph nodes, chest, heart, abdomen, extremities, and nervous system).
- Obtain height, weight, and vital signs (heart rate and blood pressure after being supine or seated for 5 minutes, and oral or tympanic temperature).
- Obtain a 12-lead ECG.
- Conduct spirometry assessments.
- Confirm subject's ability to use MDI correctly (provide coaching as needed).
- If subject qualifies to continue to Visit 2 perform the following:
  - Obtain laboratory samples (hematology, chemistry and urinalysis).
  - If Chest X-ray or CT within 6 months of Visit 1 (Screening) is not available, obtain a new Chest X-ray.
  - Stop prohibited COPD medications and change concurrent COPD medications as specified in protocol (refer to Section 5.4.1). Sponsor will provide Atrovent HFA QID for COPD maintenance and Ventolin HFA PRN for symptomatic relief.
  - Obtain subject assignment information of Atrovent HFA and Ventolin HFA from IWRS.
  - Dispense and train subject on eDiary use.
  - Schedule Visit 2.
    - In order to allow for an adequate washout of previous maintenance medications, subjects will undergo a washout period of at least 1 week (at least 2 weeks if taking Spiriva or other LAMA), but not greater than 26 days in duration prior to returning to the clinic for Visit 2.

- Subjects will be instructed to bring their eDiary, sponsor-provided Ventolin HFA and Atrovent HFA to the next scheduled clinic visit.
- Adverse events must be recorded during the Screening Period, that is, from the time of consent to the start of study treatment.

Note: Adverse events that occur between the time the subject signs the informed consent form for the study and the time when that subject is dosed with study drug will be summarized as medical history and not as a study AE, unless the event meets the definition of an SAE.

8.2 Visit 2

- Review subject diary entries and retrain subject if subject has not met diary compliance requirement of >70% subject completion of diary assessments.
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, Visit 2 must be rescheduled).
- Review inclusion/exclusion criteria and confirm subject eligibility to continue.
- If not previously reviewed, review of clinical laboratory results from Visit 1. Please note whether the results are clinically significant and include comments where applicable.
- Record COPD exacerbations and AEs (if any).

Note: Adverse events that occur during the Screening Period (Visit 1 to Visit 4, pre study drug dosing) will be summarized as medical history and not as a study AE unless the event meets the definition of an SAE.

- Obtain COPD Assessment Test (CAT) and MMRC.
- Review all prior medications and ensure adherence to COPD regimen.
- Obtain pre-bronchodilator vital signs and 12-lead ECG.
- Perform reversibility test to Ventolin HFA (refer to Section 7.1.1.1 for instructions) and confirm subject continues to meet entry criteria based on pre- and post-dose spirometry quality (refer to Exclusion Criterion 3h), and post-dose spirometry values.
- Obtain post-bronchodilator vital signs and 12-lead ECG.
- Schedule Visit 3.
  - **Note:** Visit 3 can be scheduled at minimum 1 day after Visit 2 and no later than 27 days after Visit 1 (Screening).
- Ensure subject has adequate supply of sponsor-provided Atrovent HFA and sponsor-provided rescue Ventolin HFA.
- Subjects will be instructed to bring their eDiary, sponsor-provided Atrovent HFA, and sponsor-provided Ventolin HFA to the next scheduled clinic visit.

8.3 Visit 3

- Review subject diary entries and retrain subject if subject has not met diary compliance requirement of >70% subject completion of diary assessments.
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, Visit 3 must be rescheduled).
- Review inclusion/exclusion criteria and confirm subject eligibility to continue.
- Record COPD exacerbations and AEs (if any).
  - **Note:** Adverse events that occur during the Screening Period (Visit 1 to Visit 4, pre-study drug dosing) will be summarized as medical history and not as a study AE unless the event meets the definition of an SAE.
- Review all prior medications and ensure adherence to COPD regimen.
- Obtain pre-bronchodilator vital signs and 12-lead ECG.
- Perform reversibility test to sponsor-provided Atrovent HFA (refer to Section 7.1.1.1 for instructions).
- Obtain post-bronchodilator vital signs and 12-lead ECG.

Subjects not participating in the 24-hour Holter monitoring sub-study:

- Schedule Visit 4 (Randomization Visit, Day 1).
  - **Note:** Visit 4 (Randomization Visit, Day 1) can be scheduled at minimum 1 day after Visit 3 and no later than 28 days after Visit 1 (Screening).
- Ensure subject has adequate supply of sponsor-provided Atrovent HFA and sponsor-provided rescue Ventolin HFA.
- Subjects will be instructed to bring their eDiary, Atrovent HFA, and sponsor-provided Ventolin HFA to the next scheduled clinic visit.

Subjects who choose to participate in 24-hour Holter monitoring sub-study (refer to Section 7.2.5 and Table 12):

- At Visit 3, attach Holter monitor and initiate 24-hour Holter monitor recording following the post-dose spirometry assessments.
- Subjects will be instructed to return the following day (Visit 3b) for the removal of the Holter monitor.
- At Visit 3b, site personnel will determine the acceptability of Holter monitor recording. If the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours) on the first attempt, a second attempt will be made for another 24 hours using a new Holter monitor hook-up kit.

- The subject will be instructed to continue his/her medications as per study protocol and to return the following day (Visit 3c) for the removal of the second Holter monitor.
- At Visit 3c, if the Holter monitoring quality remains unacceptable on the second attempt, no further attempts will be made and the subject will be permitted to enroll in the study but will be excluded from the Holter monitor sub-study. If clinically significant findings are noted on any of the Holter monitor recordings as defined in Section 5.2.1, the subject will be considered a screen failure and will not be eligible to enroll in the study.
  - **Note:** Subjects who have clinically significant findings (as defined in Section 5.2.1) will not be randomized.
- Schedule Visit 4 (Randomization Visit, Day 1) following completion of 24-hour Holter monitoring.
  - **Note:** Visit 4 (Randomization Visit, Day 1) can be scheduled only after reporting of the Holter monitor findings (if any) to the site by [redacted] (ie, Visit 4 cannot occur prior to sites receiving the 24-Hour Holter Monitor Report from [redacted]) and no later than 28 days after Visit 1 (Screening).
- Ensure subject has adequate supply of sponsor-provided Atrovent HFA and sponsor-provided rescue Ventolin HFA.
- Subjects will be instructed to bring their eDiary, Atrovent HFA, and sponsor-provided Ventolin HFA to the next scheduled clinic visit.

8.4 Visit 4 (Randomization)

- Review subject diary entries and screen fail subject if subject has not met diary compliance requirement of >70% subject completion of diary assessments in the last 7 days preceding Visit 4.
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, Visit 4 must be rescheduled).
- Have subject complete BDI questionnaire followed by SGRQ questionnaire before any other study procedures are performed.
- Record COPD exacerbations and AEs (if any).
- Review all concomitant medications and ensure adherence to COPD regimen.
- Collect sponsor-provided Atrovent HFA and sponsor-provided Ventolin HFA dispensed during the Screening Period.
- Complete all pre-dose assessments for subjects who are participating in the 12-hour PFT study (refer to Table 10 and Table 11).
  - Pre-dose vital signs will be obtained twice at least 5 minutes apart.
  - Pre-dose ECGs will be obtained twice at least 5 minutes apart.

- Review inclusion/exclusion criteria and confirm subject eligibility for randomization.
  - **Note:** To be randomized, all subjects must meet the reproducibility criteria. Refer to Section 7.1.1.2 for additional details. If the reproducibility entry criteria are not met at Visit 4 (Randomization) the subject will not be eligible to be randomized and will be screen failed.
- Obtain subject randomization number and treatment assignment information from IWRS (Visit 4).
- To allow for proper preparation of study drug, it is recommended that the seal around the study day treatment box is opened 15-30 minutes prior to dosing and the instructions for administration of study drug followed:
  - Refer to Section 6.7 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
  - 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 newly assigned study drug at the clinic.
- The subject is to be considered randomized after receiving a randomization number.
- Perform all post-dosing assessments (refer to Table 10).
- **Note:** If site is selected to participate in sub-study, remember to perform additional assessments in all subjects participating in the 12-hour PFT sub-study (refer to Table 11)
- Return eDiary to subjects and provide retraining if appropriate.
- Subjects will be instructed to bring their eDiary and all study medication (including used study drug, replacement MDI kit and 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 and rescue Ventolin HFA.

8.5 Visit 5 to Visit 10

- 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 the prior evening. If the time of dosing was not in accordance with the protocol, then the visit must be rescheduled.

- Confirm subject eligibility to continue.
- If applicable, have subject complete TDI questionnaire followed by SGRQ questionnaire before any other study procedures are performed,
- Collect HCRU information.
- Record COPD exacerbations and AEs (if any).
- Review all concomitant medications and ensure adherence to COPD regimen.
- Perform all pre-dose assessments (refer to Table 10).
- **Note:** At Visit 8, refer to for subjects participating in the 12-hour PFT sub-study.
- Return eDiary to subjects and provide retraining if appropriate.
- Prior to dosing (except at Visit 5), 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.
- Record/document the dose indicator readings of the used MDI and the replacement MDI.
- At Visit 5, the dose indicator count recorded by the site staff will be dose indicator count observed before and after subject dosing with the same MDI, and provided a photocopier is available, the dose indicator will be photocopied both before and after subject dosing.
- 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 dose from the new kit assigned at the visit.
- Perform all post-dose assessments (refer to Table 10).
- **Note:** At Visit 8, perform additional assessments in all subjects participating in the 12-hour PFT sub-study (refer to Table 11).
- Subjects will be instructed to track study drug dosing in their eDiary between study clinic visits.
- Subject 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 (refer to Appendix 10 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 their replacement kit, 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 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 and sponsor-provided rescue Ventolin HFA.

For subjects participating in the 24-Hour Holter monitoring study only (refer to Section 7.2.5 and Table 12):

- At Visit 6, attach Holter monitoring device and initiate 24-hour Holter Monitor recording following the pre-dose spirometry assessments but 15-30 minutes prior to the administration of the morning dose of study medication.
- Subjects will be instructed to return the following day (Visit 6b) for the removal of the Holter monitor.
- At Visit 6b, site personnel will determine the acceptability of Holter monitor recording. If the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours) on the first attempt, a second attempt will be made for another 24 hours using a new Holter monitor hook-up kit.
- The subject will be instructed to continue his/her medications as per study protocol and to return the following day (Visit 6c) for the removal of the second Holter monitor.
- At Visit 6c, no further attempts will be allowed if the second attempt is unacceptable.
- Subjects can proceed to Visit 7 (Week 8) provided no clinically significant findings (as defined in Section 5.7.1) are reported by [redacted] following review of the Holter monitor recordings.

Visit 5 to Visit 10 Reminders:

At Visit 5 (Week 2) subjects will use the study medication dispensed at Visit 4 (Randomization, Day 1) for Visit 5 (Week 2) in clinic dosing and to continue dosing at home until Visit 6.

- At Visit 8 (Week 12) perform 12-hour spirometry assessments in subjects participating in the 12-hour PFT sub-study.
- TDI will be obtained at all visits except Visit 5 (Week 2).
- SGRQ will be obtained at Visit 8 (Week 12), Visit 9 (Week 16), and Visit 10 (Week 20).
- Vital Signs:
  - Obtained within one hour pre-dosing and at 30 minutes post study drug dose administration at all treatment visits.

- Obtained at 2 hours post study drug dosing at all visits except Visit 6 (Week 4) and Visit 9 (Week 16).

- ECG:
  - An ECG will be obtained pre-dose within 1 hour prior to dosing and at 30 minutes and 2 hours post-dose at Visit 5 (Week 2) and Visit 8 (Week 12).
  - At Visit 6 (Week 4), only a pre-dose ECG will be obtained.
- Clinical laboratory tests will be obtained prior to dosing at Visit 6 (Week 4) and Visit 8 (Week 12).
- Post-dose spirometry assessments over two hours will be obtained at all visits except Visit 6 (Week 4) and Visit 9 (Week 16).

Note: At Visit 8, perform additional assessments in all subjects participating in the 12-Hour PFT sub-study (refer to Table 11).

8.6 Final Visit (Visit 11a)

- 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 the prior evening. 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 AEs (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 10) including clinical laboratory assessment, physical examination and serum pregnancy test for women of child-bearing potential.
- 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.
  - Record/document the dose indicator readings of the used MDI and the replacement MDI.

  - 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 10).
- Collect subject eDiary.
- Collect all study medication including sponsor-provided Ventolin HFA.

For those subjects not participating in the safety extension:

- At completion of all Visit 11a assessments, return subject to pre-study or appropriate 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 11a.

For those subjects who choose to participate in the safety extension study:

- Subjects who volunteer to participate in the safety extension study will complete Visit 11b procedures following informed consent (refer to Safety Extension Protocol PT003008 for more details).

8.7 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 the TDI questionnaire first, followed by SGRQ questionnaire as the second procedure, before any other study procedures are performed.
- Collect HCRU information.
- Record COPD exacerbations and AEs (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.

8.8 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 SAEs, and record SAEs (if any)
- Review concomitant medications

8.9 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
- AEs
- Administrative reasons (eg, 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 (refer to Section 5.7).

9 PLANNED STATISTICAL METHODS

9.1 Introduction

This study will be conducted as a double-blind, placebo-controlled, parallel group study evaluating the following treatments in approximately 1614 subjects:

- GFF MDI (14.4/9.6 μg BID)
- GP MDI (14.4 μg BID)
- FF MDI (9.6 μg BID)
- Placebo MDI BID

The primary objective of this study is to assess the maintenance bronchodilator effects of the fixed dose combination GFF MDI versus its components (GP MDI, FF MDI, and Placebo MDI). In addition, as primary objectives, the study will assess the maintenance bronchodilator effects of GP MDI and FF MDI versus Placebo MDI. This study will also assess the effects of GFF MDI, GP MDI, and FF MDI in terms of COPD symptoms, disease-related health status and the long-term safety and tolerability. This study will include a 24-week Treatment Period, preceded by a Screening Period and followed by enrollment into a 28-week extension study or a two-week follow-up telephone call.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

All efficacy assessments are relative to pre-dose baseline obtained at or prior to Visit 4. Lung function measurements and symptom-based endpoints will be evaluated. The primary endpoint differs by approach but is always based on morning pre-dose trough FEV_1. However, in some regions co-primary endpoints are required for registration purposes.

The three different registration approaches will be called US, EU, and Hybrid. The US approach is for countries or regions such as the United States where co-primary endpoints are not required, but evaluation of treatment efficacy at a landmark timepoint is required. The EU approach is for registration purposes in countries or regions such as Europe where co-primary endpoints are required. The Hybrid approach is for countries or regions where co-primary endpoints are only required for comparisons to Placebo MDI and not for the comparison of GFF to its components. The delineation of multiplicity controls for the primary and secondary measures are separated by approach and detailed in Section 9.3.4.

All inferential results will be based on analyses using the ITT Population (refer to Section 9.12).

9.2.1.1 Primary Efficacy Endpoints

Primary Endpoint (US):

- The primary endpoint will be the change from baseline in morning pre-dose trough FEV_1 at Week 24.

Co-Primary Endpoints (EU and Hybrid):

- The first co-primary endpoint will be the change from baseline in morning pre-dose trough FEV_1 over 24 weeks of treatment
- The second co-primary endpoint will be the TDI focal score over 24 weeks

9.2.1.2 Secondary Efficacy Endpoints

Secondary Endpoints (US):

- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks
- Peak change from baseline in FEV_1 within 2 hours post-dosing at Week 24
- Change from baseline in SGRQ total score at Week 24
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Time to onset of action on Day 1

Secondary Endpoints (EU and Hybrid):

- Peak change from baseline in FEV_1 within 2 hours post-dosing over 24 weeks
- Change from baseline in SGRQ total score over 24 weeks
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Time to onset of action on Day 1

9.2.1.3 Other Efficacy Endpoints

Day 1 Assessments (Within 2 Hours Post-dose):

- Change from baseline at each post-dose timepoint in FEV_1 as well as FEV_1 area under the curve from 0 to 2 hours (FEV_1 AUC_{0-2}) and peak change from baseline in FEV_1
- Proportion of subjects achieving an improvement from baseline in FEV_1 using different thresholds (eg, ≥10%, ≥12%, ≥200 mL, and ≥12% and ≥200 mL)

Assessments Over 24 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 24 weeks, over Week 12 to Week 24, and at each post-randomization visit (including Week 24):
  - Change from baseline in morning pre-dose trough for FEV_1, 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 three 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 morning total and individual symptom scores, and the mean evening total and individual symptom scores over 24 weeks, over Weeks 12-24, and over each 4-week interval of the 24 week treatment period
- Changes from baseline at each post-randomization visit for SGRQ total score
- TDI focal score at each post-randomization visit
- Individual components of the TDI: functional impairment, magnitude of task, and magnitude of effort over 24 weeks and at each post-randomization visit
- Percentage of subjects achieving a MCID threshold of ≥1 unit on average in TDI
- Change in individual domain scores of SGRQ: Symptoms, Activity, and Impacts over 24 weeks and at each post-randomization visit (including Week 24)
- Percentage of subjects achieving an MCID threshold of ≥4 units on average in SGRQ total score

9.2.2 12-Hour PFT Sub-study Endpoints

Primary Endpoint:

- FEV_1 AUC_{0-12} at Week 12

Additional assessments on Day 1 and Week 12:

- Serial spirometry parameters including FEV_1 area under the curve from 0 to 6 hours (FEV_1 AUC_{0-6}) and from 6 to 12 hours (FEV_1 AUC_{6-12}), and peak change in FEV_1
- FEV_1 AUC_{0-12} on Day 1
- FVC, PEFR, and FEF_{25-75} will be evaluated using AUC_{0-12}, AUC_{0-2}, and peak change from baseline
- Change from baseline in FEV_1, FVC, FEF_{25-75}, and PEFR at each post-dose time point through 12 hours post-dose including the change from baseline in 12-hour post-dose trough

9.2.3 Safety Endpoints

The safety endpoints for this study include:

- AEs
- 12-Lead ECG: Change from baseline heart rate, PR interval, QRS axis, QRS interval, QT interval and QTcF (Fridericia Corrected QT) interval
- Clinical laboratory testing
- Vital sign measurements

9.2.4 24-Hour Holter Monitoring Sub-Study Endpoints (Assessed at Week 4)

Primary Endpoint:

The primary Holter monitoring sub-study endpoint is:

- Change from baseline in mean heart rate averaged over 24 hours

Secondary Endpoints:

Secondary 24-hour Holter monitoring sub-study endpoints are:

- Change from baseline in mean nighttime (22:00 to 06:00) and daytime (06:00 to 22:00) heart rate
- Change from baseline in the maximum 24-hour heart rate
- Change from baseline in the minimum 24-hour heart rate
- Change from baseline in the frequency of ventricular ectopic events (including a single PVC)
- Change from baseline in the frequency of ventricular couplets (defined as two PVCs preceded or followed by regular beats)

- Change from baseline in the frequency of ventricular runs (defined as three or more PVCs preceded or followed by regular beats)
- Incidence of sustained VT (defined as PVCs lasting >30 seconds)
- Change from baseline in the frequency of supraventricular ectopic events
- Change from baseline in the frequency of supraventricular couplets
- Change from baseline in the frequency of supraventricular runs
- Incidence of atrial fibrillation with rapid ventricular response (>100 bpm)

Other Endpoints:

Other Holter endpoints will include the following:

- Proportion of subjects with maximum heart rate >180, >160-180, >140-160, >120-140, >100-120, and 100 bpm or less
- Proportion of subjects with minimum heart rate >60, >50-60, >40-50, and ≤40 bpm
- Proportion of subjects in each category of change from baseline in the number of PVCs per hour (no change, increase of >0-<60, 60-<120, and ≥120, and decrease of >0-<60, 60-<120, and ≥120)

9.2.5 Dose Indicator Endpoints

The primary endpoint will be the comparison of the number of doses used as displayed by the dose indicator with the number of doses used as determined by information from the eCRF and the subject diary for the first MDI used after randomization.

9.2.6 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, ER visits, and hospitalizations including days in hospital, days in ICU, days in CCU, and subject intubations will be captured and compared between treatment groups.

9.3 Efficacy Analyses

9.3.1 Primary Efficacy Analysis

For the primary comparisons, the null hypothesis for each pair-wise comparison will be that the mean test treatment effect is equal to that of Placebo MDI (or an individual component); the alternative hypothesis is then that the test treatment effect and that of Placebo MDI (or an individual component) are not equal. P-values will thus be reported as two-sided. The primary null ($H_{0)}$ and alternative (H_1) hypotheses with μ representing the mean are:

H_0: $\mu_{FF} = \mu_{placebo}$
H_1: $\mu_{FF} \neq \mu_{placebo}$

H_0: $\mu_{GP} = \mu_{placebo}$
H_1: $\mu_{GP} \neq \mu_{placebo}$

H_0: $\mu_{GFF} = \mu_{placebo}$
H_1: $\mu_{GFF} \neq \mu_{placebo}$

H_0: $\mu_{GFF} = \mu_{FF}$
H_1: $\mu_{GFF} \neq \mu_{FF}$

H_0: $\mu_{GFF} = \mu_{GP}$
H_1: $\mu_{GFF} \neq \mu_{GP}$

9.3.1.1 Change from Baseline in Morning Pre-dose Trough FEV_1

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, the treatment by visit interaction, smoking status at baseline, and ICS use at baseline as categorical covariates. Baseline is defined as the average of the non-missing -60 minute and -30 minute values obtained prior to dosing at Visit 4. 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 timepoints from the same subject; for this model, subject will be included as a random effect. Contrasts will be used to obtain estimates of the treatment differences at Week 24 and over 24 weeks. Two-sided p-values and point estimates with two-sided 95% confidence intervals (CIs) will be produced for each treatment difference. The primary analysis will be conducted using the ITT Population.

Additional supportive analyses of morning pre-dose trough FEV_1 will include the change from baseline at Week 24 and over the entire 24-week treatment period in the Per Protocol (PP) Population, treatment differences over Weeks 12-24 and at individual time points estimated by the RM model, and the analysis of weighted average (WAVE). WAVE will be calculated as the weighted average change from baseline over 24 weeks (and also over Weeks 12-24) 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 and ICS use at baseline as categorical covariates.

Sensitivity analyses to evaluate the robustness of the primary analyses to the nature of the missing data are discussed in Section 9.13.

9.3.1.2 TDI (EU/Hybrid Approaches)

Assessments of dyspnea will be obtained using the BDI/TDI. The BDI/TDI questionnaire can be found in Appendix 11. In addition, there is a practice question included in the SAC version of the BDI/TDI related to tiredness. This question is not included in the overall score, but will be summarized separately.

At Visit 4, the severity of dyspnea at baseline will be assessed using the BDI. At subsequent visits (as per schedule of events, Table 9) change from baseline will be assessed using the TDI. The difference between treatment groups in the TDI focal score over 24 weeks will be evaluated using a similar RM approach as for the change from baseline in morning pre-dose trough. 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% CIs will be produced for each treatment difference.

Primary analyses of the TDI will use 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. Refer to Section 9.12 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 post-baseline 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, and ICS use at baseline as categorical covariates. P-values and odds ratios with 95% CI will be produced for each treatment comparison.

9.3.2 Analysis of Secondary Endpoints

Secondary variables include morning pre-dose trough FEV_1 over 24 weeks (US) and onset of action on Day 1, peak FEV_1 (at Week 24 for US and over 24 weeks for EU and Hybrid approaches), rescue Ventolin HFA use over 24 weeks, and SGRQ (at Week 24 for US and over 24 weeks for EU and Hybrid approaches). Multiplicity will be controlled for the secondary variables as described in Section 9.3.4. All analyses will be performed for the ITT Population first and for the PP population as supportive. The SGRQ will also be analyzed using the Symptomatic Population as supportive.

9.3.2.1 Peak FEV_1

The peak change from baseline in FEV_1 within 2 hours post-dosing at Week 24 and over 24 weeks will be analyzed in a similar way to morning pre-dose trough FEV_1.

9.3.2.2 St. George Respiratory Questionnaire

The difference between treatment groups in the change from baseline in SGRQ at Week 24 (US) and over 24 weeks (EU and Hybrid) 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% CIs will be produced for each treatment difference.

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. Refer to Section 9.12 for further details.

As additional supportive analyses, the difference between treatments at each of the individual post-baseline 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 and reversibility to Ventolin HFA as continuous covariates and treatment, smoking status at baseline, and ICS use at baseline as categorical covariates. P-values and odds ratios with 95% CI will be produced for each treatment comparison.

9.3.2.3 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 will be used to calculate the baseline. The difference between treatment groups in the change from baseline in average daily rescue Ventolin HFA use over 24 weeks will be evaluated using a similar RM approach as for the primary endpoint. 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 and over Weeks 12-24 will be evaluated and summarized. Additionally as supportive analyses, daytime rescue Ventolin HFA use and night-time rescue Ventolin HFA use will be evaluated and summarized in a similar fashion. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference.

9.3.2.4 Time to Onset of Action

The onset of action will be determined for each treatment using the 5 minute and 15 minute post-dosing FEV_1 assessments from Day 1. The onset of action for each product (GP MDI, FF MDI, and GFF MDI) will be defined as the first timepoint where the difference from Placebo MDI is statistically significant (refer to Section 9.3.4 for procedure to control Type I error). Comparisons will be performed using ANCOVA models similar to pre-dose FEV_1 WAVE described in Section 9.3.1.

9.3.3 Analysis of Exploratory Endpoints

9.3.3.1 Other Spirometry Endpoints

The analysis of the other comparisons of changes in morning pre-dose trough FEV_1 over 24 weeks has already been described in Section 9.3.1. Treatment differences in the change from baseline in FEV_1 AUC_{0-2}, morning pre-dose trough FVC, PEFR, and FEF_{25-75} will be evaluated in a similar manner to the primary endpoint.

On Day 1 during the first two hours post-dosing, the proportion of subjects achieving an improvement from baseline in FEV_1 using different thresholds (eg, ≥10%, 12%, 200 mL, and 12% and 200 mL) will be estimated for each treatment. Logistic regression will be used to compare the treatment groups with baseline and reversibility to Ventolin HFA as continuous covariates and treatment, smoking status at baseline, and ICS use at baseline as categorical covariates. P-values and odds ratios with 95% CIs will be produced for each treatment comparison.

<u>12-Hour PFTs</u>

FEV_1 AUC_{0-12} will be measured in a subset of subjects at the randomization visit and the 12-week visit. AUC on Day 1 and Week 12 will be calculated using the trapezoidal rule and transformed into a weighted average by dividing by the time in hours from dosing of the last measurement included (typically 12 hours). For the ITT Population analysis, only 1 non-missing post-dose value is required for the calculation of AUC; for the PP Population AUC will be calculated provided that there are at least 2 non-missing values during the first 2 hours post-dose and at least 1 non-missing value at 4 hours post-dose or later. Actual time from dosing will be used if available; otherwise scheduled time will be used. The differences between treatment groups in FEV_1 AUC_{0-12} at Day 1 and Week 12 will be evaluated using an ANCOVA with baseline FEV_1 and reversibility to Ventolin HFA as continuous covariates and treatment, smoking status at baseline, and ICS use at baseline as categorical covariates. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference.

As additional supportive analyses, FEV_1 AUC_{0-2}, FEV_1 AUC_{0-6}, and FEV_1 AUC_{6-12} will be calculated and analyzed in a similar fashion as FEV_1 AUC_{0-12}.

In addition, the peak change from baseline in FEV_1 over 12 hours on Day 1 and Week 12 will be estimated and compared between treatment groups using an ANCOVA with the same model as described for pre-dose FEV_1 WAVE in Section 9.3.1.

Similar assessments of $AUC_{0\text{-}12,}$ $AUC_{0\text{-}2,}$ and peak change from baseline will be conducted for FVC, PEFR, and $FEF_{25\text{-}75}$.

Finally, treatments will be compared using change from baseline at each post-dose timepoint over 12 hours on Day 1 and Week 12 for the following variables: FEV_1, FVC, PEFR, and $FEF_{25\text{-}75}$.

9.3.3.2 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 24 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 9.3.1, but with baseline average daily rescue Ventolin HFA use instead of baseline FEV_1 as a covariate.

9.3.3.3 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 randomized medication exposure. Treatments will be compared adjusting for baseline percent predicted FEV_1, baseline CAT score, baseline COPD exacerbation history, smoking status at baseline, season at baseline (winter, spring, summer or fall) and ICS use at baseline.

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, season at baseline (winter, spring, summer, or fall), and ICS use at baseline. Estimated

adjusted hazard ratios relative to the comparator will be displayed along with the associated Wald two-sided 95% CIs and p-values. Time to first COPD exacerbation of any severity 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 24. Subjects who withdrew from the study without experiencing a COPD exacerbation will be censored at the date of withdrawal.

The rate of moderate or 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 trial, unless an exacerbation has already been recorded at that time.

9.3.3.4 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, season at baseline (winter, spring, summer or fall), and ICS use at baseline. Estimated adjusted hazard ratios will be displayed along with associated 95% CIs 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 24.

9.3.3.5 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 of cough, shortness of breath, sputum volume, and night-time awakenings and 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 24-week Treatment Period. The last seven days of the 10-14 day Screening Period will be used to calculate the baseline. The mean change from baseline in the total, daytime and nighttime symptom scores will be analyzed using a similar model as for morning pre-dose trough FEV_1 to estimate treatment effects over 24 weeks and over Weeks 12-24.
In addition, summaries of the total, daytime and nighttime symptom scores will be provided for each 4-week period. The above summaries will be repeated for individual symptom score.

Percentage of Nights with 'No Nighttime Awakenings' over 24 weeks

A night with 'no nighttime awakenings' is defined from diary data as any night where the subject did not report waking up. The percentage of nights with 'no nighttime 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 Nighttime Awakenings' Over 24 Weeks

A night with 'fewer than three nighttime 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 nighttime awakenings instead of baseline FEV_1 as a covariate.

Percentage of Days with 'No Daytime Symptoms' Over 24 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 daytime total symptom score instead of baseline FEV_1 as a covariate.

9.3.4 Control of Type I Error

There are three separate plans for control of Type I error. One is for registration purposes in countries or regions such as the United States where co-primary endpoints are not required. One is for registration purposes in countries or regions such as Europe where co-primary endpoints are required. The third is for countries or regions where co-primary endpoints are only required for comparisons to Placebo MDI and not for the comparison of GFF MDI to its components. For simplicity, these three approaches will be referred as US, EU, and Hybrid.

9.3.4.1 United States Endpoints

Strong control of the Type I error rate will be maintained at the two-sided 0.05 level for the primary endpoint across products using a sequential approach and then within each comparison for the secondary measures using a combination of sequential and simultaneous approaches as detailed below. Based on positive dependence of the test statistics (Sarkar 2008; Sarkar 1997), simultaneous control of Type I error for the relevant secondary measures will be achieved using the Hochberg procedure (Hochberg, 1988).

Control of Type I Error for GP MDI

For GP MDI, Type I error control will be achieved by comparing GP MDI to Placebo MDI using a two-sided alpha of 0.05 for the change from baseline in morning pre-dose trough FEV_1 at Week 24 first and continuing to assessment of secondary measures if this comparison is statistically significant. The first two secondary endpoints will be tested sequentially, and if both are significant, the remaining four endpoints will be tested simultaneously. The first secondary endpoint to be compared between GP MDI vs. Placebo MDI is morning pre-dose trough FEV_1 over 24 weeks. If this comparison is statistically significant (two-sided alpha = 0.05), the second secondary endpoint, peak FEV_1 at Week 24, will be compared between GP MDI vs. Placebo MDI using a two-sided alpha of

0.05. Finally, if the second secondary comparison is statistically significant, GP MDI will be compared to Placebo MDI for the remaining four secondary endpoints (SGRQ at Week 24, rescue Ventolin HFA use over 24 weeks, FEV_1 at 5 minutes post-dosing on Day 1, and FEV_1 at 15 minutes post-dosing on Day 1) using the Hochberg procedure with a two-sided alpha of 0.05.

Control of Type I Error for FF MDI

Provided that the comparison between GP MDI and Placebo MDI is significant for the primary endpoint, comparisons using FF MDI will be interpreted inferentially. Type I error control will be achieved by comparing FF MDI to Placebo MDI using a two-sided alpha of 0.05 for the change from baseline in morning pre-dose trough FEV_1 at Week 24 first and continuing to assessment of secondary measures if this comparison is statistically significant. The first two secondary endpoints will be tested sequentially, and if both are significant, the remaining four endpoints will be tested simultaneously. The first secondary endpoint to be compared between FF MDI vs. Placebo MDI is morning pre-dose trough FEV_1 over 24 weeks. If this comparison is statistically significant (two-sided, alpha=0.05), the second secondary endpoint, peak FEV_1 at Week 24, will be compared between FF MDI vs. Placebo MDI using a two-sided alpha of 0.05. Finally, if the second secondary comparison is statistically significant, FF MDI will be compared to Placebo MDI for the remaining four secondary endpoints (SGRQ at Week 24, rescue Ventolin HFA use over 24 weeks, FEV_1 at 5 minutes post-dosing on Day 1, and FEV_1 at 15 minutes post-dosing on Day 1) using the Hochberg procedure with a two-sided alpha of 0.05.

Control of Type I Error for GFF MDI

Provided that the comparison between FF MDI and Placebo MDI and between GP MDI and Placebo MDI are significant for the primary endpoint, comparisons using GFF MDI will be interpreted inferentially. Type I error will be strictly controlled for the primary endpoint and will be controlled within each treatment comparison for the secondary assessments. GFF MDI will be compared to Placebo MDI, then FF MDI, and finally GP MDI for morning pre-dose trough FEV_1 at Week 24 using a two-sided alpha level of 0.05 and continuing sequentially if each comparison is statistically significant. If GFF MDI is significantly superior to its components for the primary endpoint, the secondary measures of morning pre-dose trough FEV_1 over 24 weeks, peak FEV_1 at Week 24, SGRQ at Week 24, rescue Ventolin HFA use over 24 weeks, and for GFF MDI vs. Placebo MDI in order to evaluate onset of action, FEV_1 at 5 minutes post-dosing on Day 1 and FEV_1 at 15 minutes post-dosing on Day 1 will be evaluated for significance. Type I error will be controlled at 0.05 within each comparison (GFF MDI vs. Placebo MDI, GFF MDI vs. FF MDI, and GFF MDI vs. GP MDI) with a sequential approach for the first two secondary endpoints; trough FEV_1 over 24 weeks will be evaluated first, and if statistically significant, testing will proceed to inference for peak FEV_1. If comparisons are statistically significant for both endpoints, the remaining secondary endpoints will be tested simultaneously using the Hochberg procedure with a two-sided alpha of 0.05.

9.3.4.2 European Union Endpoints

Strong control of the Type I error rate will be maintained at the two-sided 0.05 level for the key comparisons for each product using the approaches detailed below and across products for the primary endpoints for GFF MDI.

Control of Type I Error for FF MDI

For FF MDI, Type I error control will be achieved by comparing FF MDI to Placebo MDI using a two-sided alpha of 0.05 for the change from baseline in morning pre-dose trough FEV_1 over 24 weeks first and continuing sequentially to TDI if this comparison is statistically significant. If the comparison of FF MDI to Placebo MDI is significant for TDI, this comparison will be interpreted inferentially for the first secondary measure, peak FEV_1 over 24 weeks using a two-sided alpha of 0.05. Finally, if the FF MDI vs. Placebo MDI comparison of the first secondary endpoint is statistically significant, the remaining four secondary measures (SGRQ over 24 weeks, rescue Ventolin HFA use over 24 weeks, FEV_1 at 5 minutes post-dosing on Day 1, and FEV_1 at 15 minutes post-dosing on Day 1) will be tested with a simultaneous control of Type I error achieved using the Hochberg procedure with a two-sided alpha of 0.05.

Control of Type I Error for GP MDI

For GP MDI, Type I error control will be achieved by comparing GP MDI to Placebo MDI using a two-sided alpha of 0.05 for the change from baseline in morning pre-dose trough FEV_1 first and continuing sequentially to TDI if this comparison is statistically significant. If the comparison of GP MDI to Placebo MDI is significant for TDI, this comparison will be interpreted inferentially for the first secondary measure, peak FEV_1 over 24 weeks using a two-sided alpha of 0.05. Finally, if the GP MDI vs. Placebo MDI comparison of the first secondary endpoint is statistically significant, the remaining four secondary measures (SGRQ over 24 weeks, rescue Ventolin HFA use over 24 weeks, FEV_1 at 5 minutes post-dosing on Day 1, and FEV_1 at 15 minutes post-dosing on Day 1) will be tested with a simultaneous control of Type I error achieved using the Hochberg procedure with a two-sided alpha of 0.05.

Control of Type I Error for GFF MDI

For GFF MDI, Type I error will be strictly controlled for all the comparisons to Placebo MDI and to components for trough FEV_1 and TDI. If the comparisons of FF MDI and GP MDI to Placebo MDI are significant for morning pre-dose trough FEV_1, then GFF MDI will be sequentially compared to: 1) Placebo MDI using morning pre-dose trough FEV_1; 2) FF MDI using morning pre-dose trough FEV_1; and 3) GP MDI using morning pre-dose trough FEV_1 using a two-sided alpha level 0.05. Provided the comparisons of GFF MDI to its components are significant for morning pre-dose trough FEV_1, GFF MDI will be compared to sequentially to Placebo MDI, FF MDI, and then GP MDI for TDI using a two-sided alpha of 0.05. Provided the comparisons of GFF MDI to its components are significant for TDI, GFF MDI will be compared sequentially to Placebo MDI, FF MDI, and then GP MDI for

the first secondary endpoint, peak FEV_1 over 24 weeks using a two-sided alpha of 0.05. If those comparisons are statistically significant, the remaining secondary endpoints (SGRQ over 24 weeks, rescue Ventolin HFA use over 24 weeks, and for GFF MDI vs. Placebo MDI in order to evaluate onset of action, FEV_1 at 5 minutes post-dosing on Day 1 and FEV_1 at 15 minutes post-dosing on Day 1) will be interpreted inferentially with a simultaneous control of Type I error within each comparison achieved using the Hochberg procedure with a two-sided alpha of 0.05.

9.3.4.3 Hybrid Endpoints

Strong control of the Type I error rate will be maintained at the two-sided 0.05 level for the primary endpoint for each product using the approaches detailed below, but not across products. The rationale for not controlling multiplicity across products is that each product is being considered separately for marketing authorization and all necessary comparisons are included within each trial for efficiency and ethical purposes, and to minimize subject exposure, especially to Placebo MDI. This is one of the two differences between the Hybrid approach and EU approach. The other difference is that for GFF MDI, only the Placebo MDI comparisons are included in the strict control of Type I error for TDI.

Control of Type I Error for FF MDI

For FF MDI, Type I error control will be achieved by comparing FF MDI to Placebo MDI using a two-sided alpha of 0.05 for the change from baseline in morning pre-dose trough FEV_1 first and continuing sequentially to TDI if this comparison is statistically significant. If the comparison of FF MDI to Placebo MDI is significant for TDI, this comparison will be interpreted inferentially for the first secondary measure, peak FEV_1 over 24 weeks using a two-sided alpha of 0.05. Finally, if the FF MDI vs. Placebo MDI comparison of the first secondary endpoint is statistically significant, the remaining four secondary measures (SGRQ over 24 weeks, rescue Ventolin HFA use over 24 weeks, FEV_1 at 5 minutes post-dosing on Day 1, and FEV_1 at 15 minutes post-dosing on Day 1) will be tested with a simultaneous control of Type I error achieved using the Hochberg procedure with a two-sided alpha of 0.05.

Control of Type I Error for GP MDI

For GP MDI, Type I error control will be achieved by comparing GP MDI to Placebo MDI using a two-sided alpha of 0.05 for the change from baseline in morning pre-dose trough FEV_1 first and continuing sequentially to TDI if this comparison is statistically significant. If the comparison of GP MDI to Placebo MDI is significant for TDI, this comparison will be interpreted inferentially for the first secondary measure, peak FEV_1 over 24 weeks using a two-sided alpha of 0.05. Finally, if the GP MDI vs. Placebo MDI comparison of the first secondary endpoint is statistically significant, the remaining four secondary measures (SGRQ over 24 weeks, rescue Ventolin HFA use over 24 weeks, FEV_1 at 5 minutes post-dosing on Day 1, and FEV_1 at 15 min post-dosing on Day 1) will be tested with a simultaneous control of Type I error achieved using the Hochberg procedure with a two-sided alpha of 0.05.

Control of Type I Error for GFF MDI

For GFF MDI, Type I error will be strictly controlled for all the comparisons to Placebo MDI and components for FEV_1 as well as the comparison to Placebo for TDI. GFF MDI will be sequentially compared to: 1) Placebo MDI using morning pre-dose trough FEV_1, 2) FF MDI using morning pre-dose trough FEV_1, and 3) GP MDI using morning pre-dose trough FEV_1 using a two-sided alpha of 0.05. Provided the comparisons of GFF MDI to its components are significant for FEV_1, GFF MDI will be compared to Placebo MDI for TDI. Provided the comparison of GFF MDI to Placebo MDI is significant for TDI, the comparisons of GFF MDI to its components and to Placebo MDI for peak FEV_1 will be interpreted inferentially using a two-sided alpha of 0.05. For each comparison where the peak FEV_1 is significant, then the remaining secondary endpoints including SGRQ, rescue Ventolin HFA use, FEV_1 at 5 minutes post-dosing on Day 1 and 15 minutes post-dosing on Day 1 for GFF MDI vs Placebo MDI (in order to assess onset of action), and TDI for GFF MDI vs its components will be interpreted inferentially with a simultaneous control of Type I error within each comparison achieved using the Hochberg procedure with a two-sided alpha of 0.05.

9.4 Safety Analyses

9.4.1 Adverse Events

Adverse events within each treatment arm will be summarized by the number and percent of subjects experiencing an event. They will be tabulated at the level of the Medical Dictionary for Regulatory Activities (MedDRA) preferred term, and the MedDRA System Organ Class. The version of MedDRA current at the time of database lock for the 28-week extension study will be used for final analysis of the data. Tabulations will be broken down by severity, by relationship to study drug, and AEs leading to withdrawal. No hypothesis tests will be performed. Tables will show the overall incidence of AEs, and the incidence for each treatment.

9.4.2 Cause of Death Determined by Adjudication Committees

Causes of death will be listed by subject 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.

9.4.3 Clinical Laboratory Measurements

Summary statistics (n, mean, median, standard deviation [SD], minimum, and maximum) for the baseline assessment (Day 1) and for the pre-dose value and change from baseline at each post-baseline visit and end of treatment for scheduled lab assessments of continuous laboratory variables, including serum potassium and glucose, will be tabulated. “End of Treatment” is defined as the last non-missing assessment during the treatment period.

Shift tables relative to the normal reference ranges will be produced using the categories defined by the Common Terminology Criteria for Adverse Events (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 percentage 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 Statistical Analysis Plan (SAP). No hypothesis tests will be performed.

9.4.4 Vital Signs

Summary statistics (mean, median, SD, 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.

9.4.5 ECGs

Summary statistics (mean, median, SD, and range) for raw values and change from baseline values in Heart Rate, RR Interval, 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 $(QT/(RR^{1/3}))$. RR Interval (msec) is estimated at 60,000/Heart rate. 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.

9.4.6 24-Hour Holter Monitoring

Holter monitoring will be conducted over 24 hours in a subset of approximately 150 subjects randomized to each active treatment arm and approximately 75 subjects randomized to Placebo MDI at Visit 3 (Holter Baseline) and Visit 6 (Week 4). If there is not at least 18 hours of acceptable quality monitoring for a given assessment, then the assessment is to be repeated. In these cases, the second assessment will be used whether for baseline and/or for the Visit 6 (Week 4) value. However, any incidence of AEs indicated by the incomplete Holter findings at Week 4 will be captured.

Primary Holter Monitoring Endpoint: 24-Hour HR

The change from baseline in mean 24-hour HR obtained using Holter monitoring at Week 4 will be analyzed using an ANCOVA model to evaluate treatment differences with baseline mean 24-hour HR as a covariate. LS means and estimated treatment differences with 95% CIs will be provided. The raw mean values and change from baseline values will also be summarized by treatment group.

Secondary Holter Monitoring Endpoints

The change from baseline at Week 4 (Visit 6) in the mean daytime (06:00 to 22:00) HR, mean nighttime (22:00 to 06:00) HR, maximum 24-hour HR, and minimum 24-hour HR will each be summarized and analyzed in a similar manner to the primary Holter endpoint.

A frequency distribution of the following will be provided:

- Proportion of subjects with maximum heart rate during treatment of >180, >160-180, >140-160, >120-140, >100-120, and 100 or less.
- Proportion of subjects with minimum heart rate during treatment of >60, >50-60, 40-50, and <40

The change from baseline in the number of Holter events will be summarized descriptively. This analysis will be performed for change from baseline for the following parameters (calculated per hour): number of isolated ventricular events (PVCs), number of ventricular couplets, number of ventricular runs, number of isolated supraventricular events, number of supraventricular couplets, and number of supraventricular runs. The ventricular variables will each be analyzed using an ANCOVA to evaluate treatment differences with baseline number of PVCs as a covariate. The supraventricular variables will each be analyzed using an ANCOVA to evaluate treatment differences with baseline number of supraventricular ectopic events as a covariate. LS means and estimated treatment differences with 95% CIs will be provided. The raw mean values and change from baseline values will also be summarized by treatment group. The distribution of the frequency of these events for baseline (Visit 3) and at Week 4 will be evaluated for each event and if necessary, a natural log transformation or ln (value +1) will be used to normalize (prior to calculating the change from baseline value which will be analyzed). If a log transformation is used, then both descriptive statistics as well as analysis results will be back-transformed to provide information about geometric means.

Additionally, the proportion of subjects in each category of change from baseline in the number of PVCs per hour (no change, increase of >0-<60, 60-<120, and ≥120, and decrease of >0-<60, 60-<120, and ≥120) will be tabulated.

9.5 Dose Indicator Assessment Analyses

9.5.1 Primary Analysis

Actuation consistency: The accuracy of the count of the number of actuations used as displayed by the dose indicator will be assessed by comparing the number of actuations used according to the dose indicator with the number of actuations used as inferred from the eCRF and subject diary for each device. The 2 counts will be considered to be in agreement when the dose indicator count is within 20 actuations of the eCRF and diary count. The overall number and percentage of devices with agreement between the 2 counts will be calculated and summarized.

9.5.2 Secondary Analyses

- Number of correct advances (+/- 2 actuations): The number of actuations since the previous advance of the dose indicator will be summarized. If the number is from 8 to 12 inclusive, then the advance of the indicator will be deemed correct.
- Percent of correct advances (+/- 2 actuations) = 100 x (correct advances/total advances).
- Number of correct advances (+/- 4 actuations): The number of actuations since the previous advance of the dose indicator will be summarized. If the number is from 6 to 14 inclusive, then the advance of the indicator will be deemed correct.
- Percent of correct advances (+/- 4 actuations) = 100 x (correct advances/total advances).

9.6 Health Care Resource Utilization Analyses

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

9.7 Randomization

Subjects will be randomly assigned to one of the 4 treatment arms using an IWRS in a 7:6:6:3 ratio with less subjects being assigned to the Placebo MDI arm and more subjects being assigned to the GFF MDI arm. Randomization will be stratified by disease severity (moderate vs. severe or very severe), reversibility to Ventolin HFA (yes or no), and participation in the 12-hour PFT sub-study (yes or no). Center will not be used as a stratification factor given the impracticality of enrolling a large enough number of subjects to ensure balance in each of the 8 strata formed by combining disease severity, reversibility, and participation in the 12-hour PFT sub-study.

9.8 Experimental Design

This study is a multi-center, double-blind, parallel-group, placebo-controlled design. All study treatments are given in addition to permitted COPD background therapy. There will be a screening visit where informed consent is obtained. Current COPD medications are reviewed and if necessary arrangements are made to adjust prohibited COPD therapy to allowable COPD therapy.

9.9 Sample Size

It is estimated that a sample size of 1614 subjects (514 subjects in the GFF MDI arm, 440 subjects in each of the GP MDI, and FF MDI treatment arms, and 220 subjects in the Placebo MDI arm) will provide approximately 91% power with Type I error controlled at a two-sided alpha level of 0.05 to detect differences for all five primary comparisons if the true differences from Placebo MDI are 90 mL for FF MDI, 100 mL for GP MDI, and 150 mL for GFF MDI resulting in corresponding differences between GFF MDI and FF MDI and GP MDI of 60 mL and 50 mL, respectively, in morning pre-dose trough FEV_1 at Week 24 and approximately 99% power for morning pre-dose trough FEV_1 over 24 weeks. Assumptions regarding variability for the primary endpoint are based on Pearl Therapeutics' experience with Phase IIb clinical studies and on published data for within patient variation (D'Urzo, 2001, van Noord , 2005; Maesen, 1995) and between patient variation (Dahl, 2001, Calverley, 2003). A composite value SD of 200 mL has been assumed. A within subject correlation structure has been assumed combining a block diagonal structure induced by using subject as a random effect with an AR (1) structure with ρ=0.5. Differential dropout rates have been assumed with increased dropout due to lack of efficacy ranging up to 25% in the Placebo MDI arm. Under these assumptions, based on this sample size, the study will have approximately 99% power to detect differences between FF MDI and Placebo MDI and between GP MDI and Placebo MDI in the change from baseline in morning pre-dose trough FEV_1 at Week 24 or over 24 weeks using a two-sided alpha level of 0.05.

For TDI, the true differences from Placebo MDI are assumed to be 0.7 for FF MDI and GP MDI and 1.2 for GFF MDI. A SD of 2.4 at each visit is assumed for the SAC version based on Mahler , 2007 and Mahler, 2009). The planned sample size under similar assumptions about dropout and serial correlation will provide approximately 99% power to detect differences in TDI between FF MDI or GP MDI and Placebo MDI and approximately 98% power to detect differences for all five primary comparisons required for GFF to be declared efficacious including GFF MDI compared to FF MDI, GP MDI, and Placebo MDI in addition to FF MDI and GP MDI compared to Placebo MDI. If the SD is 2.8, the power is approximately 98% for FF MDI and for GP MDI and approximately 91% for GFF MDI.

9.10 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.

9.11 Analysis Plan

All analyses will be specified in a detailed SAP 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.

9.12 Study Populations

The following analysis populations are defined in this study:

- The **Intent-To-Treat (ITT) Population** is defined as all subjects who are randomized to treatment and receive at least one dose of the study treatment. 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 **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). **Note:** The statement that a subject had no AEs also constitutes a safety assessment.
- The **Symptomatic Population** is defined as all subjects in the ITT Population with CAT scores of ≥10 at Visit 2.
- The **Holter Monitoring Population** is defined as all subjects in the Safety Population who had at least 18 hours of acceptable quality Holter monitoring data at both Visit 3 (Holter Baseline) and Visit 6 (Week 4). Exclusions from this population may be identified by Pearl Therapeutics prior to database lock and unblinding.

Analyses will be performed as follows:

Demographics will be summarized for the ITT, PP, Safety, and Non-Randomized Populations as well as for subjects participating in the 12-hr PFT and Holter sub-studies. The Safety Population will be used to summarize extent of exposure, safety and healthcare resource utilization. Analyses of Holter monitoring parameters will be performed using the

Holter Monitoring Population. Efficacy Analyses will be performed for the ITT and PP Populations, with the ITT Population being considered the primary population for these analyses. Supportive analyses for the TDI and SGRQ will be performed using the Symptomatic Population. The PP analyses will be used as sensitivity analyses.

9.13 Handling of Missing Data

All observed values 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, 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 eCRF. 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.

Additional sensitivity analyses will be implemented based on a cumulative responder approach for the change from baseline in morning pre-dose trough FEV_1 at Week 24. A cumulative distribution plot by treatment arm (Farrar, 2006) will be produced. The cumulative responder curves for each treatment will then be compared pairwise using a Kolmogorov-Smirnov test.

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.

For the subset of subjects included in the 12-hour spirometry assessment at Visit 4 (Day 1) and Visit 8 (Week 12), ITT analyses will use all available data with the trapezoidal rule to calculate AUC_{0-12} (AUC_{0-6} and AUC_{6-12}) using change from baseline values. The determination of peak change from baseline in FEV_1 requires at least one non-missing FEV_1 value during the first 2 hours post-dose. For the PP analyses, FEV_1 AUC_{0-12} will be calculated if there are at least 2 non-missing data-points during the first 2 hours post-dose and there is at least 1 non-missing value at 4 hours post-dose or later. Peak FEV_1 will be calculated if there are at least 2 non-missing data-points missing during the first 2 hours post-dose.

9.14 Statistical Software

Data processing, statistical screening, descriptive reporting and analysis of the efficacy and safety data will be performed using Statistical Analysis Software, Version 9.2 or higher. Graphs may also be produced using R (R Development , 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).
- 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 (eg, 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 laws (ie, 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 or their designee.

10.8 Study Monitoring

In accordance with applicable regulations, GCP, and Pearl Therapeutics procedures, clinical monitors will contact the site prior to 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' 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, eg, 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, and other clinical trial listings as appropriate.

11 REFERENCE LIST

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Appendix 1 Spirometry Performance Recommendations

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

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

FEV_1 AND FVC MANEUVERS

Equipment Requirements

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

Display

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

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

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

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

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

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

The time scale should be $\geq$20 mm-s^{-1}, and larger time scales are preferred ($\geq$30 mm-s^{-1}) when manual measurements are made. When the volume–time plot is used in conjunction with a flow–volume curve (ie, 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 (eg, 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, eg, $\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 (eg, 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 (eg, 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, eg, 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, eg, 0–3, 1–4, 2–5, 3–6, 4–7 and 5–8 L, for an 8-L spirometer. The linearity check is considered acceptable if the spirometer meets the volume accuracy requirements for all volumes tested.

Quality Control for Flow-Measuring Devices

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

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

VC MANEUVERS

Equipment

For measurements of VC, 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 should be included in the display of VC maneuver. Regardless of

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

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

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

FEVt: forced expiratory volume in t seconds

BTPS correction

All spirometry values should be reported at BTPS by any method (measuring temperature and barometric pressure) proven effective by the manufacturer. For volume-type spirometers, the temperature inside the spirometer should be measured for each breathing maneuver. Regardless of the BTPS correction technique used, the ambient temperature must always be recorded with an accuracy of $\pm$1°C. In situations where the ambient air temperature is changing rapidly (>3°C in <30 minutes), 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

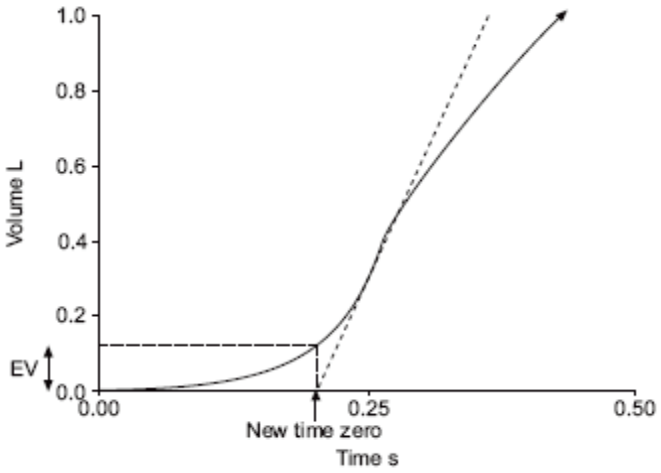
***Acceptable* Tests must meet the following 7 Criteria:**

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, ie, 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, FF and Placebo MDI

Before using GFF MDI, GP MDI, FF MDI, and Placebo 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 A4-1.

Figure A4-1. 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, FF MDI, and Placebo 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, FF MDI, and Placebo 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, FF MDI, and Placebo 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 A4-2).

Figure A4-2. Wash Actuator through Top of Actuator

3. Then wash the actuator again through the mouthpiece (see Figure A4-3).

Figure A4-3. 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

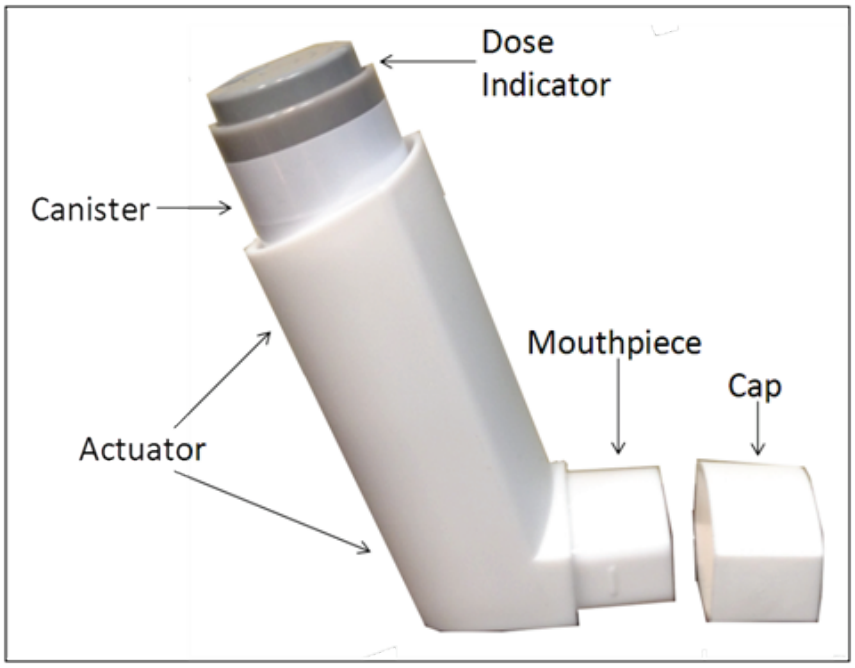
Blockage from medicine build-up is more likely to happen if the actuator is not routinely cleaned and the actuator is not air-dried completely. If the actuator gets blocked so that little or no medicine comes out of the mouthpiece, wash the actuator as described in cleaning steps 1-6.

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 A4-4. Metered Dose Inhaler Parts



Appendix 5 Instructions for Use of Atrovent HFA Inhalation Aerosol Device

Inhaler Description

ATROVENT HFA Inhalation Aerosol (Figure 1) consists of a metal canister containing the medicine and a mouthpiece that releases the medicine from the canister. The mouthpiece includes a clear colorless sleeve, a white plastic portion and a green protective dust cap.

The inhaler comes with a dose indicator you can see through a small window on the plastic mouthpiece (See Figure 1). A new inhaler first shows "200" in the dose indicator window. The dose indicator will show the approximate number of actuations (sprays) of medicine remaining in the inhaler. As you use the inhaler, the dose indicator will typically rotate during every 5 to 7 actuations (sprays) towards the next decreasing number (See Figure 2).

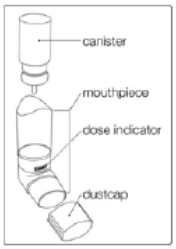


Figure 1

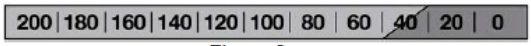


Figure 2

Instructions for Use:

1. **Insert the metal canister into the clear end of the mouthpiece (See Figure 1).** Make sure the canister is fully and firmly inserted into the mouthpiece.

   - **The ATROVENT HFA canister is to be used only with the ATROVENT HFA mouthpiece.**
   - **Do not use the ATROVENT HFA mouthpiece with other inhaled medicines.**

2. **Remove the green protective dust cap.** If the cap is not on the mouthpiece, make sure there is nothing in the mouthpiece before use. For best results, the canister should be at room temperature before use.

3. **Breathe out (exhale) deeply through your mouth.** Hold the inhaler upright (See Figure 3), between your thumb and first 2 fingers. Put the mouthpiece in your mouth and close your lips.

   - **Keep your eyes closed so that no medicine will be sprayed into your eyes.** If sprayed into the eyes, ATROVENT HFA can cause blurry vision and other vision abnormalities, eye pain or discomfort, dilated pupils, or narrow-angle glaucoma or worsening of this condition. If any combination of these symptoms develops, you should consult your physician immediately.


Figure 3

4. **Breathe in (inhale) slowly through your mouth and at the same time spray the ATROVENT HFA into your mouth.**

   - To spray ATROVENT HFA firmly press the canister against the mouthpiece 1 time (See Figure 4). Keep breathing in deeply.

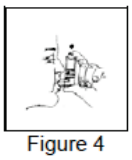


Figure 4

5. **Hold your breath for ten seconds and then take the mouthpiece out of your mouth and breathe out slowly (See Figure 5).**


Figure 5

6. **Wait at least 15 seconds and repeat steps 3 to 5 again.**

7. **Replace the green protective dust cap after use.**

8. **Keep the mouthpiece clean.** At least once a week, wash the mouthpiece, shake it to remove excess water and let it air dry all the way (see **Mouthpiece Cleaning Instructions**).

Mouthpiece Cleaning Instructions:

Step A. Remove and set aside the canister and dust cap from the mouthpiece (See Figure 1).

Step B. Wash the mouthpiece through the top and bottom with warm running water for at least 30 seconds (See Figure 6). Do not use anything other than water to wash the mouthpiece.

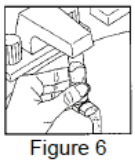


Figure 6

Step C. Dry the mouthpiece by shaking off the excess water and allow it to air dry all the way.

Step D. When the mouthpiece is dry, replace the canister. Make sure the canister is fully and firmly inserted into the mouthpiece.

Step E. Replace the green protective dust cap.

If little or no medicine comes out of the mouthpiece, wash the mouthpiece as described in Steps A to E under the "**Mouthpiece Cleaning Instructions**".

9. When to get a new ATROVENT HFA inhaler.

There are approximately 40 actuations (sprays) left when the dose indicator displays "40," where the background changes from green to red (See Figure 7a). This is when you need to refill your prescription or ask your doctor if you need another prescription for ATROVENT HFA inhalation aerosol.

The background color will be all red when the indicator approaches 20. The indicator will stop moving at "0". Discard the inhaler once the dose indicator displays "0" (See Figure 7b). Even though the canister may not be empty, you cannot be sure of the amount of medicine in each actuation (spray) once the dose indicator displays "0".

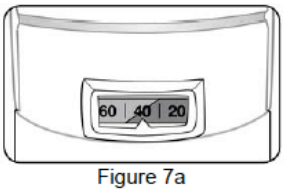


Figure 7a

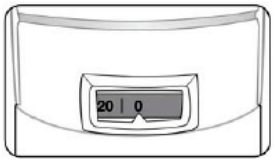


Figure 7b

Appendix 6 Instructions for Use of Ventolin HFA Inhaler

The Parts of Your VENTOLIN HFA Inhaler

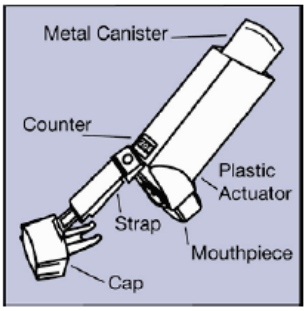


Figure A

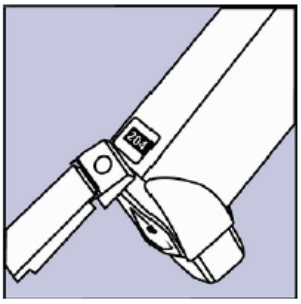


Figure B

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:

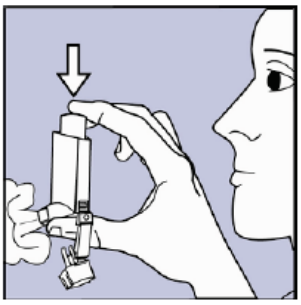


Figure C

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.

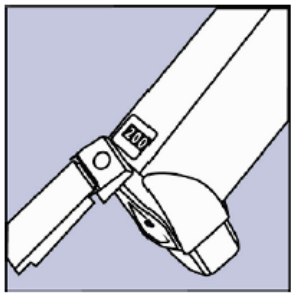


Figure D

- 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:

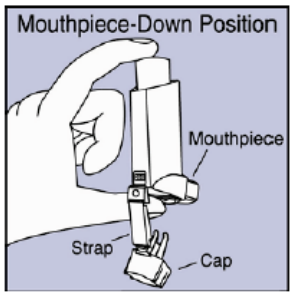


Figure E

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.

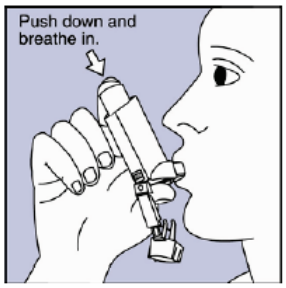


Figure F

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:

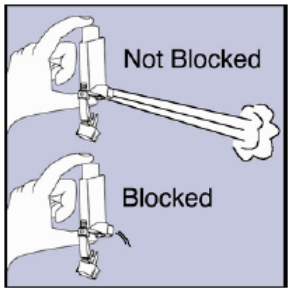


Figure G

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:

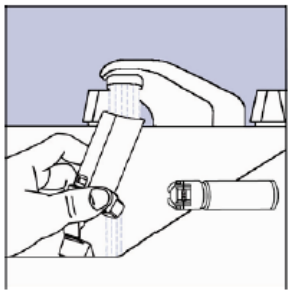


Figure H

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.

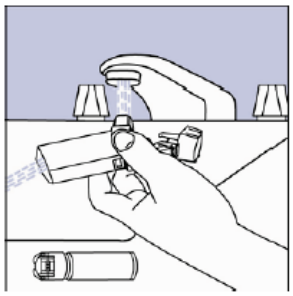


Figure I

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.

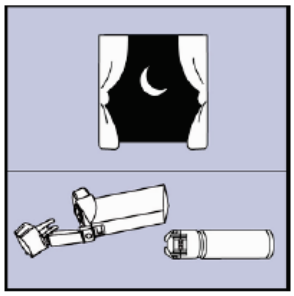


Figure J

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.

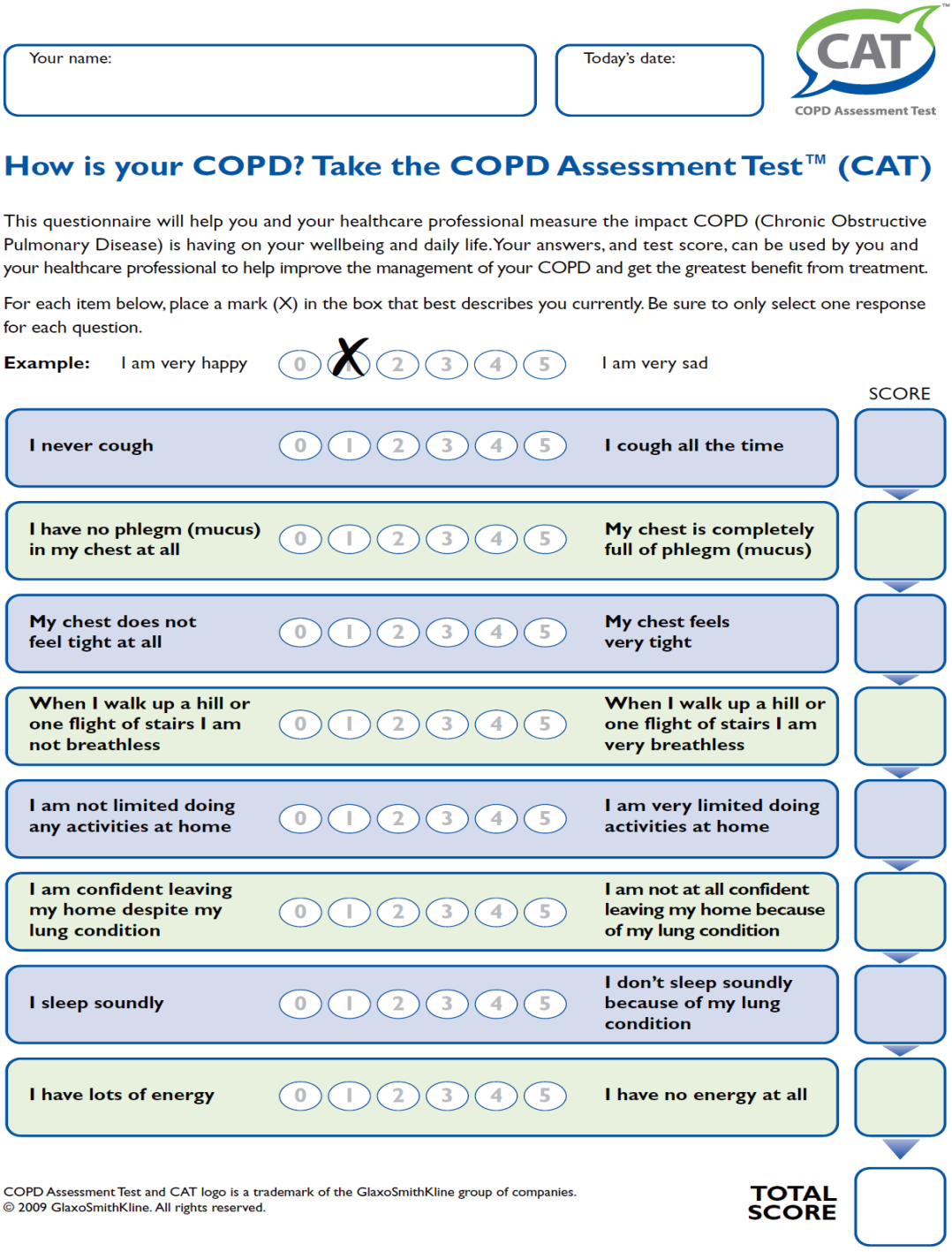
If you need to use your inhaler before the actuator is completely dry:

- 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 COPD Assessment Test



Your name:

Today's date:

CAT
COPD Assessment Test

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

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

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

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

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

Appendix 8 St. George Respiratory Questionnaire (SGRQ)

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

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
ENGLISH FOR THE UNITED STATES

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

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 problems, rather than what the doctors and nurses think your problems are.

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

Before completing the rest of the questionnaire:

Please check one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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continued...

St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 4 weeks.

Please check (✓) *one box for each question*:

	almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had wheezing attacks:	☐	☐	☐	☐	☐

5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:
- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (✓) *one*:
- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:
- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:
- No ☐
- Yes ☐

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your respiratory condition?

Please check (✓) *one*:

The most important problem I have	☐
Causes me quite a lot of problems	☐
Causes me a few problems	☐
Causes no problems	☐

If you have ever held a job:

Please check (✓) *one*:

My respiratory problems made me stop working altogether	☐
My respiratory problems interfere with my job or made me change my job	☐
My respiratory problems do not affect my job	☐

Section 2

These are questions about what activities usually make you feel short of breath <u>these days.</u>

For each statement please check (✓) ***the box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

USA / US English version 3

continued…

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St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath <u>these days</u>.

	For each statement please check (✓) ***the box*** that applies to you ***these days***: True	False
Coughing hurts	☐	☐
Coughing makes me tired	☐	☐
I am short of breath when I talk	☐	☐
I am short of breath when I bend over	☐	☐
My coughing or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

These are questions about other effects that your respiratory problems may have on you <u>these days</u>.

	For each statement, please check (✓) ***the box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My respiratory problems are a nuisance to my family, friends or neighbors	☐	☐
I get afraid or panic when I cannot catch my breath	☐	☐
I feel that I am not in control of my respiratory problems	☐	☐
I do not expect my respiratory problems to get any better	☐	☐
I have become frail or an invalid because of my respiratory problems	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

	For each statement, please check (✓) ***the box*** that applies to you ***these days:*** True	False
My treatment does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My treatment interferes with my life a lot	☐	☐

USA / US English version 4

continued…

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St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your respiratory problems.

	For each statement, please check (✓) *the box* that applies to you *because of your respiratory problems*: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time to do it	☐	☐
I walk slower than other people my age, or I stop to rest	☐	☐
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☐	☐

Section 7

We would like to know how your respiratory problems <u>usually</u> affect your daily life.

	For each statement, please check (✓) *the box* that applies to you *because of your respiratory problems*: True	False
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

St. George's Respiratory Questionnaire

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog
Doing activities or chores at home or in the garden
Sexual intercourse
Going to a place of worship, or a place of entertainment
Going out in bad weather or into smoky rooms
Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

.....
.....
.....
.....

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

It does not stop me from doing anything I would like to do ☐
It stops me from doing one or two things I would like to do ☐
It stops me from doing most of the things I would like to do ☐
It stops me from doing everything I would like to do ☐

Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.

USA / US English version 6

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Appendix 9 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 10 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 11 Sponsor Signatory

Study Title: A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multicenter Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects With Moderate to Very Severe COPD, Compared With Placebo

Study Number: PT003007-02

Final Date: [redacted]

Signature: [redacted] Date: [redacted]

Name: [redacted]

Title: [redacted]

Appendix 12 Investigator's Agreement and Signature Page

Study Title: A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multicenter Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects With Moderate to Very Severe COPD, Compared With Placebo

Study Number: PT003007-02

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: _____

_____