



Revised Clinical Study Protocol

Study Code	PT003017
NCT #	NCT02643082
Date	26 September 2016

A Randomized, Phase IIIb, Two-period, Double-blind, Two treatment, Chronic-dosing (7 Days), Single-center Crossover Study to Evaluate the Treatment Effect of PT003 on Cardiovascular Hemodynamics in Subjects With Moderate to Severe Chronic Obstructive Pulmonary Disease, Compared with Placebo

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The following Amendment(s) are included in this revised protocol:

Amendment No.	Date of Amendment
Version 1	14 October 2015
Version 2, Amendment 1	04 February 2016
Version 3, Amendment 2	26 September 2016

Clinical Trial Protocol: PT003017-02

Title: A Randomized, Phase IIIb, Two-period, Double-blind, Two-treatment, Chronic-dosing (7 Days), Single-center Crossover Study to Evaluate the Treatment Effect of PT003 on Cardiovascular Hemodynamics in Subjects With Moderate to Severe Chronic Obstructive Pulmonary Disease, Compared with Placebo

Study Number: PT003017-02

Study Phase: IIIb

Product Name: Glycopyrronium and Formoterol Fumarate Inhalation Aerosol, PT003

IND Number: 107739

Indication: COPD

Investigators: Single-center

Sponsor: Pearl Therapeutics, Inc.
[REDACTED]
[REDACTED]
[REDACTED]

Sponsor Contact: [REDACTED]

	Version Number	Date
Original Protocol:	Version 1.0	14 October 2015
Amended Protocol	Version 2.0	04 February 2016
Amended Protocol	Version 3.0	26 September 2016

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SUMMARY OF CHANGES TO AMENDED PROTOCOL VERSION 2.0, DATED 04 FEBRUARY 2016 FOR VERSION 3.0

The amended study protocol, PT003017-02 (Version 3.0), includes the following edits. When specifically mentioned, newly added or deleted text is indicated in quotation marks.

No.	Description of Change	Rationale
1	<p>Synopsis; Former Section 3.4: Exploratory Endpoints (Evaluated on Treatment Day 8); Previous Section 7.1.6: Biomarkers; Section 8.3: Visit 3 (Randomization/Day 1); Section 8.4: Visit 4 (Day 8); Section 8.6: Visit 6 (Day 8); Section 9.2.1: Efficacy Endpoints, Former Section 9.2.2: Exploratory Endpoints (Evaluated on Treatment Day 8)</p> <p>Deleted biomarker endpoints, any reference to biomarker endpoints and exploratory endpoints</p>	<p>Current biomarker endpoints considered to not add value to the study as biomarkers are not expected to show a difference between GFF MDI and Placebo MDI.</p>
2	<p>Synopsis</p> <p>Corrected that baseline for plethysmography endpoints will be defined as the pre-dose value at Visit 2 and not the -30 min value at Visit 2.</p>	<p>Corrected to align with Section 7.1.3: Plethysmography, which indicates that at Visit 2, pre-bronchodilator plethysmography assessments will be conducted. No -30 min assessment will be conducted at Visit 2.</p>
3	<p>Synopsis, Primary Efficacy Endpoint; Section 3.1: Primary Efficacy Endpoint; Section 9.2.1.1: Primary Efficacy Endpoint</p> <p>Revised that RVEDVi endpoint will be measured 2-3 hours post-dose instead of 2 hours post-dose</p>	<p>Changed to allow correct sequence in timing for the MRI</p>
4	<p>Synopsis, Secondary Efficacy Endpoints (Measured using MRI at 2 hours post-dose on Day 8); Section 3.2: Secondary Efficacy Endpoints (Measured using MRI at 2 hours post-dose on Day 8); Section 9.2.1.2: Secondary Efficacy Endpoints (Measured using MRI at 2 hours post-dose on Day 8)</p>	<p>Changed to allow site flexibility in timing for the MRI assessments</p> <p>Added to clarify that the PVR measurement is measured at a different time point than the timeframe the title indicates secondary endpoints will be measured.</p>

	<p>Revised that the MRI endpoints will be measured 2-3 hours post-dose instead of 2 hours post-dose on Day 8</p> <p>Indicated that the PVR will be measured at 30 minutes and 60 minutes post-dose</p>	
5	<p>Synopsis, Other Efficacy Endpoints (Measured at 2 hours post-dose on Day 8 unless otherwise noted); Section 3.3: Other Efficacy Endpoints (Measured at 2 hours post-dose on Day 8 unless otherwise noted); Section 9.2.1.3: Other Efficacy Endpoints (Measured at 2 hours post-dose on Day 8 unless otherwise noted)</p> <p>Deleted “(Measured at 2 hours post-dose on Day 8 unless otherwise noted)”</p> <p>Revised that the plethysmography will be measured 1-2 hours post-dose instead of 2 hours post-dose on Day 8 and the ICG assessments will occur 30 and 60 minutes post-dose instead of 2 hours on Day 8; Revised that MRI assessments will occur at 2-3 hours post-dose on Day 8 instead of 2 hours post-dose and that post-dose FEV₁, IC, and FVC will be measured at 1 hour post-dose on Day 8 instead of 2 hours post-dose</p> <p>Deleted under ICG assessments (Under second bullet) that the PVR will be measured at morning pre-dose trough and each post-dose time point (first sub-bullet); Deleted PVR on Day 1 (second sub-bullet) and Cardiac output on Day 1 (third sub-bullet) as endpoints. This leaves only one endpoint under “other efficacy endpoints” for ICG endpoints.</p>	<p>Deleted timing as each set of assessments has been changed to a different time post-dose</p> <p>Changed timings to allow site flexibility in timing for the plethysmography, ICG, MRI, and spirometry assessments</p> <p>Deleted “Morning pre-dose trough for PVR” as an other efficacy endpoint and put as a secondary endpoint as post-dose PVR measurements are also secondary endpoints; Deleted “and each post-dose time point for PVR” as an other efficacy endpoint as this is already covered under the secondary endpoint of “ Pulmonary Vascular Resistance (PVR) by ICG”; Deleted PVR on Day 1 and Cardiac output on Day 1 as endpoints as there are no post-dose assessments on Day 1</p>
6	<p>Section 1: Introduction and Study Rationale</p> <p>Updated the GOLD reference from 2014 to 2016.</p>	<p>Updated as new GOLD strategy was published in 2016.</p>

7	<p>Section 1: Introduction and Rationale</p> <p>Updated section to include Utibron™ Neohaler® and Stiolto™ Respimat® to fixed-dose LAMA/LABA combination products</p>	<p>For completeness, added all of the LAMA/LABA fixed-dose combination products commercially available.</p>
8	<p>Section 1: Introduction and Rationale</p> <p>Updated section to indicate that Pearl has developed GFF MDI as a combination product instead of is developing this product.</p>	<p>Updated as GFF MDI is now an approved product and no longer in development stage.</p>
9	<p>Section 4.1: Overall Study Design and Plan</p> <p>Corrected wording under Screening Period to indicate that subjects must meet spirometry criteria of an FEV₁/FVC ratio of <0.70 and FEV₁ of <65% at Visit 1 to qualify for study enrollment.</p>	<p>Corrected to reflect actual criterion for spirometry at Visit 1.</p>
10	<p>Section 4.1: Overall Study Design and Plan; Section 5.4.1: Prohibited COPD Medications and Required Washout Prior to Visit 2</p> <p>Corrected to indicate that Ventolin HFA (albuterol sulfate Inhalation Aerosol) will be administered PRN instead of QID</p>	<p>Corrected to indicate correct dosing regimen for Ventolin HFA.</p>
11	<p>Section 4.1: Overall Study Design and Plan (General Considerations for Treatment Visits 3 through Visit 6 (in-clinic):</p> <p>Deleted wording in bullet #7 that subjects must return to the clinic “but no later than 10:00 AM” and changed that in-clinic dosing time is before “approximately 11:00 AM”</p>	<p>To allow the subjects more flexibility with visit scheduling and to allow the site more flexibility with in-clinic dosing time to ensure all pre-dose assessments can be performed in a timely manner.</p>
12	<p>Section 4.1: Overall Study Design and Plan, Figure 1 Study Flow Diagram</p> <p>Deleted Peak FEV₁ at Visit 2 under Screening/Baseline Assessments</p> <p>Deleted Day 1 IC pre- and post-dose and</p>	<p>Deleted as these assessments are not being collected</p>

	deleted Biomarker assessments under Assessments During Treatment	
13	<p>Section 5.5.1: Illicit Drugs</p> <p>Added text to reflect that the subject will be discontinued from the study if any illicit drugs or drugs of abuse are used by the subject during the study.</p>	Clarification that subjects who use illicit drugs or drugs of abuse will be discontinued from the study.
14	<p>Section 5.6: Smoking Status</p> <p>Added text under the Note to clarify that electronic cigarettes will not be used for the calculation of pack-year history</p>	Clarification as only cigarettes can be used for calculation of pack-year history.
15	<p>Section 5.7: Reasons for Discontinuation</p> <p>Under last Note in this section, added Utibron™ Neohaler® to the list of recently marketed LABA/LAMA products</p>	For completeness, to include the entire list of recently marketed LABA/LAMA products
16	<p>Section 7: Study Procedures</p> <p>Indicated that assessments should be performed at the same time for a given subject across each treatment period.</p> <p>Clarified order of pre-dose assessments at Visit 3 and Visit 5 and order of pre-and post-dose assessments at Visit 4 and Visit 6.</p>	<p>To ensure assessments are performed at a consistent time pre-and post-dose to avoid variability in response</p> <p>Based on revised timing for some assessments, the order was changed to align with these timings.</p>
17	<p>Section 7.1.1: Pulmonary Function Tests (Spirometry)</p> <p>Under the Note, added that spirometry will be conducted at Visit 1.</p> <p>Revised timing of post-dose spirometry assessment from 2 hours to 1 hour at Visit 4 and Visit 6.</p>	<p>For completeness, added Visit 1 to the list of visits at which spirometry assessments are obtained.</p> <p>Revised timing to allow for site flexibility to allow all post-dose assessments to be conducted in a timely manner.</p>
18	<p>Section 7.1.1.2: Characterization of Reversibility</p> <p>Added that reversibility to Ventolin HFA</p>	Clarification to add Atrovent HFA since reversibility to be obtained after administration of both Ventolin HFA

	and Atrovent HFA will be determined following administration of both Ventolin HFA “and Atrovent HFA”	and Atrovent HFA
19	Section 7.1.2 Inspiratory Capacity (IC) Revised timing of IC assessment at Visit 4 and Visit 6 from 2 hours to 1 hour.	Revised timing to allow for site flexibility to ensure assessments are conducted in a timely manner
20	Section 7.1.3: Plethysmography Revised plethysmography assessment at Visit 4 and Visit 6 from 30 minutes prior to study drug administration to 60 minutes prior to study drug administration. Revised timing of Visit 4 and Visit 6 post-dose plethysmography assessment from 2 hours to 1-2 hours.	Revised timing so that plethysmography assessment would not occur at the same time as the 30 minute pre-dose spirometry assessment to allow site flexibility to obtain all pre-dose assessments. Revised timing to allow for site flexibility to ensure all post-dose assessments are conducted in a timely manner.
21	Section 7.1.4: Magnetic Resonance Imaging Added that MRI at Visit 3 will be conducted on the same day and deleted the text indicating that the MRI will be conducted 30 minutes prior to study drug administration. Text now says MRI will be conducted prior to study drug administration. Revised timing of post-dose MRI assessment at Visit 4 and Visit 6 from 2 hours to 2-3 hours.	Clarified that the MRI must be performed on the same day as the visit and removed any timing requirement for MRI assessment so the MRI would not have to be performed at the same time as the 30 minute pre-dose spirometry assessment. To allow site flexibility to perform all post-dose assessments in a timely manner and to not perform the MRI assessment any longer than 3 hours post-dose so as not to significantly interfere with peak bronchodilator effect of GFF when the MRI is conducted.
22	Section 7.1.5: Impedence Cardiography (ICG) Revised that ICG will not be conducted 60 minutes prior to administration of Ventolin HFA and Atrovent HFA to just indicate timing as prior to administration of these agents.	To allow site flexibility so that all Visit 2 pre-dose assessments will be conducted in a timely manner To allow site more flexibility to

	<p>Changed timing of Visit 3 and Visit 5 ICG assessment from 60 minutes prior to study drug administration to just prior to study drug administration.</p> <p>Changed timing of Visit 4 and Visit 6 ICG assessment from 60 minutes prior to study drug administration to prior to study drug administration and removed 2 hour post-dose ICG assessment.</p>	<p>complete all pre-dose assessments in a timely manner.</p> <p>To allow site more flexibility to complete all pre- and post-dose assessments in a timely manner.</p>
23	<p>Section 7.2.2.: Vital Sign Measurements</p> <p>Clarified that at all visits (Visit 1 through Visit 6) , not just Visit 2, that a single vital sign measurement will be obtained prior to study drug administration and following completion of the last assessment of the visit if clinically indicated.</p> <p>Removed language that at Visits 3 to 6 a single vital sign measurement will be obtained prior to study drug administration and following completion of the last assessment of the visit.</p>	<p>To provide consistency across visits when vital signs will be obtained.</p>
24	<p>Section 7.2.3: 12-Lead Electrocardiogram</p> <p>Added that ECG assessments should occur prior to spirometry assessments.</p> <p>For Visit 3, removed the within 60 minutes timing prior to study drug administration for the ECG assessment.</p> <p>For Visit 5, removed the within 30 minutes timing prior to study drug administration for the ECG assessment.</p>	<p>To minimize any effect of spirometry may have on heart rate, indicated that ECG should occur prior to spirometry assessments.</p> <p>To allow the site flexibility to obtain all pre-dose assessments in a timely manner.</p>
25	<p>Section 7.3.12: Use of Steroids during the Trial</p> <p>Deleted language indicating use of corticosteroids for the management of COPD is not a reason for early termination and language regarding management of subjects' spirometry assessments if they have taken corticosteroids within 14 days</p>	<p>Deleted as not applicable as per Section 5.7.1: Reasons for Discontinuation, subjects who suffer a moderate or severe COPD exacerbation will be discontinued from the study.</p>

	of a scheduled visit.	
26	<p>Section 8: Study Activities, Table 8.1 Schedule of Events</p> <p>Deleted Biomarker Sample Collection</p>	<p>Not applicable as samples for biomarkers will no longer be collected in this study</p>
27	<p>Section 8: Study Activities, Table 8-2</p> <p>Rearranged order of assessments, deleted spirometry assessment at -30 minutes pre-dosing and 30 minutes post-dosing at Visit 1, changed superscripts to indicate if an assessment was timed or not as applicable.</p> <p>Revised Note under Table 8-2</p>	<p>Changed order of assessments to reflect the order in which the assessments will be performed; deleted timings for spirometry at Visit 1 as there is no dosing at Visit 1, indicated the correct superscripts depending on whether an assessment was timed or not.</p> <p>Revised Note to reflect the correct order in which assessments should be performed.</p>
28	<p>Section 8: Study Activities, Table 8-3</p> <p>Rearranged order of assessments and changed timing of some assessments to be consistent with timings in Section 7.</p> <p>Revised footnote “f” to indicate new MRI timing post-dose at Visit 4 and Visit 6. Revised footnote “g” to indicate new post-dose plethysmography timing at Visit 4 and Visit 6.</p> <p>Revised Note under Table 8-3</p>	<p>Changed order of assessments to reflect the order in which the assessments will be performed. Revised timings of some assessments to allow pre-dose assessments to be performed in a timely manner and to allow post-dose assessments at Visit 4 and Visit 6 to occur at a time as to not compromise the MRI assessment timing.</p> <p>Revised footnotes for clarification of Visit 4 and Visit 6 MRI and plethysmography post-dose timings.</p> <p>Revised Note to reflect the correct order in which assessments should be performed.</p>
29	<p>Section 9.3.1.1: Primary Efficacy Analysis; Section 9.3.1.2: Secondary Efficacy Analysis</p> <p>Revised that the baseline value for RVEDVi and secondary MRI endpoints will use the value from Visit 3 instead of Visit 4</p>	<p>Correction as pre-dose MRI only performed at Visit 3</p>

30	<p>Section 9.3.1.2: Secondary Efficacy Analysis</p> <p>Added sentence “In addition, since there are two responses (30- and 60-min post-dose) per period for PVR, an unstructured covariance matrix will be fit to the repeated measures within a subject-period for this endpoint.</p>	To improve the clarity of the modeling
31	<p>Section 9.3.1.3: Other Efficacy Analysis</p> <p>Added sentence “For the ICG endpoint of change in right ventricular stroke volume, an additional unstructured covariance matrix will be fit to the repeated measures within a subject period.”</p> <p>Indicated that the baseline for the plethysmography endpoints will use the pre-bronchodilator value at Visit 2 instead of the -30 min value at Visit 2.</p> <p>Added text :”For spirometry endpoints, the mean of the -60 and -30 minute values for each visit will be obtained prior to averaging across visits.”</p>	<p>To improve the clarity of the modeling</p> <p>Correction as plethysmography is not a timed assessment at Visit 2.</p> <p>Clarification</p>
32	<p>Former Section 9.3.2 Exploratory Analysis</p> <p>Deleted text regarding analysis of biomarker endpoints</p>	Not applicable as biomarker endpoints have been removed
33	<p>Minor typographical errors were addressed but not captured as individual items in the summary of changes</p>	To improve readability

SYNOPSIS

Sponsor: Pearl Therapeutics, Inc. (“Pearl”) [REDACTED] [REDACTED]
Names of Finished Products: Glycopyrronium and Formoterol Fumarate Inhalation Aerosol, PT003; Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler (GFF MDI) Placebo for GFF MDI
Name of Active Ingredients: Glycopyrronium and Formoterol Fumarate
Study Title: A Randomized, Phase IIIb, Two-period, Double-blind, Two-treatment, Chronic-dosing (7 Days), Single-center Crossover Study to Evaluate the Treatment Effect of PT003 on Cardiovascular Hemodynamics in Subjects With Moderate to Severe Chronic Obstructive Pulmonary Disease, Compared with Placebo
Study Number: PT003017-02
Study Phase: IIIb
Primary Objective: <ul style="list-style-type: none">• To assess the effect of GFF MDI on cardiovascular hemodynamics following chronic dosing (7 days) in subjects with moderate to severe COPD
Secondary Objectives: <ul style="list-style-type: none">• To assess the effect of GFF MDI on pulmonary hemodynamics following chronic dosing (7 days)• To assess the effect of GFF MDI on lung function following chronic dosing (7 days)
Safety Objective: <ul style="list-style-type: none">• To assess the safety of GFF MDI based on adverse events (AEs), vital sign measurements, electrocardiograms (ECGs), and clinical laboratory evaluations

Study Design:

This is a randomized, two-period, double-blind, two-treatment, chronic-dosing (7 days) single-center, crossover study to evaluate the treatment effect of GFF MDI (PT003) compared with Placebo MDI on cardiovascular hemodynamics following chronic dosing (7 days) in subjects with moderate to severe chronic obstructive pulmonary disease (COPD). It is planned that approximately 40 subjects will be randomized to provide approximately 32 study completers.

Subjects will undergo a Screening Period of 7 to 28 days in duration. During the Screening Period, subjects that are receiving an inhaled corticosteroid (ICS)/long acting β 2-agonist (LABA) will discontinue the ICS/LABA, but will continue the ICS component for the duration of the study. Similarly, subjects treated with an ICS as part of their inhaled maintenance therapy will also be permitted to continue their ICS for the duration of the study.

All subjects will discontinue their previously prescribed inhaled bronchodilators and switch to Sponsor-provided Atrovent[®] HFA MDI administered four times daily (QID) as COPD maintenance therapy during the Screening Period and during the Washout Period of the study. Sponsor-provided Ventolin[®] HFA (albuterol sulfate inhalation aerosol) administered as needed for control of symptoms will be provided throughout the study. At randomization subjects will discontinue Atrovent HFA, but will be permitted to use their ICS and sponsor- provided rescue inhaler (albuterol sulfate inhalation aerosol) throughout the study.

Subjects that meet all other entry criteria but are using certain prohibited COPD medications must discontinue the use of prohibited medications at Visit 1 (Screening). Prohibited COPD medications include, but are not limited to oral β 2-agonists, LABAs, long-acting muscarinic agonists(LAMA), LABA/LAMA, ICS/LABA combination products, cromoglycate or nedocromil inhalers, leukotriene antagonists [e.g., zafirlukast, montelukast, zileuton], or tiotropium [Spiriva], aclidinium [Tudorza[™]], and umeclidinium [Incruse[®] Ellipta[®]]. The use of these medications is prohibited throughout the screening period and the duration of the study.

Subjects will be issued and trained on the use of the Subject Diary at Visit 1 (Screening) and will be instructed to collect practice data during the Screening Period (between Visit 1 and Visit 3). Subject Diary compliance will be reviewed at Visit 3, and the subject will be retrained if necessary.

All subjects will be administered both GFF MDI and Placebo MDI in separate treatment periods. Enrollment into the active period of the study will be stratified by severity of disease such that half of the subjects will have moderate COPD and half will have severe COPD as categorized by post-bronchodilator FEV₁ ($\geq 50\%$ - $<65\%$ for moderate and 30% - $<50\%$ for severe). The entire study period is scheduled to take approximately 12 weeks for each individual subject. The study is anticipated to run for approximately 6 months and duration should be approximately 12 months.

Study Population:

It is planned that approximately 40 subjects with moderate to severe COPD will be randomized to provide an estimated 32 subjects to complete the study.

Product, Dose, and Mode of Administration:

Investigational materials will be provided by Pearl Therapeutics (Pearl), as shown below:

Product Name and Dose	Product Strength	Dosage Form/ Fill Count	Administration
Study Medications			
GFF MDI (PT003) 14.4/9.6 µg ex-actuator	7.2/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
Open-Label Products			
Albuterol Sulfate inhalation aerosol 90 µg ^a ex-actuator	Ventolin [®] HFA HFA inhalation aerosol. Albuterol sulfate inhalation aerosol. Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece.	MDI/ 60 or 200 actuations	Taken as directed Supplies are open-label
Ipratropium bromide HFA inhalation aerosol 34 µg ^b ex-actuator	Atrovent [®] HFA. Ipratropium bromide HFA. Each inhalation contains 17 µg per actuation.	MDI/ 200 actuations	Taken as 2 inhalations QID Supplies are open-label
Placebo			
Placebo MDI ^c	Formulation does not contain active ingredient	MDI 120 inhalations	Taken as two inhalations BID

Abbreviations: BID=twice daily; GFF MDI= Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; HFA=hydrofluoroalkane; MDI=Metered Dose Inhaler; QID=four times daily; US=United States

- a. The Sponsor will provide Ventolin HFA for reversibility testing during Screening and as rescue medication throughout the study.
- b. The Sponsor will provide Atrovent HFA for reversibility testing during Screening and as COPD maintenance medication during the Screening Period and Washout Period.
- c. Placebo MDI will be used for training purposes and also administered as a randomized treatment. All placebos are created by Pearl in the image of the active test product, with no active moieties.

Duration of Treatment:

It is planned that each subject will receive study treatment over 2 Treatment Periods for 1 week duration each. It is anticipated that the entire study will take approximately 12 weeks for each individual subject from the time of Screening.

All efficacy assessments will be compared to a change from baseline. Baseline for Magnetic Resonance Imaging (MRI) will be defined as the pre-dose value at Visit 3. Baseline for the plethysmography endpoints will be defined as the pre-bronchodilator value at Visit 2. Baseline for the Impedance Cardiography (ICG) and spirometry endpoints will be defined as the average of the subject values obtained pre-dose on Day 1 of each Treatment Period (average of Visit 3 and Visit 5 pre-dose). The first day of treatment in each Treatment Period is Day 1. Each Treatment Period is planned to be 7 days in duration occurring between the first and last dose which will correspond to 8 calendar days. Therefore, assessments collected on Day 8 will occur following 7 days of treatment.

Primary Efficacy Endpoint:

- Right Ventricular End Diastolic Volume Index (RVEDVi) measured at 2-3 hours post-dose on Day 8

Secondary Efficacy Endpoints (Measured using MRI at 2-3 hours post-dose on Day 8 unless otherwise noted):

- Aortic left ventricular stroke volume [LVSV]
- Right Ventricular Stroke Volume (RVSV), phase contrast from pulmonic valve
- Pulmonary Artery Velocity
- Left Ventricular End Diastolic Volume Index (LVEDVi)
- Cardiac Output
- Morning pre-dose trough and post-dose Pulmonary Vascular Resistance (PVR) by ICG (Measured at 30 minutes and 60 minutes post-dose)
- Pulmonary artery/Aortic diameter ratio (PA:A)
- Left Atrial End Diastolic Volume (LAEDV)
- Left Atrial End Systolic Volume (LAESV)
- Left Atrial Ejection Fraction (LAEF)
- Left Ventricular End Systolic Volume Index (LVESVi)
- Right Ventricular End Systolic Volume Index (RVESVi)
- Pulsatility Index Aorta (PIAo)
- Pulmonary Artery Pulsatility Index (PAPi)

Other Efficacy Endpoints

- Plethysmography (Measured 1-2 hours post-dose)
 - Total airway resistance (Raw)
 - Specific airway conductance (sGaw)
 - Total lung capacity (TLC)
 - Residual volume (RV)
 - Functional residual capacity (FRC)
 - RV/total lung capacity (RV/TLC)
 - Diffusing capacity for carbon monoxide (D_LCO)
 - Inspiratory Capacity (IC)
- Impedance Cardiography (Measured at 30 and 60 minutes post-dose)
 - Change in right ventricular stroke volume
- Magnetic Resonance Imaging (Measured 2-3 hours post-dose)
 - Change in right ventricular ejection fraction (RVEF)
 - Change in left ventricular ejection fraction (LVEF)
 - Pulmonary arterial dispensability
 - Pulmonary Vascular Volume
 - Right Atrial End Diastolic Volume (RAEDV)
 - Right Atrial End Systolic Volume (RAESV)
 - Right Atrial Ejection Fraction (RAEF)
- Spirometry
 - Morning pre-dose trough FEV_1
 - Morning pre-dose trough IC
 - 1-hour post-dose FEV_1
 - 1-hour post-dose IC
 - Morning pre-dose trough and 1-hour post-dose FVC

Safety Endpoints:

- Adverse events (AEs)
- 12-lead electrocardiogram (ECG)
- Clinical laboratory testing
- Vital sign measurements

Statistical Methods:

Primary Efficacy Analysis:

A mixed model will be used to evaluate the difference between treatments in the change from baseline in right ventricular end diastolic volume indexed to body surface area (RVEDVi). Baseline will use the value from Visit 3 obtained prior to the first dosing of Treatment Period 1. The model will include adjustment for baseline, period, and treatment. Sequence will only be included in the model if found to be significant ($p < 0.10$). Subject will be treated as a random effect in order to model within subject correlation across the two

periods. Point estimates and 95% confidence intervals for the difference between GFF MDI and Placebo MDI will be produced.

Sample Size:

Based on a two-period, two-treatment crossover study comparing Breo[®] Ellipta[®] versus placebo after cardiac MRI, the within-subject SD for the change from baseline in RVEDVi was estimated to be 7.11 mL/m². Assuming that 90% of the randomized subjects will complete the trial, the study has approximately 90% probability to demonstrate a difference of 5.59 mL/m² in RVEDVi.

Safety Analyses:

Safety analyses will be based on the frequencies of adverse events (AEs).

Date of Protocol: 14 October 2015

Date of Protocol Amendment 01 (Version 2.0): 04 February 2016

Date of Protocol Amendment 02 (Version 3.0) 26 September 2016

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
BID	<i>bis in die</i> , Twice Daily
BP	Blood Pressure
BPM	Beats Per Minute
CAT	COPD Assessment Test
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
ECG	Electrocardiogram
eg	<i>Exempli gratia</i> , for example
FDA	Food and Drug Administration
FF MDI	Formoterol Fumarate Metered Dose Inhaler
FRC	Functional Residual Capacity
GCP	Good Clinical Practice
GFF MDI	Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler
GP MDI	Glycopyrronium Metered Dose Inhaler
HFA	Hydrofluoroalkane
HR	Heart Rate
IB	Investigator's Brochure
IC	Inspiratory Capacity
ICF	Informed Consent Form
ICG	Impedance Cardiography
ICS	Inhaled Corticosteroid
ie	<i>Id est</i> , that is
IRB	Institutional Review Board
ITT	Intention-to-treat
LABA	Long-acting Beta Agonist
LAEDV	Left Atrial End Diastolic Volume

LAEF	Left Atrial Ejection Fraction
LAESV	Left Atrial End Systolic Volume
LAMA	Long-acting Muscarinic Antagonist
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Volume
LVSV	Left Ventricular Stroke Volume
LVESVi	Left Ventricular End Systolic Volume Index
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MRI	Magnetic Resonance Imaging
Msec (ms)	Millisecond
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PFT	Pulmonary Function Test
PA:A	Pulmonary Artery/Aortic diameter ratio
PAPi	Pulmonary Artery Pulsatility Index
PIAo	Pulsatility Index Aorta
PVR	Pulmonary Vascular Resistance
PP	Per Protocol
PRN	<i>pro re nata</i> , As Needed
QD	<i>quaque die</i> , Once Daily
QTcF	QT corrected using Fridericia's formula ($QT/(RR^{1/3})$)
RAEDV	Right Atrial End Diastolic Volume
RAEF	Right Atrial Ejection Fraction
RAESV	Right Atrial End Systolic Volume
RV	Residual Volume
RVEDVi	Right Ventricular End Diastolic Volume Index
RVEF	Right Ventricular Ejection Fraction
RVESVi	Right Ventricular End Systolic Volume Index
SABA	Short-acting Beta Agonist
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SSRI	Selective Serotonin Reuptake Inhibitors
TLC	Total Lung Capacity
US	United States

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1 INTRODUCTION AND STUDY RATIONALE

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients. Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality worldwide and results in significant economic and social burden that is both substantial and increasing. Pharmacologic therapy in COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance [Global Initiative for Chronic Obstructive Lung Disease [GOLD, 2016]].

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are β_2 -agonists, anticholinergics, and methylxanthines used as monotherapy or in combination. Treatment with long-acting bronchodilators is more convenient and more effective at producing maintained symptom relief than treatment with short-acting bronchodilators.

Chronic obstructive pulmonary disease (COPD) is associated with resting hyperinflation as a result of expiratory flow obstruction. Although hyperinflation independently predicts exercise tolerance and mortality in COPD, pathophysiologic mechanisms to explain these findings are incompletely understood [Budweiser, 2013]. Cardiac phenotyping in COPD implicate a potential cardiac etiology for poor outcomes associated with hyperinflation. Severe emphysema is known to be associated with both decreased intrathoracic blood volume as well as reduced right ventricular (RV) size, suggesting hyperinflation and the associated increase in intrathoracic pressure may reduce RV volume through decreased RV preload [Jørgensen, 2007]. Gold-standard assessment of RV volume is performed using cardiac magnetic resonance imaging using RV end diastolic volume (RVEDV) [Lorenz, 1999]. In order to account for expected variances of RVEDV with body habitus, RVEDV is normalized to body surface area, referred to as RVEDV index (RVEDVi) [Chalal, 2012].

Treatment with combined long acting muscarinic antagonists (LAMA) and long-acting bronchodilators (LABA) can improve inspiratory capacity and reduce hyperinflation, potentially increasing pulmonary blood volume and therefore RVEDVi. Due to the Frank-Starling mechanism, decreasing RVEDVi will result in reduced RV stroke volume (SV) and cardiac output (CO), thereby resulting in multiple negative hemodynamic sequelae including decreased pulmonary perfusion, left ventricular (LV) filling, coronary perfusion, and ultimately LV forward flow.

The direct cardiac effects of LAMA and LABA therapy suggest the potential to reverse these negative hemodynamic phenomena in COPD. Preclinical data from healthy canines indicate that acute treatment with the muscarinic antagonist glycopyrrolate increases cardiac index [Jacobson, 1994]. In addition, administration of the long-acting β_2 agonist formoterol to explanted rat hearts increases left ventricular contractility [Watson, 2013]. Therefore, the improved outcomes in COPD associated with chronic LAMA/LABA therapy may be in part attributable to improved cardiac hemodynamics. Because improved LV forward flow should

parallel increases in LV preload and therefore RVEDVi, we propose to investigate the effect acute administration of combined Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI) on RVEDVi in patients with moderate to severe COPD with evidence of resting hyperinflation.

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, 2016].

Fifteen different doses of GFF MDI have been evaluated in sixteen studies conducted by Pearl. The GFF MDI doses that have been studied include the following dosing combinations: 115.2/38.4 µg, 57.6/9.6 µg, 36/9.6 µg, 28.8/9.6 µg, 28.8/7.2 µg, 18/9.6 µg, 14.4/9.6 µg, 9/9.6 µg, 7.2/9.6 µg, 4.6/9.6 µg, 3.7/9.6 µg, 2.4/9.6 µg, 2.0/9.6 µg, 1.2/9.6 µg, and 1.0/9.6 µg. Throughout this Phase IIb program, over 1100 subjects with COPD have been exposed to one or more doses of GFF MDI. GFF MDI has been evaluated in 3 Phase III clinical studies in patients with COPD, during the Phase III program over 1,000 subjects with COPD have been exposed to GFF MDI 18/9.6 µg. GFF MDI 18/9.6 µg was demonstrated to be safe and efficacious in the Phase III studies.

Currently, three fixed-dose combinations of a LABA and a LAMA are commercially available Anoro™ Ellipta® [umeclidinium and vilanterol] from GlaxoSmithKline, Utibron™ Neohaler® from Novartis, and Stiolto™ Respimat® from Boehringer Ingelheim. Combivent® [salbutamol sulfate and ipratropium bromide] from Boehringer Ingelheim is a short-acting fixed dose combination of a SABA and short acting muscarinic antagonist indicated for the treatment of COPD and is administered as two inhalations four times daily. Published studies [van Noord, 2005; van Noord, 2006; Vogelmeier, 2006] have shown that the complementary mechanisms of action of a LABA (formoterol fumarate) and a LAMA (tiotropium bromide) significantly improved bronchodilation in COPD subjects compared to the individual agents.

Pearl Therapeutics, Inc. (hereafter referred to as Pearl) has developed a combination product, Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (PT003, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler [MDI]; hereafter referred to as GFF MDI), as a maintenance bronchodilator treatment in subjects with COPD. Phase IIb studies were conducted which supported the dose selection of GFF MDI 14.4/9.6 µg BID for Phase III clinical studies, including this study.

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. GP

MDI has been evaluated in eight studies conducted by Pearl, including a single dose, single center, healthy volunteer study in Australia and seven multi-center studies in subjects with COPD conducted in the US, Australia, and New Zealand. This program has assessed the safety and efficacy of GP MDI across a wide range of doses from 115.2 µg down to 0.5 µg. Across these eight studies, approximately 350 subjects with mild 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 14.4 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. 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]. Studies in patients with COPD have demonstrated that the onset of action with formoterol fumarate is faster than with anticholinergic agents or salmeterol and similar to that of SABAs, such as albuterol, and that the duration of action is ≥ 12 hours [Berger, 2008]. Five large, placebo-controlled clinical studies of up to 12 months in duration in nearly 2500 patients demonstrated that formoterol fumarate is effective and well tolerated in patients with COPD [Dahl, 2001; Rossi, 2002; Albers, 2002; Campbell, 2005; Campbell, 2007].

Pearl 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. 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.

1.1 Study Rationale

The purpose of this study is to evaluate the effect of GFF MDI on Cardiovascular Hemodynamics following chronic dosing (7 days) in subjects with moderate to severe COPD.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To assess the effect of GFF MDI on cardiovascular hemodynamics following chronic dosing (7 days) in subjects with moderate to severe COPD

2.2 Secondary Objectives

- To assess the effect of GFF MDI on pulmonary hemodynamics following chronic dosing (7 days)
- To assess the effect of GFF MDI on lung function following chronic dosing (7 days)

2.3 Safety Objective

- To assess the safety of GFF MDI based on adverse events (AEs), and any clinically relevant findings from vital sign measurements, electrocardiograms (ECGs), and clinical laboratory evaluations

3 STUDY ENDPOINTS

All efficacy assessments are relative to pre-dose baseline obtained at or prior to Day 1. The first day of treatment in each Treatment Period is Day 1. Each Treatment Period is planned to be 7 days in duration occurring between the first and last dose which will correspond to 8 calendar days. Therefore, assessments collected on Day 8 will occur following 7 days of treatment.

3.1 Primary Efficacy Endpoint

- Right Ventricular End Diastolic Volume Index (RVEDVi) measured at 2-3 hours post-dose on Day 8

3.2 Secondary Efficacy Endpoints (Measured using MRI at 2-3 hours post-dose on Day 8 unless otherwise noted)

- Aortic left ventricular stroke volume [LVSV]
- Right Ventricular Stroke Volume (RVSV), phase contrast from pulmonic valve
- Pulmonary Artery Velocity
- Left Ventricular End Diastolic Volume Index (LVEDVi)
- Cardiac Output
- Morning pre-dose trough and post-dose Pulmonary Vascular Resistance (PVR) by ICG (Measured at 30 minutes and 60 minutes post-dose)
- Pulmonary artery/Aortic diameter ratio (PA:A)
- Left Atrial End Diastolic Volume (LAEDV)
- Left Atrial End Systolic Volume (LAESV)
- Left Atrial Ejection Fraction (LAEF)
- Left Ventricular End Systolic Volume Index (LVESVi)
- Right Ventricular End Systolic Volume Index (RVESVi)
- Pulsatility Index Aorta (PIAo)
- Pulmonary Artery Pulsatility Index (PAPi)

3.3 Other Efficacy Endpoints

- Plethysmography (Measured 1-2 hours post-dose)
 - Total airway resistance (Raw)
 - Specific airway conductance (sGaw)
 - Total lung capacity (TLC)
 - Residual volume (RV)

- Functional residual capacity (FRC)
- RV/total lung capacity (RV/TLC)
- Diffusing capacity for carbon monoxide (D_LCO)
- Inspiratory Capacity (IC)
- Impedance Cardiography (Measured 30 and 60 minutes post-dose)
 - Change in right ventricular stroke volume
- Magnetic Resonance Imaging (Measured 2-3 hours post-dose)
 - Change in right ventricular ejection fraction (RVEF)
 - Change in left ventricular ejection fraction (LVEF)
 - Pulmonary arterial dispensability
 - Pulmonary Vascular Volume
 - Right Atrial End Diastolic Volume (RAEDV)
 - Right Atrial End Systolic Volume (RAESV)
 - Right Atrial Ejection Fraction (RAEF)
- Spirometry
 - Morning pre-dose trough FEV_1
 - Morning pre-dose trough IC
 - 1-hour post-dose FEV_1
 - 1-hour post-dose IC
 - Morning pre-dose trough and 1-hour post-dose FVC

3.4 Safety Endpoints

- Adverse events (AEs)
- 12-lead electrocardiograms (ECGs)
- Clinical laboratory testing
- Vital sign measurements

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, single-center, chronic-dosing (7 days), two-period, two-treatment, crossover study to evaluate the treatment effect of GFF MDI compared to Placebo MDI on cardiovascular hemodynamics following chronic dosing (7 days) in subjects with moderate to severe COPD.

It is planned to randomize approximately 40 subjects to provide approximately 32 study completers.

All subjects will be administered GFF MDI and Placebo MDI in randomized order (see Figure 1). Enrollment into the active period of the study will be stratified by severity of disease such that half of the subjects will have moderate COPD and half will have severe COPD as categorized by post-bronchodilator FEV₁ ($\geq 50\%$ - $<65\%$ for moderate and 30% - $<50\%$ for severe). The entire study period is scheduled to take approximately 12 weeks for each individual subject. The study is anticipated to run for approximately 6 months and should not exceed 12 months.

Screening Period:

The Screening Period will be comprised of 2 study visits.

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, pregnancy test and any required documentation in order to determine eligibility for participation (i.e., inclusion/exclusion criteria). Subjects must meet spirometry criteria of an FEV₁/FVC ratio of <0.70 and FEV₁ of $<65\%$ predicted normal value 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 as described below. An ECG will also be conducted.

Subjects will undergo a Screening Period of 7 to 28 days in duration. During the Screening Period, subjects that are receiving an ICS/LABA will discontinue the ICS/LABA, but will continue an equivalent dose of the ICS component for the duration of the study.

Similarly, subjects treated with an ICS as part of their inhaled maintenance therapy will also be permitted to continue their ICS for the duration of the study.

All subjects will discontinue their previously prescribed inhaled bronchodilators and switch to Sponsor-provided Atrovent HFA administered four times daily (QID) as COPD maintenance therapy during the Screening Period and during the Washout Period of the study. All subjects will be provided with sponsor-provided Ventolin HFA (albuterol sulfate

Inhalation Aerosol) administered PRN as needed for control of symptoms throughout the study. At randomization subjects will discontinue Atrovent HFA, but will be permitted to use their ICS and sponsor- provided rescue albuterol.

At Visit 1 (Screening), subjects will be trained on and issued a Diary. Subjects will be instructed to collect practice data during the screening period (between Visit 1 and Visit 3). They are required to maintain a daily record of their study drug dosing, rescue medication use, and collection of COPD symptoms. Subjects that fail to demonstrate proper Diary compliance prior to Randomization (Visit 3) may not be enrolled to the study.

To allow for an adequate washout of previous maintenance medications Visit 2 will be scheduled a minimum of 7 days (at least 14 days if taking tiotropium) from Visit 1 (see Table 5-1 for washout period guidelines).

At Visit 2, reversibility to Ventolin (albuterol sulfate) HFA and Atrovent (ipratropium bromide) HFA will be evaluated (Refer to Section 7.1.1.2). The spirometry data obtained at Visit 2 will be used as an inclusion criterion (Refer to Section 5.1) and to characterize the population. Correspondingly, at Visit 2 a series of plethysmography maneuvers will be performed to assess total capacity and residual volume. In addition, impedance cardiography (ICG) will be performed to assess cardiac output. Subject Diary compliance will be reviewed, and the subject will be retrained, if appropriate (Refer to Section 7.1.6).

At Visit 2, subject's burden of disease will be assessed using the COPD Assessment Test (CAT).

Treatment Period:

After Visit 3 (Randomization), subjects that meet study inclusion criteria will be examined at Visit 4, Visit 5, and Visit 6. In total, each completed subject will attend 6 scheduled visits in this study for a maximum of 12 weeks. For the assessments scheduled at each of these visits, refer to the Schedule of Events (Table 8-1).

At Visit 3, all sponsor-provided Atrovent HFA provided during the screening period will be discontinued and collected by site personnel for accountability.

The Investigator will reevaluate the subject's study eligibility criteria as described at Visit 1. If a subject is assigned to GFF MDI or Placebo MDI, it will not be possible to differentiate between these treatments since they will appear to be identical in all aspects. Randomization will be stratified by COPD disease severity (moderate vs. severe) to ensure even distribution of treatment arms within each stratum.

Subjects will be required to take their blinded 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).

Pre-dose PFTs will be obtained at -60 and -30 minutes prior to dosing on Day 1 of each Treatment Period (Visits 3 and 5) (Refer to Section 7.1.1).

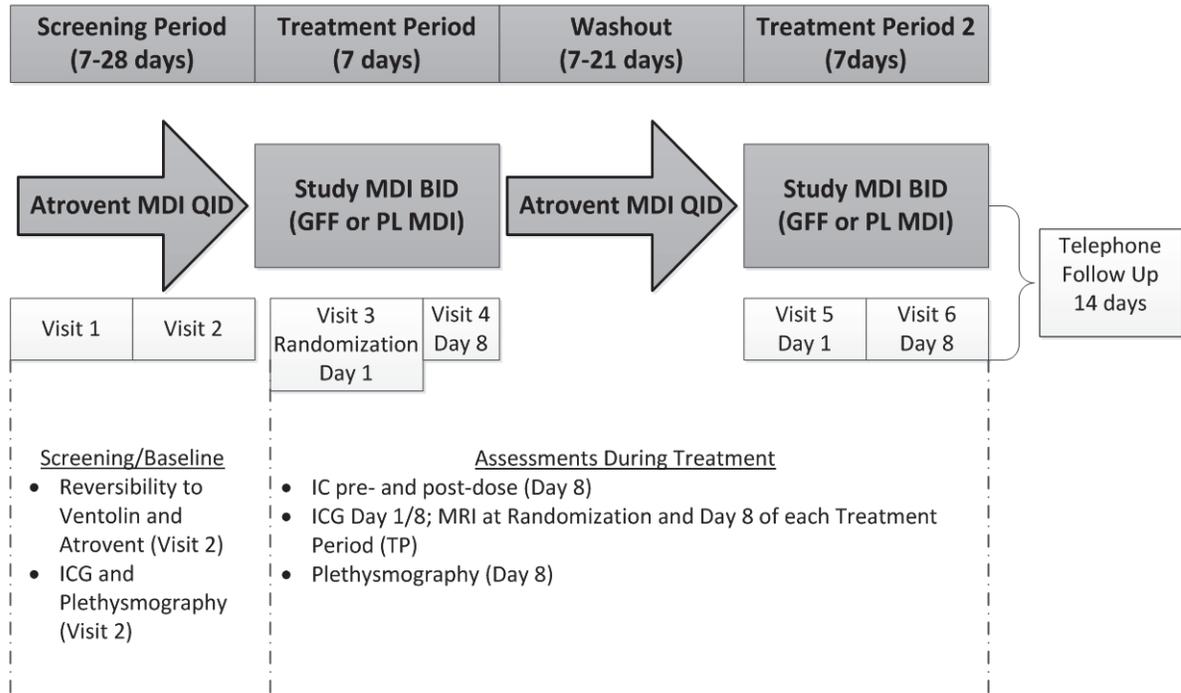
General Considerations for Treatment Visits 3 through Visit 6(in-clinic):

- At the start of each treatment visit, prior to the administration of study drug and performance of any study procedures, site personnel must confirm that the subject withheld all COPD medications (including randomized study medication, ICS and rescue medication, e.g., Ventolin HFA) for at least 6 hours by confirming the last time of dosing for all COPD medication(s).
 - **Note:** For subjects who inadvertently took COPD medication within 6 hours of the start of study procedures, the visit date must be rescheduled within the specified visit window as soon as it is practical.
 - **Note:** Before the in-clinic dose is administered, the site must confirm that the subject meets all protocol-specified requirements (e.g., FEV₁ baseline criteria; see Section 7.1.1.1).
- Protocol-adjusted ICS therapy as defined at Visit 1 (Screening) if any, should be continued and remain stable for the duration of the Study (refer to Section 5.4).
- 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) 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 approximately 11:00 AM and within 12 ± 2 hours of the prior at home evening dosing time.
- The in-clinic dosing time for study drug (GFF MDI or Placebo MDI) will be recorded as the time of administration of the second puff.
- 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 take their last dose the evening before the scheduled visit;
 - To bring their study medications and Subject Diary with them to the clinic and to withhold all COPD medications (including ICS and phosphodiesterase inhibitors) or for at least 6 hours prior to PFTs;
 - Refrain from ingesting xanthine (caffeine)-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.
- 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.
Note: If, during a Day 8 visit, a subject requires rescue Ventolin HFA and the MRI has not been obtained, the visit needs to be rescheduled.
- Subjects will complete all Visit 6 (Final Study Visit) assessments and will be scheduled for a post-study follow-up telephone call at least 14 days from Visit 6.

A Study Flow Diagram is displayed in Figure 1 below.

Figure 1. Study Flow Diagram



4.2 Rationale of Study Design

This study will assess the effect of GFF MDI 14.4/9.6 µg on cardiovascular hemodynamics following chronic dosing (7 days) in subjects with moderate to severe COPD compared to Placebo MDI.

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

Summaries of studies from the clinical development program supporting the dose selection and duration of treatment can be found in the introduction (Section 1) of this protocol.

5 STUDY POPULATION SELECTION, PRIOR AND CONCOMITANT MEDICATIONS 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 (i.e., physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal); or
 - Child bearing potential, has a negative serum pregnancy test at Visit 1, and agrees to one of the following acceptable contraceptive methods used consistently and correctly as outlined below (i.e., 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 6; or
 - 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. Evidence of lung hyperinflation; residual volume > 120% predicted normal value pre-bronchodilator at Visit 2.
5. 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.
6. Tobacco Use: Current or former smokers with a history of at least 10 pack-years of cigarette smoking. [Number of pack-years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years represent 10 pack-years)].
7. COPD Severity: Subjects with an established clinical history of COPD and severity defined as:

- At Visit 1, FEV₁/FVC ratio must be <0.70 and FEV₁ must be <65% predicted normal value calculated using NHANES III reference equations.
 - At Visit 2, post-bronchodilator FEV₁/FVC ratio of <0.70 and post-bronchodilator FEV₁ must be ≥30% to <65% predicted normal value, calculated using NHANES III reference equations.
 - At Visit 3, the average of the -60 min and -30 min pre-dose FEV₁ assessments must be <65% predicted normal value, calculated using NHANES III reference equations.
 - Symptomatic (CAT ≥10) at Screening (Visit 2).
8. Subject is willing and, in the opinion of the Investigator, able to adjust current COPD therapy as required by the protocol
 9. Screening clinical laboratory tests must be acceptable to the Investigator.
 10. Screening ECG must be acceptable to the Investigator.
 11. 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 are more than 6 months old at the time of Visit 1.
 12. 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 or conditions other than COPD which, in the opinion of the Investigator, may put the patient 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. Women who are pregnant or lactating, or are planning to become pregnant during the course of the study, or women of childbearing potential who are not using an acceptable method of contraception.
3. Respiratory
 - a) Asthma: Subjects, who in the opinion of the Investigator, have a current diagnosis of asthma. (Note: Subjects with a prior history of asthma are eligible if COPD is currently their primary diagnosis).
 - 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, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung disease, and uncontrolled sleep apnea (i.e., in the opinion of the Investigator severity of the disorder would impact the conduct of the study). 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 3).
- 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 3).
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 1a are eligible for enrollment providing the dose of oral steroids remains stable during the Screening Period (Visit 1 through Visit 3).
- 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 3).
- h) Other Respiratory tract infections that have not resolved at least 7 days prior to Screening.
- i) Spirometry Performance:
 - Acceptability: Subjects who cannot perform acceptable spirometry (i.e., meet ATS/ERS acceptability criteria)
 - Repeatability: Subjects who cannot perform technically acceptable spirometry with at least 3 acceptable flow-volume curves with 2 or more meeting ATS repeatability criteria for FEV₁ during at least 1 of the pre-bronchodilator assessments at Visit 2 (-30 minute) and at the post-bronchodilator assessment at Visit 2.
- j) Oxygen: Subjects receiving long term treatment with oxygen >4.0 liters/minute (L/min) at rest. While breathing supplemental oxygen, at rest, subjects should demonstrate an oxyhemoglobin saturation $\geq 89\%$. In order to be admitted to the trial subjects on LTOT have to be ambulatory and be able to attend clinic visits.
- k) Subject use of any non-invasive positive pressure ventilation device (NIPPV).
Note: Subjects using continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) for Sleep Apnea Syndrome are allowed in the study.
- l) Change in smoking status (i.e., 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 3).
- m) 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.
- n) 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 3)

4. Cardiac disease

- a) Subjects who have unstable ischemic heart disease, left ventricular failure, or documented myocardial infarction within 6 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:
 - Clinically significant conduction abnormalities [e.g., left bundle branch block, Wolff-Parkinson-White syndrome or evidence of second degree (Mobitz Type II) or third degree atrioventricular block (unless pacemaker or defibrillator has been inserted)].
 - Clinically significant arrhythmias (e.g., atrial fibrillation with irregular ventricular response, atrial flutter, ventricular tachycardia). Note: atrial fibrillation that has been clinically stable for at least 6 months and that has been appropriately treated with anticoagulation and controlled with a rate control strategy (i.e., 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.
 - QT interval corrected for heart rate (using Fridericia's formula; QTcF) ≥ 500 milliseconds (msec) in patients with QRS <120 msec and QTcF ≥ 530 msec in patients with QRS ≥ 120 msec
 - Ventricular rate <45 bpm.
 - 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.
 - Any other ECG abnormalities not listed above that in the opinion of the Investigator 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 4 weeks prior to Visit 1 or is altered at any point during the Screening Period (Visit 1 to Visit 3), or exceeds the maximum recommended dose.
- c) Subjects who have experienced a cerebrovascular accident within the 6 months prior to Visit 1

6. Renal

- a) Subjects with symptomatic prostatic hypertrophy that is clinically significant and not adequately controlled with appropriate therapy, in the opinion of the Investigator. Subjects with a trans-urethral resection of prostate 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 ≤ 30 mL/minute using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey, 2009) at Visit 1 and on repeat testing prior to Visit 2.

Note: Subjects with overactive bladder syndrome treated with oral anticholinergics that have been on treatment for at least one month are allowed in the Study.

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 (only in subjects clinically assessed by PI to be repeated). Note: Chronic stable hepatitis B and C is acceptable if the subject otherwise meets study entry criteria.
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 such as betaxolol, carteolol, levobunolol, metipranolol, and timolol).
11. Drug Allergy: Subjects who have a history of hypersensitivity to β_2 -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 Tables 5-1 to 5-4 in Section 5.4).
15. Subjects using any herbal inhalation and nebulizer products within 2 weeks prior to Visit 1 (Screening) and do not agree to stop using them during the study drug treatment.
16. Vaccinations: Subjects who received a live attenuated vaccination within 7 days prior to Visit 1 (Screening).
17. Non-compliance: Subjects unable to comply with study procedures, including meeting the compliance requirement of $>70\%$ subject completion of Diary

assessments in the last 7 days preceding the Randomization Visit (Visit 3) to be randomized in the study. Subjects who fail to demonstrate proper Diary compliance prior to randomization must be screen failed.

18. 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.
19. 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.
20. Subjects using prohibited medications (refer to Table 5-1)
21. 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 (i.e., studies that do not require change to medication or an additional intervention) is not exclusionary.
22. 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.
23. Previous Participation: Subjects who were previously enrolled in any previous PT001, PT003 or PT005 study conducted or sponsored by Pearl.

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 3 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 Case Report Form (CRF) page. Any additions, deletions, or changes in the dose of these medications while in the study should be entered on the CRF. Any current ongoing medications, including OTC drugs and herbal supplements, will be allowed provided they are not prohibited by the protocol (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 CRF with indication, dose, dose regimen, and dates of drug administration.

5.4.1 Prohibited COPD Medications and Required Washout Prior to Visit 2

Subjects that meet the screening criteria at Visit 1 that are being treated with any of the medications listed in Table 5-1 need to discontinue these medication and observe the minimum washout requirement before returning for Visit 2. 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 5-1. Prohibited COPD Medications and Required Washout Periods, Prior to Visit 2

Class of medication	Minimum Washout Period prior to Visit 2
LAMAs	Tiotropium: 14 days Acclidinium: 7 days Glycopyrronium: 7 days Umeclidinium: 7 days
Short-acting muscarinic antagonists (SAMA) ^a	6 hours
LABAs (inhaled)	7 days (indacaterol and olodaterol: 15 days)
Fixed-combinations of LABA/LAMA	7 days or the duration of the individual agents if longer
Fixed-combinations of LABA/ICS	7 days
Fixed-combinations of SABAs and SAMAs	6 hours
SABAs ^b	6 hours
ICS	7 days
Oral β -agonists	2 days
Theophylline (total daily dose >400 mg/day) ^c	7 days
Abbreviations: COPD=chronic obstructive pulmonary disease; HFA=hydrofluoroalkane; ICS=inhaled corticosteroid; LABA=long-acting β_2 -agonist; LAMA=long-acting muscarinic antagonist; SABA=short-acting β_2 -agonist; SAMA=short-acting muscarinic antagonist Note: Subjects taking roflumilast are allowed provided they have been on stable dose of therapy for at least 2 months prior to Randomization. a. Discontinue and use only sponsor provided Atrovent HFA during screening b. Discontinue and use only sponsor provided rescue Ventolin HFA throughout the study c. Theophylline (\leq 400 mg/day) is permitted provided the subject has been on a stable dose of therapy for at least 4 weeks prior to Randomization.	

Subjects who have received depot corticosteroids including intra-articular or intraocular corticosteroids require a 3-month washout prior to Screening (Visit 1). Subjects that have received oral, intravenous or intramuscular corticosteroids for any reason require a 6-week washout prior to Screening (Visit 1). Any subject that requires systemic corticosteroids during the Screening Period from Visit 1 up to but not including Visit 3 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 from Visit 1 up to but not including Visit 3.

During the Treatment Period (Visit 3 to Visit 6), 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 administered QID and sponsor-provided Ventolin HFA to be administered PRN 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 administered QID, and sponsor provided Ventolin HFA to be administered PRN 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, olodaterol) or currently marketed long- acting anti-muscarinic agent (LAMA) (tiotropium and aclidinium) administered alone or as a loose combination will have these medications discontinued and replaced with sponsor provided Atrovent HFA MDI administered four times per day (QID), and sponsor provided Ventolin HFA to be administered PRN for control of symptoms during the Screening Period.

The following respiratory medications are not permitted during this study (Table 5-2).

Table 5-2. 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 (e.g., zafirlukast, montelukast, and zilueton)	7 days
Cromoglycate	7 days
Nedocromil	7 days
Ketotifen ^a	7 days

^a 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 5-3). Each concomitant drug must be individually assessed against all exclusion

criteria. If in doubt, the Investigator should contact the Pearl Medical Monitor before randomizing a subject or allowing a new medication to be started:

Table 5-3. Non-COPD Medications Allowed Under Certain Condition

Medications allowed under certain conditions	Condition
SSRIs or SNRIs	Treatment regimen has been stable for at least 4 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 prior to Visit 2

Abbreviations: COPD=chronic obstructive pulmonary disease; SNRI=serotonin–norepinephrine reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors

Subjects requiring the medications presented in Table 5-4 are prohibited from participating in this study. 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, the subject should be discontinued from the study.

Table 5-4. 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 (e.g., 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

Illicit drugs or drugs of abuse will not be allowed from the start of Screening (Visit 1) to the end of Visit 6 or to whenever the 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, and the subject will be discontinued from the study. 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 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. 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 (i.e., stopping or re-starting smoking) may have an impact on the efficacy outcome measures. At all visits the subject will be asked about any recent change in their smoking status (i.e., whether a subject's status has changed from smoker to non-smoker or vice versa). Any change in smoking status during the Screening Period (Visit 1 to Visit 3) will result in a screen failure. Smoking status changes during the Treatment Period will be captured in the CRF, 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 cigarette smoking except for the calculation of pack-year history.

5.7 Reasons and Procedures for Early Termination from the Study

5.7.1 Reasons for Discontinuation

Subjects may be withdrawn from the study at any time at their own request, upon request of the Investigator, or by Pearl at any time or for any reason. If a subject is lost to follow up (i.e., fails to return for study visits), reasonable efforts must be made to contact the subject and complete study termination procedures. All subjects who discontinue the study because of AEs will be followed up at suitable intervals in order to evaluate the course of the AE and to ensure the reversibility or stabilization of the abnormality. All subjects who prematurely discontinue the study after Randomization, regardless of the cause, should undergo only 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 clinically relevant change from baseline as determined by the Investigator.
- Calculated QTcF intervals >500 msec, and have increased by 60 msec or more over baseline value obtained at Randomization (Visit 3).
- Hepatic impairment defined as abnormal liver function test of AST, ALT or total bilirubin ≥ 3 times upper limit of normal on repeat testing.

Subjects who suffer a moderate or severe COPD exacerbation will be discontinued from the study.

A COPD 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 days, is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication. 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
- Subjects who failed to meet FEV₁ baseline stability criteria may be discontinued at the investigators discretion (see Section 7.1.1.1)
- An Investigator may choose to discontinue a subject from study participation at any time or for any reason, with sufficient notice by the Investigator, as per the terms of the contract with Pearl. The reason for discontinuation will be documented in the source documents.
- Pearl 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, in a timeframe that is compatible with the subjects' well-being.

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

- Initiation of maintenance therapy with any prohibited medications (see Section 5.4).

- Initiation of maintenance therapy with a marketed LABA (e.g., salmeterol, formoterol, indacaterol, vilanterol, olodaterol) administered alone or in combination with an ICS or a marketed LAMA (e.g., tiotropium, aclidinium, umeclidinium, or glycopyrronium bromide [Seebri]).
- Note: Includes recently marketed LABA/LAMA (tiotropium/olodaterol [Stiolto™ Respimat®], umeclidinium/vilanterol [Anoro® Ellipta®], and indacaterol/glycopyrrolate [Utibron™ Neohaler®])

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 7.3.11).

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. Treatments will be blinded in terms of dose administered. The characteristics of the single GFF MDI dose that will be administered during the study are provided in Table 6-1.

An envelope-based randomization system will be used to assign blinded study medication to subjects. The site will receive two large portfolio envelopes aligned to the two subject stratification criteria, with one envelope containing subject randomization envelopes for subjects with Moderate COPD, and the other containing subject randomization envelopes for subjects with Severe COPD. Each large portfolio envelope contains a series of subject randomization envelopes, identified by a unique randomization number and organized in sequential order. Only subjects eligible for randomization will be assigned the next-in-sequence randomization envelope, drawn from the large portfolio envelope specific to the subject's stratification (Moderate or Severe COPD).

The subject randomization envelope contains two smaller envelopes, one marked Treatment Period 1 and the other marked Treatment Period 2. The Treatment Period 1 envelope contains a form which provides the blinded component IDs to be assigned to the subject for Visit 3 and Visit 4 (specific to blinded treatment assigned for Treatment Period 1). The form will also indicate a "Reserve" replacement component ID which will be kept at the site and will not be dispensed to the subject unless the subject requests the replacement component ID in the case of an emergency, and will return to the site to obtain the replacement medication. After the washout period from Treatment Period 1, the site would open the Treatment Period 2 envelope and follow the same process as for Treatment Period 1 and dispense component IDs aligned to the second treatment (blinded) independently at Visit 5 and Visit 6. A replacement component ID for Treatment Period 2 will also be provided, but will only be dispensed at the request of the subject in case of emergency. Twenty of the planned 40 subjects will be included in each treatment sequence. Should all subjects complete the study, the design is balanced for period and first-order carryover effects.

For each subject, single dose administration of study drug during each of the two Treatment Periods should occur at approximately the same time of day.

6.2 Product Descriptions and Primary Packaging and Labeling Information

Investigational materials will be packaged by Pearl as summarized in Table 6-1. Atrovent (ipratropium bromide) HFA and Ventolin HFA supplies will be supplied as open-label MDIs.

Table 6-1. Product Descriptions

Product Name & Dosage	Product Strength	Dose Form/Fill Count	Administration
Study Medications			
GFF MDI (PT003) 14.4/9.6 µg ex-actuator	7.2/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
Open-label Products			
Albuterol sulfate inhalation aerosol 90 µg ^a ex-actuator	Ventolin [®] HFA HFA inhalation aerosol. Albuterol sulfate inhalation aerosol. Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece	MDI/ 60 or 200 actuations	Taken as directed Supplies are open- label
Ipratropium bromide inhalation aerosol 34 µg ^b per ex-actuator	Atrovent [®] HFA. Ipratropium bromide HFA. Each inhalation contains 17 µg per actuation	MDI/ 200 actuations	Taken as 2 inhalations QID Supplies are open- label
Placebo			
Placebo MDI ^c	Formulation does not contain active ingredient	MDI/ 120 inhalations	Taken as 2 inhalations BID
Abbreviations: BID=twice daily; GFF MDI= Glycopyrronium and Formoterol Fumarate 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. a. The Sponsor will provide Ventolin HFA for reversibility testing during Screening and as rescue medication throughout the study. b. The Sponsor will provide Atrovent HFA for reversibility testing during Screening and as COPD maintenance medication during the Screening Period and Washout Period. c. Placebo MDI will be used for training purposes and also administered as a randomized treatment. All placebos are created by Pearl in the image of the active test product.			

6.3 Primary Packaging and Labeling Information

Investigational materials will be packaged by the Sponsor. Atrovent HFA and Ventolin HFA 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.

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

Lot # (Packaging Lot Trace ID) Space for entry of screening # Component ID # Space for entry of randomization # Fill Count & Dosage Form Visit # (Space for Entry of Interval ID)	Storage Conditions Protocol # Country regulatory requirements Sponsor address Translation Key
--	--

ID = identification; # = number

6.4 Secondary Packaging and Labeling Information

Blinded investigational drug and open-label (Atrovent HFA, Ventolin HFA) supplies will be packaged in individual boxes as outlined in Table 6-2. Box configuration is subject to change as a result of packaging constraints.

Table 6-2. Description of Boxes

Drug Supplies	Individual Box Contents
Blinded	1 MDI
Atrovent HFA	1 MDI
Ventolin HFA	1 MDI

Abbreviations: HFA=hydrofluoroalkane; MDI=metered dose inhaler

Each box will be labeled with a 2-part label printed with black ink and may include the following text:

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

6.5 Emergency Unblinding of Treatment Assignment

Pearl will provide disclosure envelopes with the clinical supplies for the purpose of unblinding. Emergency unblinding envelopes (bright red in color) which contain the unblinded treatment sequence associated with each randomization number, are also provided and to be stored in a separate, secure location accessible by the Site Investigator. 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 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 should be stored below 25° C (77° F) in a dry place. Excursions permitted up to 30° C (86° F).

Ventolin[®] HFA supplies: Store between 15°C and 25°C (59°F 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°C to 30°C (59°F to 86°F) [Refer to United States Pharmacopoeia 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 (49°C) 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 accordance with 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 and Placebo MDI

Refer to Appendix 3 for instructions on the administration and cleaning of GFF MDI and Placebo MDI.

6.7.2 Atrovent[®] HFA (Ipratropium Bromide)

Refer to Appendix 4 for the manufacturer's instructions on the administration of Atrovent[®] HFA.

6.7.3 Ventolin HFA[®] (Albuterol Sulfate)

Refer to Appendix 5 for the manufacturer's instructions on the administration of Ventolin HFA.

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, the amount dispensed to and returned by the subject, and the amount remaining at the conclusion of the study. Study medication should be handled in accordance with Good Pharmacy Practices (i.e., gloves should always be worn by study personnel if directly handling tablets or capsules that are returned). The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned as directed by Pearl.

Sites should check with the Pearl 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 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 using the Product Complaints Form provided in the site's regulatory binder. Pearl will contact the site to evaluate the nature of the complaint and determine what further action is needed

7 STUDY PROCEDURES

A time and events schedule is provided in Table 8-1. Detailed schedules for pre- and post-dose procedures to be performed at Screening and at each treatment visit are provided in Table 8-2 and Table 8-3, respectively.

Every effort should be made to conduct study assessments at approximately the same time for a given subject across each treatment period.

All pre-dose assessments for Visit 3 and Visit 5 are recommended to be conducted in the following order: vital signs, clinical laboratory assessments, ICG, ECG, MRI (Visit 3 only) and spirometry (IC, when conducted should be obtained prior to all other spirometry assessments).

All pre-dose assessments for Visit 4 and Visit 6 are recommended to be conducted in the following order: vital signs, clinical laboratory assessments, ICG, plethysmography, and spirometry (IC, when conducted should be obtained prior to all other spirometry assessments).

All post-dose assessments for Visit 4 and Visit 6 are recommended to be conducted in the following order: ICG, ECG, spirometry (IC, when conducted should be obtained prior to all other spirometry assessments), plethysmography, and MRI.

7.1 Efficacy Assessments

7.1.1 Pulmonary Function Tests (Spirometry)

Forced expiratory spirometry for derivation of FEV₁ and FVC, 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 e.g., at <2 L/sec, 4-6 L/sec and >8 L/sec with temperature and barometric pressure correction. The calibration syringe must meet ATS specifications and must not be used beyond the expiry date. Required accuracy is ± 3%, i.e., 3.09 L to 2.91 L (ATS/ERS). The results will be printed and maintained in a calibration log, which will be monitored for compliance during the monitoring visits (Refer to Appendix 2, Spirometry Assessment Criteria).

All PFTs including FEV₁ and FVC as defined in ATS/ERS guidelines will be performed in accordance with ATS criteria (Miller, 2005).

To standardize spirometry, the site will use the identical spirometry systems across all subjects and study visits. Site will document in their site study file and provide the sponsor a listing the manufacture, make and model of spirometry equipment used for this study. Site will be responsible for maintaining calibration and maintenance records of all spirometry equipment used for this study and provide these records to the sponsor upon request.

Note: Spirometry must meet both acceptability and repeatability criteria (Refer to exclusion criterion 3i).

Spirometry assessments will be obtained at:

- Visit 1
- At Visit 2, pre-bronchodilator spirometry assessments will be conducted 30 minutes prior to Ventolin HFA and Atrovent HFA administration and at 30 minutes post Ventolin HFA and Atrovent HFA administration. At Visits 3 and 5 (Day 1 of each Treatment Period), spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration.

Note: The mean of the -60 minutes and -30 minutes pre-dose spirometry assessments conducted at Visit 3 and Visit 5 will be used to establish baseline FEV₁ and FVC.

- At Visits 4 and 6 (Day 8 of each Treatment Period), spirometry will be conducted 30 minutes prior to study drug administration and at 1 hour post study drug administration.

7.1.1.1 FEV₁ Baseline Stability Criteria

It is important to ensure that the baseline FEV₁ is stable and reflective of the subject's COPD severity prior to continuation in the second treatment period. As such, the baseline FEV₁ at Visit 5 must be within $\pm 20\%$ or 200 mL of the pre-dose FEV₁ obtained at the Randomization Visit (Visit 3).

At Visit 5, if the pre-dose FEV₁ average is outside of the $\pm 20\%$ or 200 mL range, but the 30-minute pre-dose assessment is within $\pm 22\%$ or 220 mL, then another assessment may be conducted 30 minutes later. If the last two assessments meet the reproducibility requirements (i.e., within $\pm 20\%$ 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 baseline FEV₁ is not within $\pm 20\%$ or 200 mL, the visit may be rescheduled (for a maximum of three attempts) at the Investigator's discretion (e.g., within 1 week), or the subject may be discontinued.

7.1.1.2 Characterization of Reversibility

Reversibility is defined as $\geq 12\%$ and ≥ 200 mL improvement in baseline FEV₁ following administration of four puffs of Ventolin HFA followed by four puffs of Atrovent HFA. Reversibility to Ventolin HFA and Atrovent HFA will be evaluated at Screening (Visit 2) to characterize the subject population. The procedure is as follows:

- Reversibility testing to Ventolin HFA and Atrovent HFA (Visit 2 Only):
 - Perform pre-bronchodilator PFTs -30 minutes prior to administration of Ventolin HFA and Atrovent HFA
 - Administer 4 puffs of Ventolin HFA followed by four puffs of Atrovent HFA

- Perform post-bronchodilator PFT 30 minutes after the administration of Ventolin HFA and Atrovent HFA

Reversibility will be a comparison of the average best FEV₁ effort obtained -30 min pre-bronchodilator to the best FEV₁ effort obtained at 30 minutes post- bronchodilator. A subject is determined to be reversible to Ventolin HFA and Atrovent HFA, if the improvement in FEV₁ approximately 30 minutes following administration of 4 puffs of Ventolin HFA and Atrovent HFA is $\geq 12\%$ and ≥ 200 mL.

7.1.2 Inspiratory Capacity (IC)

On all test days throughout the conduct of the study, IC assessments will be conducted at the same time points, and just prior to all other spirometry assessments. The average of the two assessments on Day 1 of each Treatment Period will be used to establish the baseline IC. Specifically, IC data will be analyzed for secondary and other assessments.

- On Day 1 of each Treatment Period (Visits 3 and 5): IC assessments will only be conducted 30 minutes prior to study drug administration.
- On Day 8 of each Treatment Period (Visits 4 and 6): IC assessments will be conducted 30 minutes prior to study drug administration and at 1 hour post study drug administration.

All subjects will be instructed on the performance of the IC maneuver. Subjects must be tested in the seated position wearing a nose clip with no air leaks between the mouth and mouthpiece. Subjects should be relaxed with shoulders down and asked to breathe regularly for several breaths until the end-expiratory lung volume is stable (this usually requires at least five tidal maneuvers). They are then urged to take a deep breath to total lung capacity with no hesitation. From at least three acceptable trials, the two largest IC measurements should agree within 5% or 200 mL, both of these IC values will be captured and analyzed.

7.1.3 Plethysmography

Plethysmography is the measurement of changes in the volume of organs or other body parts, particularly those changes resulting from blood flow. It has been demonstrated be a reliable lung tests that assess lung diseases, which are often associated with a decrease in total lung capacity (TLC). Plethysmographic measurements are based on defining the relationship between the pressure and volume of a gas. The test also follows the course of a disease and its response to treatment, measures your resistance to airflow and measures your response to bronchodilator medications.

Assessments will be performed using a Plethysmograph. To standardize plethysmographic measurements, the site will use the identical plethysmography systems across all subjects and study visits. Site will document in their site study file and provide the sponsor a listing the manufacture, make and model of plethysmography equipment used for this study. Site will be responsible for maintaining calibration and maintenance records of all plethysmography equipment used for this study and provide these records to the sponsor upon request.

Measurements will be classified performed as follows:

- Total airway resistance (Raw)
 - Specific airway conductance (sGaw)
 - Total lung capacity (TLC)
 - Residual volume (RV)
 - Functional residual capacity (FRC)
 - RV/total lung capacity (RV/TLC)
 - Diffusing capacity for carbon monoxide (D_LCO)
- At Visit 2, pre-bronchodilator plethysmography assessments will be conducted. Thereafter, four puffs of Ventolin HFA will be administered followed immediately by administration of four puffs of Atrovent HFA. Post-bronchodilator plethysmography assessments will be obtained 30 to 60 minutes after administration of both Ventolin HFA and Atrovent HFA.
 - On Day 8 of each Treatment Period (Visits 4 and 6): plethysmography assessments will be conducted 60 minutes prior to study drug administration and at 1-2 hours post study drug administration.

7.1.4 Magnetic Resonance Imaging (MRI)

Assessments will be performed using standard MRI equipment. To standardize MRI, the site will use the identical MRI systems across all subjects and study visits. Site will document in their site study file and provide the sponsor a listing the manufacture, make and model of spirometry equipment used for this study. Site will be responsible for maintaining calibration and maintenance records of all MRI equipment used for this study and provide these records to the sponsor upon request. Subjects using oxygen should continue use of oxygen at the same flow (L/min) they normally use while the MRI is being performed.

Assessments will be as follows:

- Right Ventricular Stroke Volume (RVSV), phase contrast from pulmonic valve
 - Pulmonary artery velocity
 - Pulmonary vascular volume
 - Right Ventricular End Diastolic Volume (RVEDV)
 - Left Ventricular End Diastolic Volume (LVEDV)
 - Cardiac output
 - Pulmonary vascular resistance (PVR) by ICG
 - Pulmonary artery/Aortic diameter ratio (PA:A)
- At Visit 3 only (Randomization), MRI assessments will be conducted on the same day prior to study drug administration
 - On Day 8 of each Treatment Period (Visits 4 and 6): MRI assessments will be conducted 2-3 hours post study drug administration

7.1.5 Impedance Cardiography (ICG)

Assessments will be performed using standard ICG equipment. To standardize ICG, the site will use the identical ICG systems across all subjects and study visits. Site will document in their site study file and provide the sponsor a listing the manufacture, make and model of ICG equipment used for this study. Site will be responsible for maintaining calibration and maintenance records of all ICG equipment used for this study and provide these records to the sponsor upon request.

Assessments will be as follows:

- Morning pre-dose trough and each post-dose time point for PVC
 - PVR
 - Change to right ventricular stroke volume
- At Visit 2, ICG assessments will be conducted prior to administration of Ventolin HFA and Atrovent HFA
 - On Day 1 of each Treatment Period (Visits 3 and 5), ICG assessments will be conducted prior to study drug administration
 - On Day 8 of each Treatment Period (Visits 4 and 6) ICG assessment will be conducted prior to study drug administration, 30 minutes and 1 hour post study drug administration

7.1.6 Subject Diary Data Collection

Subjects will be provided with a Diary to be completed BID to record their study drug dosing, and rescue medication use.

- Starting at Screening (Visit 1) and for the duration of the study, subjects will be issued and trained on diary collection. They will be asked to maintain a daily record of their study drug dosing, and rescue medication use

Site personnel will review the Diary entries during the Screening Period to assess the subject's compliance and understanding of how to use the Diary to maintain a daily record of their study drug dosing, and rescue medication use

- At the Randomization Visit (Visit 3), subjects should meet the compliance requirement of $\geq 70\%$ subject completion of Diary assessments in the last 7 days preceding the Randomization Visit to be randomized in the study. Subjects who fail to demonstrate proper Diary compliance prior to Randomization must be screen failed.

Note: In-clinic dosing times will be documented in the source by the site staff and will not be entered by subjects into their Diary.

- At all treatment visits (Visits 3 to 5) site personnel must review the Diary prior to dosing study drug in the clinic Table 8-1)

The patient is to return the completed diary at each scheduled visit. The study coordinator will be responsible for reviewing the diary for completeness and accuracy with the patient. All fields should be completed by the patient. The patient will sign (initial) and date each page of the diary on the day it was completed and the study coordinator will initial and date each diary page at the site visit when the diary is returned to validate the authenticity of the entries. If discrepancies or omissions of data are observed at this review, the patient, not the study coordinator, should make the corrections. The patient should draw a single line through the error and initial and date all corrections. The patient should make all entries in the diary in blue or black ink.

Furthermore, in conjunction with review of the diary, the patient will be prompted by the study coordinator about missed doses of study medication and additional COPD medication. The patient should be instructed to record this information in the diary. Missing data from >24 hours prior to the site visit should be left blank. Subjects should be instructed to record the time and doses of study medication and rescue medication in hours and minutes a.m. or p.m., not in 24-hour clock time. Study sites will enter the Diary information into the eCRF.

7.1.7 Rescue Ventolin HFA Use

The subject will record the total number of puffs of rescue Ventolin HFA used in the Diary on a PRN basis. The number of puffs of rescue Ventolin HFA to be recorded is the number of actuations of the canister. For example, when rescue Ventolin HFA is required and two actuations are inhaled, this should be recorded as two puffs. In the event the subject requires four actuations, this should be recorded as four puffs. Subjects requiring more than eight puffs per day on three or more consecutive days with worsening symptoms should contact the site.

7.1.8 Medication Compliance

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

7.1.9 Chronic Obstructive Pulmonary Disease Assessment Test (CAT)

The CAT is a self-administered questionnaire designed to assess the condition of subjects and overall impact of COPD [Jones, 2009]. 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 Modified Medical Research Council Dyspnea Scale, SGRQ, and the 6-minute walk test.

Subjects will complete the CAT (Refer to Appendix 6) at Visit 2. The CAT score will describe the burden and symptomatic impact of COPD in subjects enrolled in the Study and will be used to determine subject eligibility to participate in the study at Visit 2.

7.2 Safety Assessments

The safety assessments include AEs, vital sign measurements, ECGs, and clinical laboratory testing.

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 3)

- 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 6 (Final Visit) or Treatment Discontinuation/Withdrawal 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
- Height assessed in ordinary indoor clothing with shoes removed will be recorded at Visit 1 (Screening) only
- Weight assessed in ordinary indoor clothing with shoes removed will be recorded at Visit 1, Visit 3, Visit 4, Visit 5, and Visit 6

7.2.2 Vital Sign Measurements

Heart rate and systolic and diastolic blood pressure, and oral and/or tympanic temperature ('vital signs') will be assessed as outlined below; assessments may be obtained in a supine position at all times.

- At Visit 1 and the Treatment Discontinuation/Withdrawal Visit, if applicable, a single vital sign assessment will be obtained
- At all visits (Visit 1 through Visit 6) a single vital sign assessment will be obtained prior to study drug administration and following the completion of the last assessment of the visit if clinically indicated.
- Temperature will be obtained at Screening (Visit 1), 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

Assessments will be performed using standard ECG equipment. The Principal Investigator (PI) and study staff responsible for performing ECGs will receive standardized training at the site initiation visit. Study personnel are required to demonstrate proficiency in performance abilities and the use of the equipment.

Each test should be labeled with the study number, patient initials, subject number, date, and kept in the source documents at the study site.

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 > 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 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 Medical Monitor must be contacted immediately.

All ECG assessments should occur prior to spirometry assessments.

- A single 12-Lead ECG will be obtained at Visit 1 (Screening) and the Treatment Discontinuation/Withdrawal Visit, if applicable
- Visit 3 only (Randomization), 12-Lead ECGs will be obtained twice at least five minutes apart prior to study drug administration
- At Visit 5, a 12-Lead ECG will be obtained once prior to study drug administration
- At Visit 4 and Visit 6, a 12-Lead ECG will be obtained at 1 hour after study drug administration

The ECG parameters that will be assessed include heart rate, PR interval, QRS axis, QRS interval, and QT/QTcF interval.

7.2.4 Clinical Laboratory Tests

Clinical safety laboratory tests, hematology (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count), and clinical chemistry (comprehensive metabolic panel) will be analyzed by the site's local 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 the Treatment Discontinuation/Withdrawal Visit, if applicable

- At Visit 3 (Randomization), Visit 4, Visit 5, and Visit 6 prior to study drug administration

The site’s local laboratory will supply procedures for the preparation and collections of these samples refer to Table 7-1 below.

Table 7-1 Clinical Laboratory Tests

Hematology	
Hemoglobin	Mean corpuscular hemoglobin
Hematocrit	Mean corpuscular hemoglobin concentration
White blood cell count with differential	Mean corpuscular volume
Red blood cell count	Eosinophils
Platelet count	
Clinical Blood Chemistry	
Liver Enzyme and Other Liver Function Tests	Other Clinical Blood Chemistry
Alanine aminotransferase ^a	Albumin ^a
Aspartate aminotransferase ^a	Blood Urea Nitrogen (BUN) ^a
Alkaline phosphatase ^a	Calcium ^a
Bilirubin, total ^a	Chloride ^a
Gamma-glutamyl transferase ^a	Cholesterol ^a
	Bicarbonate
	Creatinine ^a
	Glucose ^a
	Magnesium ^a
	Potassium ^a
	Phosphate ^a
	Protein, total ^a
	Sodium ^a
	Triglycerides ^a
Other Tests	
Pregnancy test (women of childbearing potential only): Serum hCG at Visits 1 and 6, and the Treatment Discontinuation/Withdrawal Visit, if applicable and urine hCG at Visits 3, and 5.	
Creatinine clearance will be estimated by the CKD-EPI published formula.	
Abbreviations: CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration Equation (according to National Kidney Disease Education Program); hCG=human chorionic gonadotropin	
^a Parameters included in the Comprehensive Metabolic Panel.	

7.2.4.1 Pregnancy Test

The pregnancy test should be performed prior to ECG, spirometry, or blood collection for laboratory assessments.

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 prior to dosing at Visit 6 and the Treatment Discontinuation/Withdrawal Visit, if applicable
- A urine pregnancy test will be performed at Visits 3 and Visit 5

If any of these tests are positive, the subject must be discontinued from the study.

7.3 Adverse Events

7.3.1 Performing Adverse Events Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's CRF and on the AE Reporting Form. If the AE is "alarming," the Investigator must report the AE immediately to Pearl. In addition, certain AEs (as described in Section 7.3.9) are classified as "serious" and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as an SAE to Pearl or its designee.

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

7.3.2 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 adverse event 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 leads to the procedure are an AE (e.g., bleeding esophageal varices, dental caries).
- Overdose of either study drug or concurrent medication without any clinical signs or symptoms.
- Non-clinically significant abnormal laboratory values. (If accompanied by signs/symptoms, the signs or symptoms are considered an AE).

7.3.3 Pre-Randomization Adverse Events

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

7.3.4 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.

7.3.5 Relationship

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

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

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

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

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

7.3.6 Chronic Obstructive Pulmonary Disease Exacerbations

All COPD exacerbations must be captured using the COPD Exacerbation eCRF. COPD exacerbations of any severity will be considered expected study endpoints and will not be reported as adverse events (AEs) unless considered a serious AE (SAE).

Exacerbation(s) of COPD is expected to occur as a progression of disease despite standardized drug treatment, or treatment(s) with combination therapies. As a result, the Sponsor has classified this event as a protocol specified criteria expected event. Any individual case safety reports received related to exacerbation of COPD will not be submitted on an expedited basis as a Suspected Unexpected Serious Adverse Reaction (SUSAR) unless otherwise required as per the Sponsor's medical assessment.

7.3.7 Adverse Events of Special Interest

Paradoxical bronchospasm may occur following inhalation from an MDI.

Monitoring for paradoxical bronchospasm will occur at each visit during the Treatment Period (Visits 4 through 6). In this study, paradoxical bronchospasm is defined as a reduction in FEV₁ of >20% from test day baseline (i.e., the mean FEV₁ values obtained 60 and 30 minutes prior to study drug administration) with associated symptoms of wheezing, shortness of breath, or cough. All AEs and SAEs will be recorded, as appropriate.

7.3.8 Clinical Laboratory Adverse Events

Many laboratory abnormalities observed during the course of a study will be included under a reported AE describing a clinical syndrome (e.g., elevated blood urea nitrogen and creatinine in the setting of an AE of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). However, when an isolated laboratory abnormality is considered clinically significant by the Investigator, it must be reported as an AE.

Criteria for a "clinically significant" laboratory abnormality are:

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

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

7.3.9 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 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 adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of the Investigator or Sponsor, its occurrence places the subject or subjects 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 AE or suspected adverse reaction is considered unexpected if it is not listed in the current Investigator Brochure (IB) or is not listed at the specificity or severity that has been observed.

7.3.9.1 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 Pharmacovigilance or designee. All SAEs must be reported to Pearl no later than 24 hours after the Investigator recognizes/classifies the event as a serious adverse event. At a minimum, a description of the event and the Investigator’s judgment of causality must be provided at the time of the initial report using the appropriate form (e.g., SAE Report Form). After the initial report, as necessary, the Investigator must provide any additional information on the SAE to Pearl Pharmacovigilance or designee within two

working days after he/she receives that information. This follow-up information may include copies of hospital records, case reports, and autopsy reports, and other pertinent documents.

Post-study SAEs occurring up to 14 days following the last dose of study drug must be reported to Pearl Pharmacovigilance as described in Section 7.3.9.3.

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

7.3.9.2 Supplemental Investigations of SAEs

The Investigator and supporting personnel responsible for subject care should discuss with the Pearl Medical Monitor or designee any need for supplemental investigations of SAEs. The results of these additional assessments conducted must be reported to Pearl. 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.

7.3.9.3 Post-Study Follow-Up of Adverse Events

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. Pearl retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

7.3.9.4 Notification of Post-Study Serious Adverse Events

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

7.3.9.5 Investigational Research Board/Independent Ethics Committee Notification of Serious Adverse Events

The Investigator is responsible for promptly notifying her/his Institutional Review 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. Documentation of the submission to the IRB/IEC must be retained for each safety report. The Investigator is also responsible for notifying Pearl if their IRB/IEC requires revisions to the informed consent form or other measures based on its review of an SAE report.

7.3.9.6 Health Authority Safety Reports

Pearl 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 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-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.

7.3.10 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 and Primary Packaging and Labeling Information) 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 or designee. The Investigator should refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug(s) being used in this study. Such document may include, but not be limited to, the Investigator's brochure for GFF MDI.

7.3.11 Pregnancy

To ensure subject safety, each pregnancy in a female subject from Visit 1 (Screening) until study completion must be reported to Pearl 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 Paper Pregnancy Form and reported by the Investigator to Pearl Pharmacovigilance or designee. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Pearl study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.3.12 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 corticosteroids should be documented.

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.

7.4 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.

Pearl 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, 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 8-1. Tables 8-2 and 8-3 present details about timed activities conducted pre and post-dose at Visits 1 through 6.

Table 8.1 Schedule of Events

Procedures	Screening ^a		Treatment Period				Follow-Up/ Final
	Visit 1	Visit 2	Visit 3 (Day 1)	Visit 4 (Day 8)	Visit 5 (Day 1)	Visit 6 (Day 8)	
Study Day^a	-28 to -1 ^a		1 ^a	8±2 ^a	1 ^a	8±2 ^a	14±2 ^a
Informed Consent	X						
Review Inclusion/Exclusion Criteria	X		X				
Verify Continued Eligibility		X		X	X	X	
Reversibility to Ventolin and Atrovent HFA (including FEV ₁ and FVC) ^b		X					
Demographics & Medical/Surgical History	X	X					
COPD Assessment Test (CAT)		X					
Prior/Concomitant Medications ^c	X	X	X	X	X	X	X
Spirometry (including FEV ₁ and FVC) ^b	X	X	X	X	X	X	
Inspiratory Capacity (IC) ^b			X	X	X	X	
Plethysmography ^b		X		X		X	
Magnetic Resonance Imaging (MRI) ^b			X	X		X	
Impedance Cardiography (ICG) ^b		X	X	X	X	X	
Physical Examination ^b	X						
Vital Signs ^b	X	X	X	X	X	X	
12-Lead ECG ^b	X		X	X	X	X	
Serum Pregnancy Test ^b	X					X	
Urine Pregnancy Test ^b			X		X		
Clinical Laboratory Testing ^b	X		X	X	X	X	
Adjust COPD Medications ^d	X	X				X	
COPD Exacerbations and Adverse Events	X	X	X	X	X	X	X
Inhalation Device Training	X		X	X	X	X	
Study Drug Administration ^e			X	X	X	X	
Dispense Subject Diary	X		X		X		
Collect/Review Subject Diary		X	X	X	X		
Study Drug Dispensing			X	X	X	X	
Study Drug Collection			X	X	X	X	

- a Screening period of at least 14 days and up to 28 days. Subjects are to return to the clinic within 7 days following initiation of each treatment arm. There must also be at least 7 days (not to exceed 21 days) between Visits 4 and 5 to allow for appropriate washout of study drug. The indicated Study Days are estimates calculated based on a 7-day treatment period and a 7-day washout period.
- b Refer to Section 7 for specific assessments and specific time points to be performed at each treatment visit.
- c At all visits beyond Screening, note time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, visit should be rescheduled).
- d At Screening, stop prohibited COPD medications and change COPD medications as specified in protocol Section 7 (i.e., Sponsor-provided Atrovent HFA with or without ICS). At the end of the Visit 6, return subject to pre-study or other appropriate inhaled maintenance COPD medications.
- e At the start of each treatment visit, subject must withhold all COPD medications, including study medication, rescue medications (Albuterol) and ICS for at least 6 hours prior to start of test day procedures

Table 8.2 Timed Assessments at Screening Visit 1 and Visit 2

Clinical Variable ^a	Visit 1 (Screening)				Visit 2 (Screening)					
	Pre-dosing		Post-dosing		Pre-dosing		Post-dosing			
	-60 min	-30 min	30 min	1 hr	2hr	-60 min	-30 min	30 min	1 hr	2 hr
Review Diary Data						X ^b				
Vital Signs ^c	X ^b					X ^b				
COPD Assessment Test (CAT) ^b						X ^b				
Clinical Laboratory Testing ^c	X ^b									
12- Lead ECG ^c	X ^b									
Impedance Cardiography (ICG) ^c						X ^b				
Spirometry (FEV ₁ , FVC) ^c	X ^b						X	X		
Plethysmography ^c						X ^b		X	X	
Run-in Medication Dispensing ^d	X ^d									

- In-clinic dosing time is recorded as time of the second puff. Safety assessments (vital signs and ECG) should be started approximately 5 to 10 minutes ahead of the specified time point to ensure that spirometry for FEV₁ and FVC assessments will be conducted as close to the specified time points as possible (i.e., FEV₁ and FVC assessments need to be conducted within ±15 minutes of specified time points prior to study drug administration and ±5 minutes of specified time points for the first 60 minutes post study drug administration..)
- 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.
- Refer to Section 7 for specific assessments and specific time points to be performed at each treatment visit.
- Sponsor provided screening medication will be provided only after a subject is determined to be eligible to proceed to Visit 2 (i.e. only if a subject meets COPD definition following spirometry assessments at Screening), and will be collected prior to Randomization at Visit 3.

Note: Sites should plan to perform these activities so as not to interfere with collection of timed assessments such as spirometry. Assessments should be conducted in the following order: Vital signs, CAT (Visit 2 only), Clinical laboratory testing (Visit 1 only), ECG (Visit 1 only), ICG (Visit 2 only), Spirometry and Plethysmography (Plethysmography at Visit 2 only).

Table 8.3 Timed Assessments at Treatment Visits 3 and 5 (Day 1) and Visits 4 and 6 (Day 8)

Clinical Variable ^a	Visits 3 and 5 (Day 1)				Visits 4 and 6 (Day 8)				
	Pre-dosing		Post-Dosing		Pre-dosing		Post-Dosing		
	-60 min	-30 min	30 min	2 hr	-60 min	-30 min	30 min	1 hr	2hr
Study Drug Collection ^b	X ^b				X ^b				
Review Diary Data	X ^c				X ^c				
Vital Signs ^d	X ^c				X ^c				
Clinical Laboratory Testing ^d	X ^c				X ^c				
Impedance Cardiography (ICG) ^d	X ^c				X ^c		X	X	
12-Lead ECG ^d	X ^c				X ^c			X	
Magnetic Resonance Imaging (MRI) ^d	X ^{c,e}								X ^f
Plethysmography ^d					X			X ^g	
Inspiratory Capacity (IC) ^d		X				X		X	
Spirometry(FEV ₁ , FVC) ^d	X	X				X		X	
Study Drug Dispensing ^h	X ^h								

- a. In-clinic dosing time is recorded as time of the second puff. Safety assessments (vital signs and ECG) should be started approximately 5 to 10 minutes ahead of the specified time point to ensure that spirometry for FEV₁ and FVC assessments will be conducted as close to the specified time points as possible (i.e., FEV₁ and FVC assessments need to be conducted within ±15 minutes of specified time points prior to study drug administration and ±5 minutes of specified time points for the first 60 minutes post study drug administration
- b. At the start of each treatment visit, subject must withhold all COPD medications, including study drug, rescue medication, and ICS for at least 6 hours prior to start of test day procedures. 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.
- c. 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.
- d. Refer to Section 7 for specific assessments and specific time points to be performed at each treatment visit.
- e. At Visit 3 only
- f. MRI to be performed 2-3 hours post-dose at Visit 4 and Visit 6.
- g. Plethysmography to be performed 1-2 hours post-dose at Visit 4 and Visit 6.
- h. Sponsor provided screening medication will be collected prior to Randomization at Visit 3 and dispensing of study drug.

Note: Sites should plan to perform these activities so as not to interfere with collection of timed assessments such as spirometry. Assessments should be conducted in the following order: Visit 3 and Visit 5 pre-dose: Vital signs, Clinical Laboratory Assessments, ICG, ECG, MRI (Visit 3 only), and Spirometry. For pre-dose assessments at Visit 4 and Visit 6, assessments should be collected in the following order: Vital signs, Clinical laboratory testing, ICG, Plethysmography, and Spirometry. For post-dose assessments at Visit 4 and Visit 6, assessments should be collected in the following order: ICG, ECG, Spirometry, Plethysmography, and MRI.

8.1 Visit 1 (Screening)

- Obtain informed consent
- Review inclusion/exclusion criteria
- Site will assign 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
- Obtain medication history, including COPD medications
- Conduct spirometry assessments
- Conduct a complete physical examination. Refer to Section 7.2.1 for additional details
- Obtain vital signs. Refer to Section 7.2.2 for additional details
- Obtain a 12-lead ECG. Refer to Section 7.2.3 for additional details
- 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
- Obtain laboratory samples (hematology and chemistry). Refer to Section 7.2.4 for additional details
- Record COPD Exacerbations and AEs (if any)

Note: Adverse events that occur between the time when 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 adverse event unless the event meets the definition of an SAE.

- Confirm subject's ability to use MDI correctly (provide coaching as needed)
- Assign Atrovent (ipratropium bromide) HFA and Ventolin (albuterol sulfate) HFA
- Dispense subject Diary and provide instruction to record needed information on Diary completion
- 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), but not greater than 26 days in duration prior to returning to the clinic for Visit 2
- Subjects will be instructed to bring their Diary, 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.

8.2 Visit 2 (Screening)

- Review inclusion/exclusion criteria and confirm subject eligibility to continue
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, Visit 2 must be rescheduled)

- Perform reversibility test to Ventolin HFA and Atrovent HFA respectively, and confirm subject continues to meet entry criteria based on pre- and post-dose spirometry quality (Refer to exclusion criterion 3i), and post-dose spirometry values. Conduct plethysmography measures. Refer to Section 7.1 for additional details on measurements
- Conduct Impedance Cardiography (ICG) measures. Refer to Section 7.1.5 for additional details on measurements
- 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
- Obtain Vital Signs. Refer to Section 7.2.2 for additional details
- Review all prior medications, if any, and ensure adherence to COPD regimen
- Complete COPD Assessment Test (CAT)
- Record COPD exacerbations and adverse events (if any)
Note: Adverse events that occur during the Screening Period (Visit 1 to Visit 3, pre study drug dosing) will be summarized as medical history and not as a study adverse event unless the event meets the definition of an SAE
- Schedule Visit 3 (Randomization Visit, Day 1)
Note: Visit 3 (Randomization Visit, Day 1) can be scheduled at minimum 1 day after Visit 2 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 Diary, Atrovent HFA, and sponsor-provided Ventolin HFA to the next scheduled clinic visit

8.3 Visit 3 (Randomization/Day 1)

- Review inclusion/exclusion criteria and confirm subject eligibility for randomization
- Review all concomitant medications, if any, and ensure adherence to COPD regimen
- 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 3
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, Visit 3 must be rescheduled)
- Record COPD exacerbations and adverse events (if any)
- Collect sponsor-provided Atrovent HFA and sponsor-provided Ventolin HFA dispensed during the Screening Period
- Perform all pre-dose assessments. (Refer to Table 8.3)
- Conduct Pregnancy test (Urine HCG) for women of child- bearing potential only
- Conduct inspiratory capacity measures
- Conduct spirometry measures
- Obtain vital signs Refer to Section 7.2.2 for additional details.

- Obtain a 12-lead ECG
- Conduct MRI assessments. Refer to Section 7.1.4 for additional details on measurements
- Conduct ICG measures.
- Obtain laboratory samples (hematology and chemistry)
- 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 6.7.1 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits
- Subject will administer first dose of newly assigned study drug at the clinic
- Return Diary to subjects and provide retraining if appropriate
- Subjects will be instructed to bring their Diary and all study medication (including used study drug and rescue Ventolin HFA) to the next scheduled clinic visit
- Schedule next visit and ensure subject has adequate supply of study drug and rescue Ventolin HFA

8.4 Visit 4 (Day 8)

- Confirm subject eligibility to continue
- Collect study drug including sponsor-provided Ventolin HFA and ICS
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, Visit 4 must be rescheduled)
- Confirm the subject took their last dose of randomized study medication as scheduled the prior evening
- Review all concomitant medications, if any, and ensure adherence to COPD regimen
- Review subject diary for data collection compliance
- Record COPD exacerbations and adverse events (if any)
- Perform all pre-dose assessments. (Refer to Table 8.3)
- Conduct spirometry measures
- Conduct plethysmography measures
- Conduct ICG measures
- Obtain Vital Signs
- Obtain laboratory samples (hematology and chemistry)
- Conduct IC measures
- 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 6.7.1 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
- Perform all post-dose assessments (Refer to Table 8.3)
- Conduct ICG measures
- Conduct MRI measures.
- Conduct spirometry measures
- Conduct plethysmography measures
- Conduct IC measures
- Obtain vital signs Refer to Section 7.2.2 for additional details.
- Obtain a 12-lead ECG
- Subject will administer one dose of newly assigned study drug at the clinic
- Return Diary to subjects and provide retraining if appropriate
- Subjects will be instructed to bring their Diary and all study medication (including used study drug and rescue Ventolin HFA and Atrovent HFA) to the next scheduled clinic visit
- Schedule next visit and ensure subject has adequate supply of rescue Ventolin HFA and Atrovent HFA

8.5 Visit 5 (Day 1)

- Confirm subject eligibility to continue
Note: To be randomized, all subjects must meet the FEV₁ Baseline Stability criteria (Refer to Section 7.1.1.1) for additional details. If the FEV₁ Baseline Stability entry criteria are not met at Visit 3 (Randomization) the subject will not be eligible to be randomized and will be screen failed
- Collect study drug including sponsor-provided Ventolin HFA and ICS
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, Visit 5 must be rescheduled)
- Confirm the subject took their last dose of randomized study medication as scheduled the prior evening
- Review all concomitant medications, if any, and ensure adherence to COPD regimen
- Review subject diary for data collection compliance
- Record COPD exacerbations and adverse events (if any)
- Perform all pre-dose assessments. (Refer to Table 8.3)
- Conduct Pregnancy test (Urine HCG) for women of child- bearing potential only
- Conduct spirometry measures
- Obtain vital signs Refer to Section 7.2.2 for additional details.

- Obtain a 12-lead ECG
- Conduct ICG measures
- Conduct inspiratory capacity measures
- Obtain laboratory samples (hematology and chemistry)
- 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 6.7.1 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
- Subject will administer first dose of newly assigned study drug at the clinic
- Return Diary to subjects and provide retraining if appropriate
- Subjects will be instructed to bring their Diary and all study medication (including used study drug and rescue Ventolin HFA) to the next scheduled clinic visit
- Schedule next visit and ensure subject has adequate supply of study drug and rescue Ventolin HFA

8.6 Visit 6 (Day 8)

- Confirm subject eligibility to continue
- Collect study drug including sponsor-provided Ventolin HFA and ICS
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, Visit 6 must be rescheduled)
- Confirm the subject took their last dose of randomized study medication as scheduled the prior evening
- Review all concomitant medications, if any, and ensure adherence to COPD regimen
- Review subject diary for data collection compliance
- Record COPD exacerbations and adverse events (if any)
- Perform all pre-dose assessments. (Refer to Table 8.3)
- Conduct a complete physical examination
- Conduct a serum pregnancy test
- Conduct spirometry measures
- Conduct plethysmography measures
- Conduct ICG measures
- Obtain vital signs Refer to Section 7.2.2 for additional details.
- Obtain laboratory samples (hematology and chemistry)
- Conduct IC measures

- 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 6.7.1 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits
- Subject will administer first dose of newly assigned study drug at the clinic
- Record/document the dose indicator readings of the used MDI and the replacement MDI
- Perform all post-dose assessments (Refer to Table 8.3)
- Conduct ICG measures
- Conduct MRI measures
- Conduct spirometry measures
- Conduct plethysmography measures
- Conduct IC measures
- Obtain vital signs
- Obtain a 12-lead ECG
- Return subject to pre-study or appropriate maintenance COPD medications
- Collect Subject Diary
- Schedule the follow-up telephone call at least 14 days from Visit 6

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:

- Collect all study drugs, including rescue medications
- Record COPD exacerbations and adverse events (if any)
- Review concomitant medications, if any
- Conduct a physical examination, including vital signs
- Perform ECG and collect blood samples for hematology and chemistry
- Conduct a serum pregnancy test for women of child-bearing potential only
- Collect subject Diary
- 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 COPD exacerbations and adverse events and record AEs (if any)
- Review concomitant medications, if any

8.9 Completion of the Study

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

Subject discretion (document reason)

Investigator or designee considers it to be in the best interest of the subject

AEs

Administrative reasons (e.g., early termination of the study)

Subject lost-to-follow-up

Lack of efficacy

Major protocol deviation

Death

Completion of the study

Protocol-specific discontinuation criteria (see Section 5.7.1)

9 PLANNED STATISTICAL METHODS

9.1 Introduction

This study will be conducted as a randomized, double-blind, single-center, chronic-dosing (7 days), two-period, two-treatment, crossover study evaluating the effect of the following treatments on cardiovascular hemodynamics in approximately 32 subjects:

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

The primary objective of this study is to evaluate the effect of GFF MDI on cardiovascular hemodynamics following chronic dosing (7 days) in subjects with moderate to severe COPD.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

All efficacy assessments will be compared to baseline values. Baseline for the MRI endpoint will be defined as the pre-dose value at Visit 3. Baseline for the plethysmography endpoints will be defined as the pre-bronchodilator value at Visit 2. Baseline for the ICG and spirometry endpoints will be defined as the average of the subject values obtained pre-dose on Day 1 of each Treatment Period (average of Visit 3 and Visit 5 pre-dose). For spirometry endpoints, the mean of the -60 and -30 minute values for each visit will be obtained prior to averaging across visits. The first day of treatment in each Treatment Period is Day 1. Each Treatment Period is planned to contain 7 days between the first and last dose corresponding to a span of 8 calendar days. Therefore, assessments collected on Day 8 will occur following 7 days of treatment.

The MRI endpoints RVEDV, LVEDV, LVESV, and RVESV will be normalized to body surface area (BSA) to provide the indexed counterpart, e.g.:

$$\text{RVEDV}_i = \text{RVEDV} / \text{BSA}$$

Prior to calculating the change from baseline, the baseline and post-dose RVEDV values will each be normalized separately using the respective BSA values.

9.2.1.1 Primary Efficacy Endpoint

- Right Ventricular End Diastolic Volume Index (RVEDV_i) measured at 2-3 hours post-dose on Day 8

9.2.1.2 Secondary Efficacy Endpoints (Measured using MRI at 2-3 hours post-dose on Day 8 unless otherwise noted)

- Aortic left ventricular stroke volume [LVSV]
- Right Ventricular Stroke Volume (RVSV), phase contrast from pulmonic valve

- Pulmonary Artery Velocity
- Left ventricular End Diastolic Volume Index (LVEDVi)
- Cardiac Output
- Morning pre-dose trough and post-dose Pulmonary Vascular Resistance (PVR) by ICG (Measured at 30 minutes and 60 minutes post-dose)
- Pulmonary artery/Aortic diameter ratio (PA:A)
- Left Atrial End Diastolic Volume (LAEDV)
- Left Atrial End Systolic Volume (LAESV)
- Left Atrial Ejection Fraction (LAEF)
- Left Ventricular End Systolic Volume Index (LVESVi)
- Right Ventricular End Systolic Volume Index (RVESVi)
- Pulsatility Index Aorta (PIAo)
- Pulmonary Artery Pulsatility Index (PAPi)

9.2.1.3 Other Efficacy Endpoints

- Plethysmography (Measured 1-2 hours post-dose)
 - Total airway resistance (Raw)
 - Specific airway conductance (sGaw)
 - Total lung capacity (TLC)
 - Residual volume (RV)
 - Functional residual capacity (FRC)
 - RV/total lung capacity (RV/TLC)
 - Diffusing capacity for carbon monoxide (D_LCO)
 - Inspiratory Capacity (IC)
- Impedance Cardiography (Measured at 30 and 60 minutes post-dose)
 - Change in right ventricular stroke volume
- Magnetic Resonance Imaging (Measured 2-3 hours post-dose)
 - Change in right ventricular ejection fraction (RVEF)
 - Change in left ventricular ejection fraction (LVEF)
 - Pulmonary arterial distensibility
 - Pulmonary Vascular Volume
 - Right Atrial End Diastolic Volume (RAEDV)
 - Right Atrial End Systolic Volume (RAESV)
 - Right Atrial Ejection Fraction (RAEF)
- Spirometry
 - Morning pre-dose trough FEV_1
 - Morning pre-dose trough IC

- 1-hour post-dose FEV₁
- 1-hour post-dose IC
- Morning pre-dose trough and 1-hour post-dose FVC

9.2.2 Safety Endpoints

- AEs
- 12-Lead ECG
- Clinical Laboratory Testing
- Vital Sign Measurements

9.3 Analysis

9.3.1 Efficacy Analysis

9.3.1.1 Primary Efficacy Analysis

A mixed model will be used to evaluate the difference between treatments in the change from baseline in RVEDVi. Baseline will use the value from Visit 3 obtained prior to the first dosing of Period 1. The model will include adjustment for baseline, period, and treatment. Sequence will only be included in the model if found to be significant ($p < 0.10$). Subject will be treated as a random effect in order to model within subject correlation across the two periods. Point estimates and 95% confidence intervals for the difference between GFF MDI and Placebo MDI will be produced. 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:

$H_0: \mu_{\text{GFF}} = \mu_{\text{placebo}}$

$H_1: \mu_{\text{GFF}} \neq \mu_{\text{placebo}}$

The primary analysis will use the modified Intent-to-Treat (mITT) Population. Analyses using the Intent-to-Treat (ITT) Population will be considered supportive.

9.3.1.2 Secondary Efficacy Analysis

Change from baseline in each of the secondary efficacy endpoints will be analyzed using a similar mixed model as for the primary endpoint, change in RVEDVi. In addition, since there are two responses (30- and 60-min post dose) per period for PVR, an unstructured covariance matrix will be fit to the repeated measures within a subject-period for this endpoint. If sequence is found to be significant ($p < 0.10$) in the primary analysis model, a term for sequence will also be included in each of the models for the secondary endpoints. Baseline for the MRI endpoints will use the value from Visit 3 obtained prior to the first dosing of Period 1. Baseline for the ICG endpoint, pulmonary vascular resistance, will be defined as the average of the subject values obtained pre-dose on Day 1 of each Treatment Period (average of Visit 3 and Visit 5 pre-dose). Point estimates, 95% confidence intervals and two-sided p-values will be reported for the difference between GFF MDI and Placebo MDI.

The secondary analyses will use the modified Intent-to-Treat (mITT) Population. Analyses using the Intent-to-Treat (ITT) Population will be considered supportive.

9.3.1.3 Other Efficacy Analysis

Change from baseline in each of the other efficacy endpoints will be analyzed using a similar mixed model as for the primary endpoint, change in RVEDVi. For the ICG endpoint of change in right ventricular stroke volume, an additional unstructured covariance matrix will be fit to the repeated measures within a subject period. If sequence is found to be significant ($p < 0.10$) in the primary analysis model, a term for sequence will also be included in each of the models for the other efficacy endpoints. Baseline for the plethysmography endpoints will use the pre-bronchodilator value at Visit 2. Baseline for the ICG and spirometry endpoints will be defined as the average of the subject values obtained pre-dose on Day 1 of each Treatment Period (average of Visit 3 and Visit 5 pre-dose). For spirometry endpoints, the mean of the -60 and -30 minute pre-dose values for each visit will be obtained prior to averaging across visits. Point estimates, 95% confidence intervals and two-sided p-values will be reported for the difference between GFF MDI and Placebo MDI.

The other efficacy analyses will use the Intent-to-Treat (ITT).

9.3.2 Safety Analysis

9.3.2.1 Adverse Events

Adverse events during each Treatment Period will be summarized by the number 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 will be used for the final analysis of data. Tabulations will be broken down by severity, seriousness, AEs leading to discontinuation, and by relationship to study drug. No hypothesis tests will be performed. Tables will show the overall incidence of AEs, and the incidence for each treatment.

9.4 Randomization

Subjects will be randomly assigned using the treatment sequence AB or BA in a 1:1 ratio where A= GFF MDI 14.4/9.6 μg BID and B= Placebo MDI BID, respectively. All subjects who complete the study will receive both treatments. Randomization will be stratified by severity of disease such that half of the subjects will have moderate COPD and half will have severe COPD as categorized by post-bronchodilator FEV_1 ($\geq 50\%$ - $<65\%$ for moderate and 30% - $<50\%$ for severe).

9.5 Experimental Design

The experimental design was chosen to be balanced with respect to period and first-order carryover effects.

9.6 Sample Size Consideration

Based on a two-treatment, two-period crossover study comparing Breo® Ellipta® versus placebo after cardiac MRI (Stone, 2015), the within-subject SD for the change from baseline in RVEDVi was estimate to be 7.11 mL/m². Assuming that 90% of the randomized subjects will complete the trial, the study has approximately 90% probability to demonstrate a difference of 5.59 mL/m² in RVEDVi.

9.7 Data Validation and Transformation

In general, the data captured within this study are expected to follow a normal distribution. However, under certain circumstances, (e.g., during a COPD exacerbation unrelated to treatment) extreme and atypical values can arise. Such values may disproportionately affect model-based estimates of the fixed effect and variance parameters. Prior to database lock and unblinding, the change from baseline values for efficacy endpoints will be examined as part of data quality management. This will include production of normal probability plots, kernel density estimates, and normal order outlier statistics. Based on this blinded evaluation, if a single or small number of extreme values are identified, nonparametric methods or data transformations (e.g. logarithmic or normal rank transformation) will be considered.

If erroneous values are detected, every effort will be made to correct them prior to database lock; however if these values cannot be corrected, they will be considered for removal from analysis.

9.8 Analysis Plan

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

9.9 Study Populations

The following analysis populations are defined in this study:

- The **ITT Population** is defined as all subjects who are randomized to treatment. Subjects will be analyzed according to the treatment assigned per the sequence randomization regardless of the treatment actually received.
- The **mITT Population** is a subset of the ITT Population including subjects who received treatment and have post-treatment efficacy data from both Treatment Periods. Data judged to be impacted by major protocol deviations will be determined prior to unblinding and excluded. Statistical tabulations and analyses will be by randomized treatment, but data obtained after subjects receive an incorrect treatment will be excluded from the affected periods.
- The **Safety Population** is defined as all subjects who are randomized to treatment and receive at least one dose of the study treatment. Statistical tabulations will be by the treatment actually received.

- The **Not Randomized Population** is defined as subjects who did not receive a randomization number and therefore did not receive a dose of study treatment (e.g., subjects who were screen failures or stopped participation prior to having been randomized).

Analyses will be performed as follows:

Demographics will be summarized for the ITT, mITT, Safety, and the Not Randomized Populations. Extent of exposure will be summarized for the Safety Population. The Safety Population will be used to summarize safety.

Analyses for the primary and secondary efficacy endpoints will be performed for the mITT and ITT Populations, with the mITT Population being considered the primary population for these analyses. Analyses for the other efficacy endpoints and the exploratory endpoints will be conducted with the ITT Population.

9.10 Handling of Missing Data

All observed values will be included in the ITT Population for the efficacy and exploratory analyses. All observed values meeting specified criteria will be included in the mITT Population.

Missing data will be maintained as missing in the analysis datasets, unless specified otherwise. For variables where missing data is imputed, the analysis dataset will contain a new variable with the imputed value and the original variable value will be maintained as missing.

9.11 Statistical Software

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

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

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

Pearl 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 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 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. Pearl 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 that information furnished to the Investigator by Pearl 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 (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. 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 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 or their designee.

10.8 Study Monitoring

In accordance with applicable regulations, GCP, and Pearl 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.
- 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's Quality Assurance auditors, and authorized representatives of the FDA or other applicable regulatory agencies.

10.9 Retention of Data

Documents that individually and collectively permit evaluation of the conduct of the study and the quality of the data produced must be maintained for review by Pearl's quality assurance auditors and by all applicable regulatory authorities. The period of time these documents must be maintained is governed by applicable regulations. Pearl or its designee will inform the Investigator when these documents may be destroyed. Pearl 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 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.

10.12 Publication Policy

A study site may not publish results of a study until after a coordinated multicenter publication has been submitted for publication or until one year after the study has ended, whichever occurs first. Therefore, the study site will have the opportunity to publish the results of the study, provided that "THE SPONSOR" has had the opportunity to review and comment on the study site's proposed publication prior to its being submitted for publication with the prior advice of "LEGAL" (intellectual property council) and with proper regard to the protection of subjects' identities.

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12 APPENDICES

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), 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.

FEV₁ AND FVC MANEUVERS

Equipment Requirements

The spirometer must be capable of accumulating volume for ≥ 15 s (longer times are recommended) and measuring volumes of ≥ 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 ± 0.050 L, whichever is greater, with flows between 0 and 14 L·s⁻¹. The total resistance to airflow at 14.0 L·s⁻¹ must be < 1.5 cmH₂O 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 ≥ 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 $\geq 10 \text{ mm L}^{-1}$ (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}	$2.5 \text{ mm L}^{-1} \text{ s}^{-1}$	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 $\geq 20 \text{ mm-s}^{-1}$, and larger time scales are preferred ($\geq 30 \text{ mm-s}^{-1}$) 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 ₂ O (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 ± 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 $\pm 3.5\%$ is appropriate.

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

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

At least quarterly, volume spirometers must have their calibration checked over their entire volume range using a calibrated syringe or an equivalent volume standard. The measured volume should be within $\pm 3.5\%$ of the reading or 65 mL, whichever is greater. This limit includes the 0.5% accuracy limit for a 3-L syringe. The linearity check procedure provided by the manufacturer can be used if it is equivalent to one of the following procedures: 1) consecutive injections of 1-L volume increments while comparing observed volume with the corresponding cumulative measured volume, 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 $\pm 3.5\%$. For devices using disposable flow sensors, a new sensor from the supply used for patient tests should be tested each day.

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

VC 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 or, ideally, both inspiratory and expiratory maneuvers should be included in the display of VC maneuver. Regardless of whether the inspiratory or expiratory

maneuver is used for deriving measurements, a display of the entire recorded VC maneuver must be provided. The maximal expiratory volume must be assessed to determine whether the subject has obtained a plateau in the expiratory effort. For display of the slow VC, the time scale may be reduced to 5 mm-s⁻¹.

TECHNICAL CONSIDERATIONS

Minimal recommendations for spirometry systems

Accurate results require accurate equipment. Spirometer equipment recommendations apply to all spirometers and are minimal requirements. In some circumstances, it may be appropriate to exceed these requirements (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-s ⁻¹)	Time (s)	Resistance and Back Pressure	Test Signal
VC	0.5–8 L, $\pm 3\%$ of reading or ± 0.050 L, whichever is greater	0-14	30		3-L Calibration syringe
FVC	0.5–8 L, $\pm 3\%$ of reading or ± 0.050 L, whichever is greater	0-14	15	$< 1.5 \text{ cm H}_2\text{O L}^{-1} \text{ s}^{-1}$ ($0.15 \text{ kPa L}^{-1} \text{ s}^{-1}$)	24 ATS waveforms, 3-L Cal Syringe
FEV ₁	0.5–8 L, $\pm 3\%$ of reading or ± 0.050 L, whichever is greater	0-14	1	$< 1.5 \text{ cm H}_2\text{O L}^{-1} \text{ s}^{-1}$ ($0.15 \text{ kPa L}^{-1} \text{ s}^{-1}$)	24 ATS waveforms
Time Zero	The timepoint from which all FEV _t measurements are taken.			Back extrapolation	

FEV_t: 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 $\pm 1^{\circ}\text{C}$. In situations where the ambient air temperature is changing rapidly ($>3^{\circ}\text{C}$ in <30 min), continuous temperature corrections may be necessary. Spirometer users should be aware of potential problems with testing performed at lower ambient temperatures: 17°C is the lower limit for ambient temperature, unless a manufacturer states that their spirometer will operate accurately at lower ambient temperatures. If barometric pressure is not used in calculating the BTPS correction factor, the range of barometric pressures over which the BTPS correction factor is valid must be published.

Appendix 2 Spirometry Assessment Criteria

Acceptable Versus Usable Tests

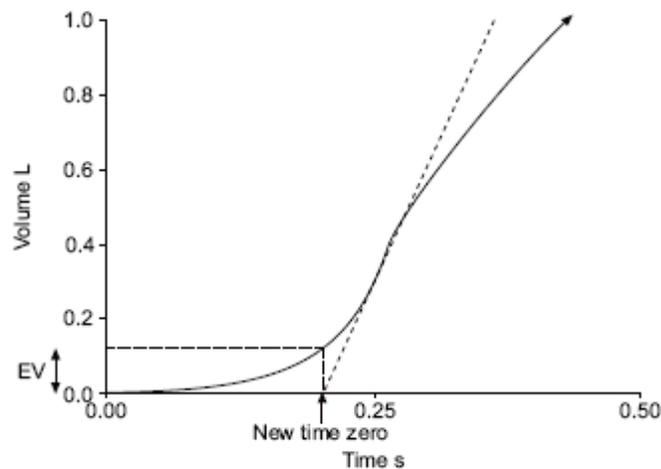
Acceptable Tests must meet the following 7 Criteria:

1. Acceptable start of exhalation with brisk upstroke, no hesitation or false start, and back extrapolation volume (EV) < 5% of FVC or 0.150 L, whichever is the greater. (Refer to example in Figure A2-1)
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 \geq 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 FEV₁ Baseline Stability 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 FEV₁ 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 FEV₁ and the highest FVC obtained at each testing time-point (even if from different reproducible tracings), will be collected.

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

Appendix 3 Subject Instructions for Use of GFF and Placebo MDI

Before using GFF 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 2.

Figure 2. Indicator at Top of Canister



2. Take the cap off the inhaler and inspect the front of the inhaler and make sure there is nothing inside the mouthpiece of the inhaler. Make sure the canister is fully and firmly inserted into the actuator.
3. The inhaler should be stored at room temperature.

How to prime GFF MDI 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 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 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 (Refer to Figure 3).

Figure 3. Wash Actuator through Top of Actuator



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

Figure 4. Wash Actuator through Mouthpiece



4. Shake off as much water from the actuator as you can. Look into the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any visible build-up, repeat steps 2 and 3.
5. Let the actuator air dry completely, such as overnight.
6. When the actuator is dry, put the canister in the actuator, making sure the canister is fully and firmly fitted into the actuator. Shake the inhaler gently for 5-10 seconds and spray it 2 times into the air away from your face, shaking gently 5-10 seconds before each spray. Put the cap back on the mouthpiece.

If the actuator becomes blocked

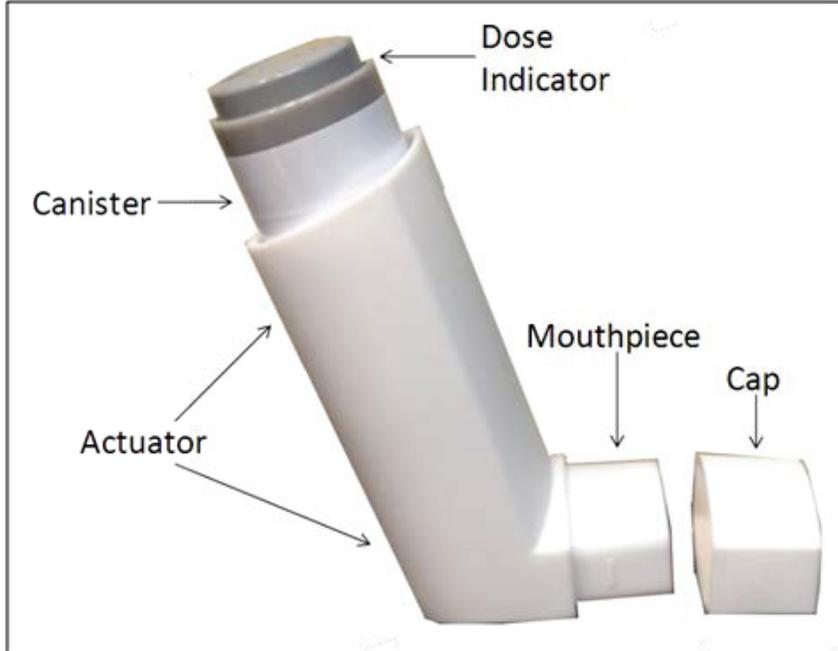
Blockage from medicine build-up is more likely to happen if the actuator is not routinely cleaned and the actuator is not air-dried completely. If the actuator gets blocked so that little or no medicine comes out of the mouthpiece, wash the actuator as described in cleaning steps 1-6.

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

How to read the inhaler dose indicator

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

Figure 5. Metered Dose Inhaler Parts



Appendix 4 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).

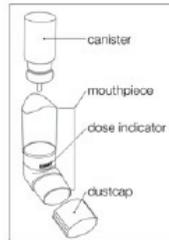


Figure 1



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.

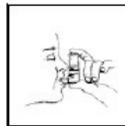


Figure 3

- 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.

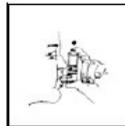


Figure 4

- 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.

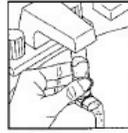


Figure 6

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".

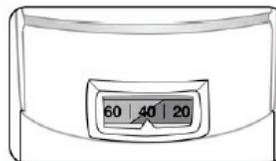


Figure 7a

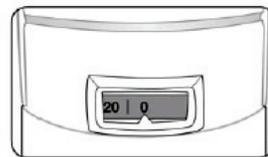


Figure 7b

Appendix 5 Instructions for Use of Ventolin HFA Inhaler

The Parts of Your VENTOLIN HFA Inhaler

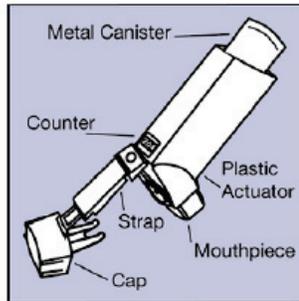


Figure A

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.

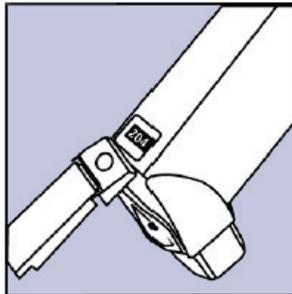


Figure B

Priming your VENTOLIN HFA inhaler:

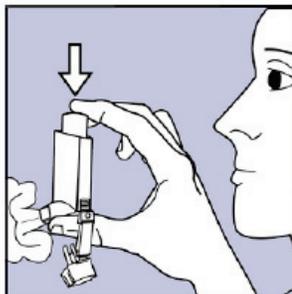


Figure C

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.

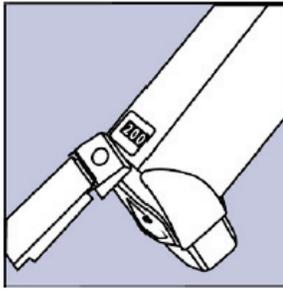


Figure D

- 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 accidentally spraying a dose of VENTOLIN HFA into the air.

Using your VENTOLIN HFA inhaler:

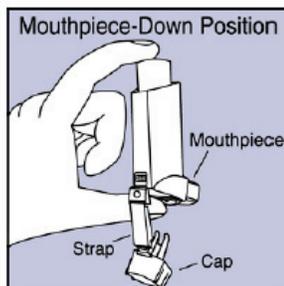


Figure E

- 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.

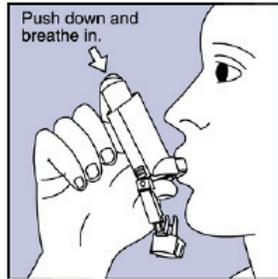


Figure F

- 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:

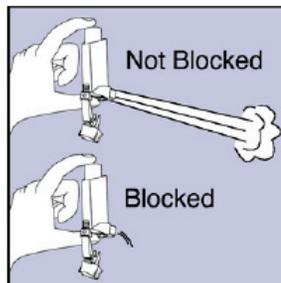


Figure G

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:

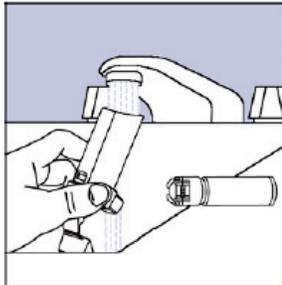


Figure H

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.

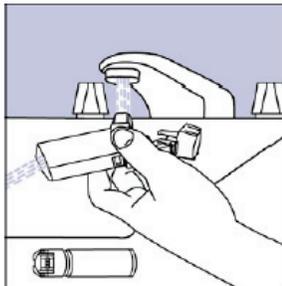


Figure I

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.

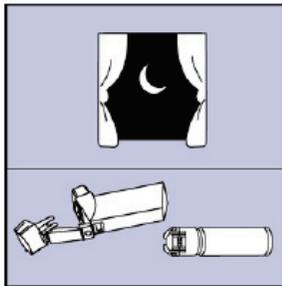


Figure J

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 6 COPD Assessment Test

Your name:

Today's date:



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) (1) (2) (3) (4) (5) I am very sad

				SCORE
I never cough	(0) (1) (2) (3) (4) (5)	I cough all the time		<input type="text"/>
I have no phlegm (mucus) in my chest at all	(0) (1) (2) (3) (4) (5)	My chest is completely full of phlegm (mucus)		<input type="text"/>
My chest does not feel tight at all	(0) (1) (2) (3) (4) (5)	My chest feels very tight		<input type="text"/>
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		<input type="text"/>
I am not limited doing any activities at home	(0) (1) (2) (3) (4) (5)	I am very limited doing activities at home		<input type="text"/>
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		<input type="text"/>
I sleep soundly	(0) (1) (2) (3) (4) (5)	I don't sleep soundly because of my lung condition		<input type="text"/>
I have lots of energy	(0) (1) (2) (3) (4) (5)	I have no energy at all		<input type="text"/>
				TOTAL SCORE <input type="text"/>

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Appendix 7 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				
 <p>If your dose indicator display looks like this record 120+</p>	 <p>If your dose indicator display looks like this record 120</p>	 <p>If your dose indicator display looks like this record 110</p>	 <p>If your dose indicator display looks like this record 100</p>	 <p>If your dose indicator display looks like this record 90</p>
 <p>If your dose indicator display looks like this record 80</p>	 <p>If your dose indicator display looks like this record 70</p>	 <p>If your dose indicator display looks like this record 60</p>	 <p>If your dose indicator display looks like this record 50</p>	 <p>If your dose indicator display looks like this record 40</p>
 <p>If your dose indicator display looks like this record 30</p>	 <p>If your dose indicator display looks like this record 20</p>	 <p>If your dose indicator display looks like this record 10</p>	 <p>If your dose indicator display looks like this record 0</p>	

Appendix 8 Sponsor Signatory

A Randomized, Phase IIIb, Two-period, Double-blind, Two-treatment, Chronic-dosing (7 Days), Single-center Crossover Study to Evaluate the Treatment Effect of PT003 on Cardiovascular Hemodynamics in Subjects With Moderate to Severe Chronic Obstructive Pulmonary Disease, Compared with Placebo

Study Number: PT003017-02

Final Date: 26 September 2016

Signature: _____

Date: _____

Name: _____

Title: _____

Appendix 9 Investigator's Agreement and Signature Page

Study Title: A Randomized, Phase IIIb, Two-period, Double-blind, Two-treatment, Chronic-dosing (7 Days), Single-center Crossover Study to Evaluate the Treatment Effect of PT003 on Cardiovascular Hemodynamics in Subjects With Moderate to Severe Chronic Obstructive Pulmonary Disease, Compared with Placebo

Study Number: PT003017-02

Final Date: 26 September 2016

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.

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 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

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 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: _____
