Revised Clinical Study Protocol

Study Code	PT010006
NCT #	NCT02497001
Date:	25AUGUST2017

A Randomized, Double-Blind, Parallel-Group, 24-Week, Chronic-Dosing, Multi-Center Study to Assess the Efficacy and Safety of PT010, PT003, and PT009 Compared with Symbicort® Turbuhaler® as an Active Control in Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease

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

Amendment No.	Date of Amendment
Version 1	18 MAY 2015
Version 2, Amendment 1	04 MAY 2016
Version 3, Amendment 2	25 AUGUST 2017

Clinical Trial Protocol: PT010006-02

Study Title:	A Randomized, Double-Blind, Parallel-Group, 24-Week, Chronic-Dosing, Multi-Center Study to Assess the Efficacy and Safety of PT010, PT003, and PT009 Compared with Symbicort® Turbuhaler® as an Active Control in Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease
Study Number:	PT010006-02
Study Phase:	III
Product Name:	Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol, PT010 Glycopyrronium and Formoterol Fumarate Inhalation Aerosol, PT003 Budesonide and Formoterol Fumarate Inhalation Aerosol, PT009
EudraCT Number:	2014-005672-29
Indication:	COPD
Investigators:	Multicenter
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]

	Version Number	**Date:**
Original Protocol	Version 1.0	18 May 2015
Amended Protocol	Version 2.0	04 May 2016
Amended Protocol	Version 3.0	25 Aug 2017

SUMMARY OF CHANGES TO PT010006-01 VERSION 2.0, DATED 04 MAY 2016

Section(s)/Description of Change	Rationale
Synopsis, Section 2.2/Secondary Objectives, and Section 3.2/Secondary Efficacy Endpoints Added rate of moderate or severe COPD exacerbations. Added time to Clinically Important Deterioration (CID)-except for the US approach	Exacerbations are an important endpoint and there is sufficient sample size to observe at least a numerical benefit in the form of a trend, even though the study is not optimized to demonstrate statistical significance. Time to CID encompasses lung function, symptomatic benefit, and exacerbations into a single endpoint.
Section 2.3/Other Efficacy Objective Removed the rate of moderate or severe COPD exacerbations. Added time to sustained CID. Added time to CID (since not included as a secondary endpoint in US approach).	The rate of moderate or severe exacerbations is now a secondary objective.
Synopsis and Study Endpoint Sections 3, 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.3.2, 3.4, 3.5, 3.6.1, 3.6.2, 3.6.3.2, and 9.1. Added the following sentence to Section 3 "Study Endpoints", Section 9.1 and Synopsis: Countries not specifically mentioned will be decided by regulatory requirements and included in one of the three defined registration approaches. Addition of US endpoints The EXACT Total Score which was a secondary endpoint is now an Other endpoint. The E-RS:COPD RS-Total Score, which was an other endpoint, is instead a secondary endpoint in place of the EXACT Total Score for the EU/CAN approach.	Added sentence to clarify the registration approach for countries that are not specifically mentioned. Added US endpoints to support registration in the US and other markets that use similar endpoints. The E-RS:COPD RS-Total score is more aligned with the population included in this study. The EXACT total is more appropriate for an exacerbation study. Though underpowered, analyses of severe COPD exacerbations will be conducted as well due to their clinical relevance. A table is needed to support the plot of FEV_1 over time in the 12-hr PFT sub-study. AUC_{0-4} is assessed in subjects outside of the

Severe COPD exacerbations were added Clarification of the endpoints for the 12-hr PFT sub-study AUC and trough SC at Week 24 were removed as HPA axis secondary endpoints. Day 1 assessments were clarified.	sub-study as well, so is not needed. The AUC_{0-24} is already a key component in the primary endpoint. Trough SC concentration is not being defined as a distinct endpoint, since there will be summaries of serum cortisol concentration by time point. Day 1 assessments were edited to reflect that FEV_1 AUC_{0-4} is already covered by that endpoint being specified elsewhere, and response defined as an improvement of 100 mL is also of interest.
Synopsis, Section 9.4.2, and Section 9.4.4.2 A separate margin of 75 mL is specified for post-dose FEV_1 measures.	The margin for FEV_1 AUC_{0-4} is larger since larger benefits and greater variability is expected.
Section 5.4.4/Other Prohibited Medications Table 3 - Added NaSSAs to row containing SSRIs and SNRIs. Added note to specify/clarify use topical medications. Table 4 - Moved Carvedilol from table to a footnote. Added footnote to clarify usage. Paragraph below Table 4 - For consistency added language clarifying continuation in the study after randomized treatment discontinuation.	Added or reorganized language to provide consistency across protocol sections.
Section 5.7/Reasons for Treatment Discontinuation or Study Withdrawal Created third-level sections for “Reasons for Treatment Discontinuation” and “Reasons for Study Withdrawal”.	Reorganized language to separate reasons for treatment discontinuation and study withdrawal.
Sections 4.1, 7.1.4.5 and 9.4.4.5 and Appendix 12 Modified based on name change. The EXACT name was used in the protocol	Noted the updated EXACT questionnaire nomenclature based on recognition of the new name “the Evaluating Respiratory Symptoms (E-RS) measure”, announced 7 March 2016. When referring specifically to its use in COPD, the proposed context of use

unless specifically noted otherwise.	for qualification, the full name is now "Evaluating Respiratory Symptoms in COPD (E-RS™: COPD)".
Section 7.2.1/Medical/Surgical History and Physical Examination. Added "or Treatment Discontinuation Withdrawal Visit".	Changed to maintain consistency throughout the protocol and reflect study conduct.
Section 7.5.7.3/Pneumonia Replaced PAC with CEC.	Corrected the name of the adjudication committee.
Section 7.5.13/Paternal Exposure Added New Section "Paternal Exposure".	Added to clarify protocol conduct and consistency across protocol sections.
Section 9.3/Study Populations A more complete definition of the mITT Population is provided. Demography and baseline characteristics will be produced for the mITT Population.	Added to provide additional clarity about the data to be included in the mITT Population. The main population for demography and baseline characteristics was changed from the ITT to the mITT Population to reflect the primary analyses. Note that the baseline information is expected to be identical for the mITT and ITT Populations.
Section 9.4/Efficacy Analyses Added Section 9.4.1 on "Estimands" and modified text based on estimands in Sections 9.4.2.1, 9.4.2.2, 9.4.3, 9.4.3.7, 9.4. Added the attributable estimand. Added missing approaches by comparison in 9.4.2.1. Added estimands to Section 9.4.5 "Control of Type I Error" and sub-sections 9.4.5.1, 9.4.5.2, and 9.4.5.3. Added Type I error control for the US approach. Added Estimands to Section 9.15 "Handling	The efficacy analysis section has been updated using wording around estimands in keeping with current statistical thinking. As such, analyses previously using the mITT Population, the ITT Population, and the Per-Protocol Population have been replaced with the efficacy estimand and attributable estimand, the treatment policy estimand, and the per-protocol estimand, respectively. The new estimand called the attributable estimand has been added to further evaluate benefit of treatments in the context of having missing data. This attributable estimand has been added to the Type I error control. Type I error control was added for the US approach corresponding to the addition of US endpoints.

of Missing Data". The non-inferiority margin for TDI was changed from 1.0 to 0.75.	The TDI margin was tightened to be less than the minimum clinically relevant difference. Non-inferiority margins for other secondary measures are specified in the SAP.
Section 9.5/Subgroup Analyses Important Chinese and Asian subgroups were added as were primary endpoints.	The Chinese and Asian subgroups are also important to mention that they are planned for analysis. The mention of primary endpoints was inadvertently left out of previous versions.
Section 9.7/Pharmacokinetic Analyses Comparison to Symbicort was added.	The comparison to Symbicort TBH was inadvertently left out of previous versions.
Section 9.15/Handling of Missing Data Text was edited to specify that exploration of the potential impact of missing data will be explored and that details will be provided in the SAP.	It is not considered optional to explore the potential impact of missing data.
Other administrative changes to correct and/or clarify protocol language were also addressed. These changes included edits for consistency, grammar, and typographical errors, which are not summarized in this table.	

SYNOPSIS

Sponsor: Pearl Therapeutics, Inc. ("Pearl") [redacted]
Name of Finished Product: Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (PT010, BGF metered dose inhaler [MDI]) Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (PT003, GFF MDI) Budesonide and Formoterol Fumarate Inhalation Aerosol (PT009, BFF MDI) Symbicort® Turbuhaler® (TBH) Inhalation Powder
Name of Active Ingredient: Budesonide, Glycopyrronium, and Formoterol Fumarate Glycopyrronium and Formoterol Fumarate Budesonide and Formoterol Fumarate
Study Title: A Randomized, Double-Blind, Parallel-Group, 24-Week, Chronic-Dosing, Multi-Center Study to Assess the Efficacy and Safety of PT010, PT003, and PT009 Compared With Symbicort® Turbuhaler® as an Active Control in Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease
Study Number: PT010006-02
Study Phase: Phase III
Primary Objective: • To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on lung function.
Secondary Objectives: • To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on dyspnea • To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on quality of life • To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on symptoms of chronic obstructive pulmonary disease (COPD) • To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on COPD exacerbations • To determine the time to onset of action of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH

Safety Objective:

- To assess the safety of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH

Healthcare Resource Utilization Objective:

- To assess overall and COPD-specific Healthcare Resource Utilization of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH.

12-Hour Pulmonary Function Test Sub-study Objective:

- To assess the effect of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on pulmonary function test (PFT) parameters over 12 hours.

Pharmacokinetic Sub-study Objective:

- To characterize the steady state pharmacokinetics of budesonide, glycopyrronium, and formoterol based on pharmacokinetic (PK) assessments.

HPA Axis Sub-study Objective:

- To assess the effect of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on hypothalamic-pituitary-adrenal (HPA) axis function.

Study Design:

This is a multicenter, randomized, double-blind, parallel-group, chronic-dosing (24 weeks) study to assess the efficacy and safety of BGF MDI, GFF MDI, BFF MDI compared with Symbicort TBH as an active control, in subjects with moderate to very severe COPD.

This study will be conducted at approximately 160 sites, contributing approximately 10 to 20 subjects per site. Across these sites, it is planned that approximately 1800 subjects with moderate to very severe COPD will be randomized to the study to provide approximately 1600 subjects who will complete the study.

Subjects will be randomized in a 2:2:1:1 scheme. Approximately 600 subjects each will be randomized to the BGF MDI and GFF MDI treatment groups, and 300 subjects each will be randomized to the BFF MDI and Symbicort TBH treatment groups. Randomization will be stratified by reversibility to Ventolin HFA, country, and disease severity.

This study will evaluate the benefit of BGF MDI compared to BFF MDI, GFF MDI, and Symbicort TBH, and will also compare BFF MDI to Symbicort TBH with respect to lung function in subjects with moderate to very severe COPD that remain symptomatic (COPD Assessment Test ≥10) on 2 or more inhaled maintenance therapies. A history of exacerbations in the prior year will be obtained to characterize the population, but the entry criteria do not require an exacerbation in the prior year. COPD severity as defined as post-bronchodilator forced expiratory volume in 1 second (FEV_1) must be <80% predicted normal value, calculated using the Third National Health and Nutrition Examination Survey reference equations or local reference equations provided by the Sponsor, and the measured FEV_1 must also be ≥25% of predicted normal value.

Reversibility of FEV_1 to Ventolin HFA, a short acting β2 agonist and to Atrovent HFA, a short-acting muscarinic antagonist will be tested at Visits 2 and 3, respectively. The spirometry data obtained at Visit 2 will be used for stratification purposes.

After the Randomization Visit (Visit 4), subjects will be examined at Visit 5 (Week 4), Visit 6 (Week 8), Visit 7 (Week 12), Visit 8 (Week 16), Visit 9 (Week 20) and Visit 10a (Week 24).

For subjects who remain on treatment throughout the study (i.e., complete Visit 10a), a follow-up telephone call will be performed at least 14 days after the last study drug dose.

Subjects who discontinue study treatment prior to Week 24 (Visit 10a) will be encouraged to remain in the study to complete all remaining study visits during the 24 week treatment period. Subjects who agree to continue to be followed post treatment discontinuation will sign an ICF addendum. All subjects who agree to continue study participation beyond treatment discontinuation will complete a Treatment Discontinuation/Withdrawal Visit (refer to Table 8) prior to transitioning back to regularly scheduled study visits. Subjects participating in a sub-study who choose to discontinue from treatment will only complete regularly scheduled visits and not complete any remaining sub-study assessments. Treatment discontinuation subjects will return to appropriate maintenance COPD medications, per the investigators discretion. For subjects recorded as Treatment Discontinuations that do not complete at least one post-treatment data collection a telephone follow-up call is required at least 14 days after last study drug dose.

If a subject chooses not to continue with study assessments, at a minimum the subject will complete the Treatment Discontinuation/Withdrawal Visit (refer to Table 8). These subjects will return to appropriate maintenance COPD medications, per the investigators discretion. A follow-up telephone call will be performed at least 14 days after the last study drug dose. In the event the Treatment Discontinuation/Withdrawal Visit is performed >14 days post last study drug dosing, a follow-up telephone call will not be required. These subjects will be followed for vital status at 24 weeks post randomization in accordance with the informed consent.

Subjects participating at study centers in Japan will be invited to participate in a 28-week safety extension study, Study PT010007. Any additional assessments required for this extension study will be obtained as stipulated in the Study PT010007 protocol.

This study includes the following 3 sub-studies: 12-hour Pulmonary Function Test (PFT), Pharmacokinetic (PK) Profile, and HPA Axis.

12-Hour Pulmonary Function Test Sub-study: Serial PFTs will be conducted over 12 hours in a subset of approximately 600 randomized subjects (200 subjects from each of BGF MDI and GFF MDI treatment groups, and 100 subjects from each of the BFF MDI and Symbicort TBH treatment groups) at Visit 10a (Week 24).

The PFT sub-study will be conducted at specific sites in the United States (US) that have agreed to participate. Once the target number of subjects has been met, no further enrollment will be allowed in the PFT sub-study.

Pharmacokinetic Sub-study: Pharmacokinetic assessments will be performed in a subset of subjects who participate in the PFT sub-study. Approximately 240 randomized subjects (80 subjects from each of the BGF MDI and GFF MDI treatment groups, and 40 subjects from each of the BFF MDI and Symbicort TBH treatment groups) will be assessed at Visit 10a (Week 24).

Pharmacokinetic assessments will be performed on a subset of PFT sub-study subjects at the sites in the US that have agreed to participate. Once the target number of subjects has been met, no further enrollment will be allowed in the PK sub-study.

HPA Axis Sub-study: Adrenocorticosteroid activity will be assessed in a subset of subjects in the PK sub-study. Serum cortisol will be measured in approximately 108 randomized

subjects (36 subjects from each of the BGF MDI and GFF MDI treatment groups, and 18 subjects from each of the BFF MDI and Symbicort TBH treatment groups) over 24 hours between Visits 3 and 4 prior to dosing at Randomization and Visit 10a (Week 24).

Adrenocorticosteroid activity assessments will be conducted on a subset of PK sub-study subjects at specific sites in the US that have agreed to participate in the HPA axis sub-study. Once the target number of subjects has been met, no further enrollment will be allowed in the HPA axis sub-study.

Study Population:

It is planned that approximately 1800 subjects with moderate to very severe COPD will be randomized to provide approximately 1600 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 & Dose	Product Strength	Dosage Form/ Fill Count	Administration
Study Medications			
BGF MDI (PT010) 320/14.4/9.6 µg ex-actuator	160/7.2/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
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
BFF MDI (PT009) 320/9.6 µg ex-actuator	160/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
Open-Label Products			
Budesonide and formoterol fumarate inhalation powder (Symbicort Turbuhaler) 400/12 µg[a]	EU Source: Symbicort Turbuhaler 200/6 µg per actuation Each metered dose contains: budesonide 200 µg per inhalation and formoterol fumarate dihydrate 6 µg which corresponds to a delivered dose of 160 µg budesonide and 4.5 µg formoterol fumarate dihydrate per inhalation.	DPI/ 60 inhalations	Taken as 2 inhalations BID Supplies are open-label
Albuterol Sulfate inhalation aerosol 90 µg[b] ex-actuator[c]	US source[d]: Ventolin® HFA HFA inhalation aerosol will be the US-supplied product." 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 ex-actuator[e]	US source[d]: Atrovent® HFA HFA will be the US-supplied product." Ipratropium bromide HFA Each inhalation contains 17 µg per actuation	MDI/ 200 actuations	Taken as 2 inhalations QID during Screening Supplies are open-label

BID=twice daily; BGF MDI=Budesonide, Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; GFF MDI=Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; BFF MDI=Budesonide and Formoterol Fumarate Inhalation Aerosol; HFA=Hydrofluroalkane; MDI=Metered Dose Inhaler; DPI=dry powder inhaler; QID=4 times daily; EU=Europe; US=United States.

[a] Active control. Symbicort Turbuhaler is also known as Symbicort Turbohaler in some countries

[b] Active control. Albuterol sulfate is also known as salbutamol sulfate in some countries.

[c] Reversibility testing at Visit 2, rescue medication during the study.

[d] US-sourced products are the preferred product. In cases where it is not possible for the US-sourced product to be used, a locally available product will be provided by Pearl.

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

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

Note: It is preferred that Atrovent and Ventolin be US-sourced products. In cases where it is not possible for the US-sourced product to be used, a locally available product will be provided by the Sponsor. The EU-sourced Symbicort TBH must be used for the active control, and a locally available product cannot be substituted for the sponsor-provided Symbicort TBH.

Duration of Treatment:

It is planned that each subject will receive study treatment for 24 weeks.

Duration of Study:

The entire study period is scheduled to take approximately 30 weeks (expected range between 27 to 30 weeks) for each individual subject. The study is anticipated to run for approximately 18 months and is not expected to exceed 30 months.

Efficacy Assessments:

All efficacy assessments are relative to pre-dose baseline obtained at or prior to Visit 4. The primary endpoints, treatment comparisons of interest, and analysis timeframes may differ by country or region due to local regulatory agency requirements. The 3 different registration approaches will be called: (1) Japan/China, (2) Europe (EU)/Canada, and (3) US. Countries not specifically mentioned will be decided by regulatory requirements and included in one of the three defined registration approaches. The multiplicity controls for the primary and secondary measures will be delineated by approach.

Primary Efficacy Endpoints:

Primary Endpoint (Japan/China Approach)

- Change from baseline in morning pre-dose trough FEV_1 over Weeks 12 to 24 (BGF MDI versus BFF MDI, BGF MDI versus GFF MDI, and BFF MDI versus Symbicort TBH)

Primary Endpoints (EU/Canada Approach)

- FEV_1 area under the curve from 0 to 4 hours (AUC_{0-4}) over 24 weeks (BGF MDI versus BFF MDI and BGF MDI versus Symbicort TBH)
- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks (BGF MDI versus GFF MDI and BFF MDI versus Symbicort TBH[non-inferiority])

Primary Endpoints (US Approach)

- FEV_1 AUC_{0-4} at Week 24 (BFG MDI versus BFF MDI)
- Change from baseline in morning pre-dose trough FEV_1 at Week 24 (BGF MDI versus GFF MDI)

Secondary Efficacy Endpoints:

Endpoints that are not considered primary for an approach or region have been included under secondary endpoints. In addition, perspectives vary about time points to be included from some end points. Therefore, secondary endpoints differ between approaches.

Secondary Endpoints (Japan/China Approach):

- Change from baseline in morning pre-dose trough FEV_1 over 24 Weeks
- FEV_1 area under the curve from 0 to 4 hours (AUC_{0-4}) over Weeks 12 to 24 (BGF MDI versus BFF MDI and BFF MDI versus Symbicort TBH)
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score over Weeks 12 to 24
- Transition Dyspnea Index focal score over Weeks 12 to 24
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Peak change from baseline in FEV_1 within 4 hours post-dosing over Weeks 12 to 24
- Time to clinically important deterioration (CID)
- Time to onset of action on Day 1

Secondary Endpoints (EU and Canada Approach):

- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks (BGF MDI versus BFF MDI)
- Transition dyspnea index (TDI) focal score over 24 weeks (EU only)
- Change from baseline in St. George Respiratory Questionnaire (SGRQ) total score over 24 weeks
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Peak change from baseline in FEV_1 within 4 hours post-dosing over 24 weeks
- Rate of moderate or severe COPD exacerbations
- Change from baseline in the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) RS-Total score over 24 weeks
- Time to CID
- Time to onset of action on Day 1

Secondary Endpoints (US Approach):

- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks

- Percentage of subjects achieving an MCID of 4 units or more in SGRQ total score (SGRQ responders) at Week 24
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Peak change from baseline in FEV_1 within 4 hours post-dosing at Week 24
- Rate of moderate or severe COPD exacerbations
- Time to onset of action on Day 1

Safety Endpoints:

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

12-Hour Pulmonary Function Test Sub-study Endpoints:

The primary endpoint is:

- FEV_1 AUC_{0-12} at Week 24

Additional assessments at Week 24:

- FEV_1 at each time point
- Serial spirometry parameters including FEV_1 AUC_{0-6}, FEV_1 AUC_{6-12}, and time to peak FEV_1
- FVC, PEFR, and FEF_{25-75} will be evaluated using AUC_{0-12}

Pharmacokinetic Sub-study Endpoints:

The endpoints at Week 24 are:

- Steady state AUC_{0-12}
- Time to peak concentration (T_{max})
- Maximum (or peak) serum concentration (C_{max})
- Terminal elimination rate (λ_z) and terminal half-life ($t_{1/2}$)
- Minimum observed concentration (C_{min}), time-average concentration (C_{avg}), %Fluctuation, %Swing

HPA Axis Sub-study Endpoints:

Primary Endpoint:

- Ratio to Baseline of the 0- to 24-hour weighted mean serum cortisol concentration curve at Visit 10a (Week 24)

Statistical Methods:

Primary Efficacy Analysis:

The change from baseline in pre-dose trough FEV_1 will be analyzed using a linear model with repeated measures. The model will include visit, treatment, treatment by visit, and ICS

use at Screening as categorical covariates and baseline trough FEV_1, baseline eosinophil count, and percent reversibility to Ventolin HFA as continuous covariates. An unstructured covariance matrix will be used to model correlation within a subject. If this model fails to converge, a first order autoregressive structure will be used; for this model, subject will be considered a random effect. Two-sided p-values and point estimates with

2-sided 95% confidence intervals will be produced for each treatment difference. All comparisons will be for superiority, except the comparison of BFF MDI to Symbicort TBH, which will be for non-inferiority and will use margins of 50 mL for trough FEV_1 and 75 mL for FEV_1 AUC_{0-4}. Analyses of change from baseline in FEV_1 AUC_{0-4} will use a similar model to trough FEV_1. Sensitivity analyses will also be conducted to evaluate the robustness of the primary analyses to the nature of the missing data.

Sample Size:

It is estimated that a sample size of 1800 randomized subjects (600 per arm in the BGF MDI and GFF MDI groups and 300 per arm in the BFF MDI and Symbicort TBH groups) will provide the following power estimates, all assuming Type I error control at a 2-sided alpha level of 0.05 unless specified otherwise: 99% power to detect a difference of 75 mL between BGF MDI and BFF MDI in FEV_1 AUC_{0-4} over 24 weeks; 96% power to detect a difference of 35 mL between BGF MDI and GFF MDI in morning pre-dose trough FEV_1 over 24 weeks and approximately 92% power over Weeks 12 to 24; 97% power to detect a difference of 50 mL between BGF MDI and BFF MDI in morning pre-dose trough FEV_1 over Weeks 12 to 24; and 96% power to demonstrate non-inferiority of BFF MDI to Symbicort TBH in morning pre-dose trough FEV_1 over 24 weeks and approximately 92% power over Weeks 12 to 24 based on a margin of 50 mL (1-sided, alpha=0.025) assuming no true difference.

Assumptions regarding variability for the primary endpoint are based on Pearl's experience with Phase IIb and III clinical studies. A composite value standard deviation (SD) of 200 mL for the change from baseline at each visit has been assumed for trough FEV_1 and 220 mL for FEV_1 AUC_{0-4}. Dropout is anticipated to be approximately 12% by the end of the study. Based on the repeated-measures analysis, an effective SD for the change over 24 weeks of 157 mL and 173 mL for trough FEV_1 and FEV_1 AUC_{0-4}, respectively, is assumed. For Weeks 12 to 24, an effective SD for trough FEV_1 of 171 mL is assumed.

Data Monitoring and Clinical Endpoint Committees:

Data Monitoring Committee:

An external Data Monitoring Committee will be set up to provide systematic and unbiased assessment of safety for Study PT010006. Members of the DMC will review data at predetermined intervals. If significant safety issues arise in between scheduled meetings, ad hoc meetings will be scheduled to review the data. Based on the safety implications of the data, the DMC may recommend modification or termination of the study.

Clinical Endpoint Committee:

An external clinical endpoint committee will be established for this study. The committee will provide systematic and unbiased assessment of pre-defined, Investigator reported adverse events. The committee will consist of experts who will provide a centralized review functioning independently of Pearl. Three Clinical Endpoint Adjudication Charters will outline the clinical endpoints for adjudication.

- Cardiovascular and Cerebrovascular Clinical Endpoint Adjudication Charter
- Cause-Specific Mortality Clinical Endpoint Adjudication Charter
- Pneumonia Clinical Endpoint Adjudication Charter

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANOVA	analysis of variance
AP	alkaline phosphatase
AST	aspartate aminotransferase (SGOT)
bid	twice daily
BMI	body mass index
BUN	blood urea nitrogen
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COPD	Chronic Obstructive Pulmonary Disease
CRF	case report form
CV	coefficient of variation
E-RS-COPD	Evaluating Respiratory Symptoms in COPD
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
Hct	hematocrit
Hgb	hemoglobin
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
LDH	lactic dehydrogenase

MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
qd	once daily
qid	four times daily
RBC	red blood cell (count)
SAE	serious adverse event
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
tid	three times daily
US	United States
WBC	white blood cell (count)

1 INTRODUCTION

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 as described in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and Japanese Respiratory Society (JRS) guidelines (GOLD 2014, JRS 2013)

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are β2-agonists, anticholinergics, and methylxanthines used as monotherapy or in combination. Treatment with long acting bronchodilators is more convenient and more effective at producing maintained symptom relief than treatment with short acting bronchodilators.

Regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function, and quality of life and reduces the frequency of exacerbations in subjects with COPD with a forced expiratory volume in 1 second (FEV_1) value of <60% of predicted. Withdrawal from treatment of ICS may lead to exacerbations in some patients. When combined with a long acting β2 agonist (LABA), an ICS is more effective than the individual components in improving lung function, quality of life, and reducing exacerbations in subjects with moderate to very severe COPD (GOLD, 2014).

Pearl Therapeutics, Inc. (hereinafter referred to as Pearl) is developing the fixed-dose ICS/ long-acting anti-muscarinic agent (LAMA)/LABA triple combination product, Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (PT010), hereafter referred to as budesonide, glycopyrronium, and formoterol fumarate metered dose inhaler (BGF MDI), for the treatment of patients with COPD. Budesonide and Formoterol Fumarate Inhalation Aerosol (PT009, hereinafter referred to as budesonide and formoterol fumarate (BFF) MDI is also being developed as a twice daily (BID) fixed dose ICS/LABA treatment for patients with COPD. Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (PT003) hereinafter referred to as glycopyrronium and formoterol fumarate (GFF) MDI is being developed as a BID maintenance bronchodilator treatment in patients with COPD.

Budesonide is a well-established corticosteroid approved worldwide in monotherapy and combination therapies for treatment of asthma and allergic rhinitis. It is available in both intranasal and orally inhaled formulations. Inhaled budesonide in combination with formoterol fumarate dihydrate, i.e., Symbicort is approved for use in patients with COPD.

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 for the

treatment of COPD. In addition, tiotropium bromide (Spiriva®) is approved worldwide and has been shown to reduce the rate of COPD exacerbations and to improve the effectiveness of pulmonary rehabilitation (Niewoehner, 2005; Casaburi, 2005).

Formoterol fumarate is a selective LABA approved worldwide for use in asthma and COPD. In addition, formoterol fumarate is also approved worldwide in combination with budesonide (e.g., Symbicort® MDI, Symbicort® Turbuhaler® (TBH [AstraZeneca, LP]) for use in patients with asthma and COPD. When inhaled, formoterol fumarate acts locally in the lung as a bronchodilator. Formoterol fumarate stimulates β2-adrenoreceptors in the airways, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction.

In clinical studies, Symbicort MDI 320/9 µg administered BID demonstrated significant improvements in lung function compared with Budesonide MDI 320 µg BID or formoterol fumarate (Oxis® Turbuhaler) 9 µg BID in patients with COPD. In the clinical studies, improvements in secondary endpoints of morning and evening peak expiratory flow and reduction in rescue medication use were supportive of the efficacy of Symbicort MDI 320/9 µg (Symbicort Inhalation Aerosol Prescribing Information, 2012; Rennard, 2009; Tashkin, 2008).

This study will assess the efficacy of the triple combination therapy (BGF MDI) to its relevant LABA/LAMA and ICS/LABA dual combinations (GFF MDI and BFF MDI) as well as to an approved ICS/LABA product (Symbicort TBH). The study will also evaluate the safety of BGF MDI, BFF MDI, GFF MDI, and Symbicort TBH for subjects with moderate to very severe COPD.

1.1 Study Rationale

This Phase III study is designed to assess the long-term efficacy and safety of BGF MDI compared with GFF MDI, BFF MDI, and Symbicort TBH on lung function, subject-reported symptom outcomes, and health status over 24 weeks. While studies of shorter duration (e.g., 8 to 12 weeks) may be sufficient for the assessment of bronchodilators, Pearl has chosen to characterize efficacy and safety of the aforementioned investigational products for at least 24 weeks to fully characterize the ICS benefit compared with GFF MDI and to fully characterize the LAMA benefit compared with BFF MDI to allow for global registration of BGF MDI.

Consistent with feedback from global regulatory agencies, this study will evaluate a patient population that remains symptomatic despite treatment with 2 or more inhaled maintenance medications. Due to the duration of the Study, a randomized, double-blind (other than the open-label active control), parallel-group design was adopted in order to minimize bias in treatment allocation and to allow unbiased comparisons of treatment groups.

BGF MDI, GFF MDI, and BFF MDI will be randomly assigned in a double-blind fashion, while Symbicort TBH is included as an open-label treatment arm to allow for safety and efficacy comparisons relative to an approved ICS/LABA dual combination.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on lung function.

2.2 Secondary Objectives

- To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on dyspnea.
- To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on quality of life.
- To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on symptoms of COPD.
- To assess the effects of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on COPD exacerbations
- To determine the time to onset of action of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH.

2.3 Safety Objective

- To assess the safety of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH.

2.4 Healthcare Resource Utilization Objective

- To assess overall and COPD-specific Healthcare Resource Utilization (HCRU) of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH

2.5 Sub-study Objectives

2.5.1 12-Hour Pulmonary Function Test Sub-study Objective

- To assess the effect of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on pulmonary function test (PFT) parameters over 12 hours

2.5.2 Pharmacokinetic Sub-study Objective

- To characterize the steady state pharmacokinetics of budesonide, glycopyrronium, and formoterol based on pharmacokinetic (PK) assessments.

2.5.3 HPA Axis Objective

- To assess the effect of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on hypothalamic-pituitary-adrenal (HPA) axis function.

3 STUDY ENDPOINTS

All efficacy assessments are relative to pre-dose baseline obtained at or prior to Visit 4. The primary endpoints, treatment comparisons of interest, and analysis timeframes may differ by country or region due to local regulatory agency requirements. The 3 different registration approaches will be called: (1) Japan/China, (2) Europe (EU)/Canada, and (3) United States (US). Countries not specifically mentioned will be decided by regulatory requirements and included in one of the three defined registration approaches. The delineation of multiplicity controls for the primary and secondary measures will be separated by approach.

3.1 Primary Efficacy Endpoints

3.1.1 Primary Endpoint (Japan/China Approach)

- Change from baseline in morning pre-dose trough FEV_1 over Weeks 12 to 24 (BGF MDI versus BFF MDI, BGF MDI versus GFF MDI, and BFF MDI versus Symbicort TBH)

3.1.2 Primary Endpoints (EU/Canada Approach)

- FEV_1 AUC_{0-4} over 24 weeks (BGF MDI versus BFF MDI; BGF MDI versus Symbicort TBH)
- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks (BGF MDI versus GFF MDI and BFF MDI versus Symbicort TBH[non-inferiority])

3.1.3 Primary Endpoints (US Approach)

- FEV_1 AUC_{0-4} at Week 24 (BFG MDI versus BFF MDI)
- Change from baseline in morning pre-dose trough FEV_1 at Week 24 (BGF MDI versus GFF MDI)

3.2 Secondary Efficacy Endpoints

Endpoints that are not considered primary for an approach or region have been included under secondary endpoints. In addition, perspectives vary about time points to be included from some end points. Therefore, secondary endpoints differ between approaches.

3.2.1 Secondary Endpoints (Japan/China Approach):

- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks
- FEV_1 area under the curve from 0 to 4 hours (AUC_{0-4}) over Weeks 12 to 24 (BGF MDI versus BFF MDI and BFF MDI versus Symbicort TBH)
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score over Weeks 12 to 24
- Transition Dyspnea Index focal score over Weeks 12 to 24

- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Peak change from baseline in FEV_1 within 4 hours post-dosing over Weeks 12 to 24
- Time to clinically important deterioration (CID)
- Time to onset of action on Day 1

3.2.2 Secondary Endpoints (EU/Canada Approach):

- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks (BGF MDI versus BFF MDI)
- Transition dyspnea index (TDI) focal score over 24 weeks (EU only)
- Change from baseline in SGRQ total score over 24 weeks
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Peak change from baseline in FEV_1 within 4 hours post-dosing over 24 weeks
- Rate of moderate or severe COPD exacerbations
- Change from baseline in the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) RS-Total score over 24 weeks
- Time to CID
- Time to onset of action on Day 1

3.2.3 Secondary Endpoints (US Approach)

- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks
- Percentage of subjects achieving an MCID of 4 units or more in SGRQ total score (SGRQ responders) at Week 24
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Peak change from baseline in FEV_1 within 4 hours post-dosing at Week 24
- Rate of moderate or severe COPD exacerbations
- Time to onset of action on Day 1

3.3 Other Efficacy Endpoints:

Endpoints that are not considered secondary for an approach have been included under other endpoints.

3.3.1 Day 1 Assessments:

- Change from baseline at each post-dose time point in FEV_1, forced vital capacity (FVC), peak expiratory flow rate (PEFR), and forced expiratory flow between 25% to 75% (FEF_{25-75})
- Proportion of subjects achieving an improvement from baseline in FEV_1 using different thresholds (e.g., ≥10%, ≥12%, , ≥100 mL, ≥200 mL; and ≥12% and ≥200 mL)

3.3.2 Assessments Over 24 Weeks (Unless Otherwise Stated)

- Rate of moderate or severe COPD exacerbations
- Rate of COPD exacerbations of any severity
- Rate of severe COPD exacerbations
- Time to first moderate or severe exacerbation
- Time to first COPD exacerbation of any severity
- Time to first severe COPD exacerbation
- Time to CID
- Time to sustained CID
- Time to treatment failure (discontinuation for any cause, moderate or severe exacerbation, or death).
- Additional spirometry assessments over 24 weeks, over Weeks 12 to 24, and at each post randomization visit:
  - Change from baseline in morning pre-dose trough for FEV_1, FVC, PEFR, and FEF_{25-75}
  - Peak change from baseline within 4 hours in FEV_1, FVC, PEFR, and FEF_{25-75}
  - FEV_1 AUC_{0-4}, FVC AUC_{0-4}, PEFR AUC_{0-4}, and FEF_{25-75} AUC_{0-4}
- Change from baseline in: the EXACT total score, the E-RS:COPD Total Score, as well as 3 subscale scores (RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms) over each 4-week interval of the 24-week Treatment Period
- TDI focal score at each post-randomization visit
- Individual components of the TDI: functional impairment, magnitude of task, and magnitude of effort over 24 weeks, over Weeks 12 to 24, and at each post-randomization visit
- Percentage of subjects achieving a minimal clinically important difference (MCID) threshold of 1 unit or more on average in TDI focal score over 24 weeks and over Weeks 12 to 24
- Changes from baseline at each post-randomization visit for SGRQ total score
- Change in individual domain scores of SGRQ: Symptoms, Activity, and Impacts over 24 weeks, over Weeks 12 to 24, and at each post-randomization visit
- Percentage of subjects achieving an MCID of 4 units or more in SGRQ total score, at Week 24, over 24 weeks, and over Weeks 12 to 24
- Quality-of-Life Endpoints: European Quality-of-Life-5 Dimensions (EQ-5D-5L) Questionnaire scored at each post-randomization visit

3.4 Safety Endpoints

- Adverse events (AEs)
- 12-lead electrocardiograms (ECG)

- Clinical laboratory testing
- Vital sign measurements

3.5 Health Care Resource Utilization Endpoints:

- Number of days missed from work due to COPD
- Number of days that primary caregivers of subjects missed from work as a result of the subject's COPD
- Percentage of subjects with telephone calls to health care providers
  - call to any health-care provided (physician or other)
  - calls to physician
  - calls to other healthcare provider
- Mean number of telephone calls to health care providers
  - call to any health-care provided (physician or other)
  - calls to physician
  - calls to other healthcare provider
- Percentage of subjects with visits to health care providers
  - visits to any health-care provider (general practitioner [GP], specialist, or other)
  - visits to general practitioner (GP)
  - visits to specialist
  - visits to other health-care provider
- Mean number of visits to health care providers
  - visits to any health-care provider (GP, specialist, or other)
  - visits to GP
  - visits to specialist
  - visits to other health-care provider
- Percentage of subjects with Emergency Room (ER) visits
- Mean number of visits to ERs
- Percentage of subjects hospitalized
- Mean number of subject hospitalizations
- Mean number of days in the hospital
- Mean number of hospitalizations in which subject spent some time in the ICU or CCU
- Percentage of subjects hospitalized with some time spent in the ICU or CCU
- Mean number of days in the hospital with some time spent in the ICU or CCU
- Mean number of hospitalizations in which subject spent no time in the ICU or CCU
- Percentage of subjects hospitalized with no time in the ICU or CCU
- Mean number of days in the hospital with no time spent in the ICU or CCU
- Mean number of days in Intensive Care Units (ICU)
- Percentage of subjects in the ICU

- Mean number of days in Coronary Care Units (CCU)
- Percentage of subjects in the CCU
- Percentage of subjects who required ambulance transport
- Mean number of times ambulance transport was required

3.6 Sub-Study Endpoints

3.6.1 12-Hour Pulmonary Function Test Sub-study Endpoints:

- Pulmonary function tests will be performed at Visit 10a (Week 24).

3.6.1.1 Primary 12-Hour Pulmonary Function Test Endpoint

- FEV_1 AUC_{0-12} at Week 24

3.6.1.2 Other Pulmonary Function Test Assessments at Week 24

- FEV_1 at each time point
- Serial spirometry parameters including FEV_1 AUC_{0-6}, FEV_1 AUC_{6-12}, and time to peak FEV_1
- FVC, PEFR, and FEF_{25-75} will be evaluated using AUC_{0-12}

3.6.2 Pharmacokinetic Sub-study Endpoints:

Pharmacokinetic assessments will be performed at Visit 10a (Week 24).
Pharmacokinetic Endpoints

- AUC_{0-12}
- Time to peak concentration (T_{max})
- Maximum (or peak) plasma concentration (C_{max})
- Terminal elimination rate (λ_z) and terminal half-life ($t_{1/2}$)
- Minimum observed concentration (C_{min}), time-average concentration during a dosing interval (C_{avg}), %Fluctuation, %Swing

3.6.3 HPA Axis Sub-study Endpoints:

3.6.3.1 Primary Endpoint

- Ratio to Baseline of the 0- to 24-hour weighted mean serum cortisol (SC) concentration curve at Visit 10a (Week 24)

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a multi-center, randomized, double-blind, parallel-group, chronic-dosing (24 weeks), active-controlled study to assess the efficacy and safety of BGF MDI, GFF MDI, BFF MDI, compared with Symbicort TBH as an active control in subjects with moderate to very severe COPD.

This study will assess the benefit of BGF MDI compared with BFF MDI, GFF MDI, and Symbicort TBH and will also compare BFF MDI to Symbicort TBH with respect to lung function in subjects with moderate to very severe COPD that remain symptomatic (COPD Assessment Test [CAT] ≥10) on 2 or more inhaled maintenance therapies. A history of exacerbations in the prior year will be obtained to characterize the population, but the entry criteria do not require an exacerbation in the prior year. COPD severity as defined as post-bronchodilator FEV_1 must be <80% predicted normal value, calculated using Third National Health and Nutrition Examination Survey (NHANES III) reference equations or local reference equations provided by the Sponsor, and the measured FEV_1 must also be ≥25% of predicted normal value.

This study will be conducted at approximately 160 sites, contributing approximately 10 to 20 subjects per site. Across these sites, approximately 1800 subjects with moderate to very severe COPD will be randomized into the study to provide approximately 1600 subjects to complete the study.

Subjects will be randomized in a 2:2:1:1 scheme. Approximately 600 subjects each will be randomized to the BGF MDI and GFF MDI treatment groups, and 300 subjects each will be randomized to the BFF MDI and Symbicort TBH treatment groups. Randomization will be stratified by reversibility to Ventolin HFA, country, and disease severity.

The Screening Period will be comprised of 3 study visits.

At Visit 1 (Screening), all subjects are to sign an informed consent form (ICF) prior to the conduct of any screening assessments. Subject participation in the sub-studies also will be determined at Screening, prior to any study procedures. At the Screening Visit, the Investigator will obtain a medical history including specific cardiovascular history, COPD exacerbations within the last year, clinical laboratory tests, physical examination, and any required documentation in order to determine eligibility for participation (i.e., inclusion /exclusion criteria). Subjects must meet spirometry criteria for COPD as detailed in the inclusion/exclusion criteria.

During the screening period subjects that are receiving an ICS/LABA will discontinue the ICS/LABA, but will continue the ICS component for the remainder of the screening period.

Similarly, subjects treated with an ICS as part of their inhaled maintenance therapy will also be permitted to continue their ICS for the remainder of the screening period. All subjects will receive sponsor-provided open-label Atrovent® hydrofluoroalkane (HFA; ipratropium

bromide inhalation aerosol) administered QID for COPD maintenance. All subjects will receive sponsor-provided Ventolin® HFA (albuterol sulfate inhalation aerosol) for rescue use throughout the study. NOTE: ICS and Atrovent HFA administered during screening will be discontinued at Visit 4 prior to randomization.

Subjects will be issued and trained on the use of the electronic diary (eDiary) at Visit 1 (Screening) and will be instructed to collect practice data during the Screening Period (between Visit 1 and Visit 4). Subject eDiary compliance will be reviewed at Visits 2 and 3, and the subject will be retrained if necessary.

Subjects who meet all entry criteria (Section 5.1 and Section 5.2) will discontinue any prohibited COPD medications for the duration of the study, with a minimum washout period observed between Visits 1 and 2 (see Table 1) followed by an adjustment of medications to protocol-allowable COPD therapy (see Section 5.4.1)

Reversibility of FEV_1 to Ventolin HFA, a short acting β2 agonist (SABA) and to Atrovent HFA, a short-acting muscarinic antagonist (SAMA) will be tested at Visit 2 and 3, respectively. Reversibility testing is described in Section 7.1.1.1. The spirometry data obtained at Visit 2 will be used as an inclusion criterion (Section 5.1). Re-screening is not allowed for subjects who do not meet the spirometry criteria at Visit 1.

Subjects participating at study centers in Japan will be invited to participate in a 28-week safety extension study, Study PT010007. Any additional assessments required for this extension study will be obtained as stipulated in the Study PT010007 protocol.

This study includes the following 3 sub-studies: 12-hour pulmonary function test (PFT), pharmacokinetic (PK), and HPA axis.

12 Hour Pulmonary Function Test Sub-study (US sub-study only): Serial PFTs will be conducted over 12 hours in a subset of approximately 600 randomized subjects (200 subjects from each of BGF MDI and GFF MDI treatment groups, and 100 subjects from each of the BFF MDI and Symbicort TBH treatment groups) at Visit 10a (Week 24). On the test day, additional serial spirometry will be obtained at 6, 8, 10, 11.5 and 12 hours post-dose (refer to Section 7.1.1 and Table 10 for details).

The PFT sub-study will be conducted at specific sites in the US that have agreed to participate. Once the target number of subjects for recruitment has been met, no further enrollment will be allowed in the PFT sub-study.

Pharmacokinetic Sub-study: Pharmacokinetic assessments will be performed in a subset of subjects who participate in the PFT sub-study. Approximately 240 randomized subjects (80 subjects from each of the BGF MDI and GFF MDI treatment groups, and 40 subjects from each of the BFF MDI and Symbicort TBH treatment groups) will be assessed at Visit 10a (Week 24). Refer to Section 7.3 for PK sample collection requirements and Table 10 for timing of PK assessments.

Pharmacokinetic assessments will be performed on a subset of PFT sub-study subjects at specific sites in the US that have agreed to participate. Once the target number of subjects for recruitment has been met, no further enrollment will be allowed in the PK sub-study.

Pharmacokinetic assessments will be performed on a subset of PFT sub-study subjects at specific sites that have agreed to participate. Once the target number of subjects for recruitment has been met, no further enrollment will be allowed in the PK sub-study.

HPA Axis Sub-study: Adrenocorticosteroid activity will be assessed in a subset of subjects in the PK sub-study. Serum cortisol (SC) will be measured in approximately 108 randomized subjects (36 subjects from each of the BGF MDI and GFF MDI treatment groups, and 18 subjects from each of the BFF MDI and Symbicort TBH treatment groups) over 24 hours, between Visits 3 and 4 prior to dosing at Randomization and Visit 10a (Week 24). Refer to Section 7.4 for HPA Axis sample collection requirements and Table 10 for timing of HPA Axis assessments.

Adrenocorticosteroid activity assessments will be conducted on a subset of PK sub-study subjects at specific sites in the US that have agreed to participate in this HPA Axis sub-study. Once the target number of subjects for recruitment has been met, no further enrollment will be allowed in the HPA Axis sub-study.

At Visit 4 (Day 1, Randomization), subject eDiary compliance will be reviewed, and subjects who are unable to meet the compliance requirement (>70% subject completion of diary assessments) in the last 7 days preceding Visit 4, or who are unable to meet the FEV_1 baseline stability criteria, will be considered screen failures (Refer to Section 7.1.2). Subjects will be evaluated for FEV_1 baseline stability criteria (baseline FEV_1 at Visit 4 must be within ±20% or 200 mL of mean of the pre-dose FEV_1 values obtained at the 2 preceding visits [see Section 7.1.1.2]). Those subjects who remain eligible for participation in the study will discontinue their ICS and Atrovent HFA administered during screening and will be randomized into 1 of the 4 treatment arms. Randomization will be centralized through the use of an Interactive Web Response System (IWRS).

Subjects will inhale 2 puffs from their MDI in the morning between 6:00 and 10:00 AM (breakfast time) and in the evening between 6:00 and 10:00 PM (dinner time). Symbicort TBH also will be administered as 2 inhalations twice daily.

After the Randomization Visit (Visit 4), subjects will be examined at Visit 5 (Week 4), Visit 6 (Week 8), Visit 7 (Week 12), Visit 8 (Week 16), Visit 9 (Week 20) and Visit 10a (Week 24). In total, each completed subject will attend 10 scheduled visits in this study for a maximum of 30 weeks. For the assessments scheduled at each of these visits, refer to the Schedule of Events (Table 8).

Mean pre-dose morning PFTs will be assessed at every visit. Post-dose PFTs will also be assessed at all visits (refer to Section 7.1.1 for details).

Throughout the course of the study the subjects will be required to complete the following questionnaires; Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) , St. George's

Respiratory Questionnaire (SGRQ), EuroQol 5 Dimensions Questionnaire (EQ-5D-5L), Chronic Obstructive Pulmonary Disease Assessment Test (CAT) and Exacerbations of Chronic Pulmonary Disease Tool – Patient Reported Outcomes (EXACT, please note new name in Section 7.1.4.5 and see Section 8 for details and timing of the assessments). The EXACT nomenclature will be used throughout the protocol unless otherwise noted. Site will be requested to complete HCRU questionnaire throughout the study (see Section 8 for details and timing of the assessments).

For subjects who remain on treatment throughout the study (i.e., complete Visit 10a), a follow-up telephone call will be performed at least 14 days after the last study drug dose.

Subjects who discontinue study treatment prior to Week 24 (Visit 10a) will be encouraged to remain in the study to complete all remaining study visits during the 24 week treatment period. Subjects who agree to continue to be followed post treatment discontinuation will sign an ICF addendum. All subjects, who agree to continue study participation beyond treatment discontinuation, will complete a Treatment Discontinuation/Withdrawal Visit (refer to Table 8) prior to transitioning back to regularly scheduled study visits. Subjects participating in a sub-study who choose to discontinue from treatment will only complete regularly scheduled visits and not complete any remaining sub-study assessments. Treatment discontinuation subjects will return to appropriate maintenance COPD medications, per the investigators discretion. For subjects recorded as Treatment Discontinuations that do not complete at least one post-treatment data collection a telephone follow-up call is required at least 14 days after last study drug dose.

If a subject chooses not to continue with study assessments, at a minimum the subject will complete the Treatment Discontinuation/Withdrawal Visit (refer to Table 8). These subjects will return to appropriate maintenance COPD medications, per the investigators discretion. A follow-up telephone call will be performed at least 14 days after the last study drug dose. In the event the Treatment Discontinuation/Withdrawal Visit is performed >14 days post last study drug dosing, a follow-up TC will not be required. These subjects will be followed for vital status at 24 weeks post randomization in accordance with the informed consent.

Further details will be provided in the DMC charter and in the Statistical Analysis Plan (SAP).

General Considerations for Treatment Visits 4 through Visit 10a

- Subjects that are randomized will be instructed to discontinue all previous inhaled medication used during the screening period, including protocol adjusted ICS therapy as defined at Visit 1 (screening), and only use sponsor provided inhaled study medications for the remainder of the study.
- At the start of each study visit, prior to any study procedures being performed, site personnel must confirm the subject withheld all COPD medications, including study medication, rescue Ventolin HFA or locally available product (where necessary), for at least 6 hours, by confirming the last time of dosing for all COPD medication(s).

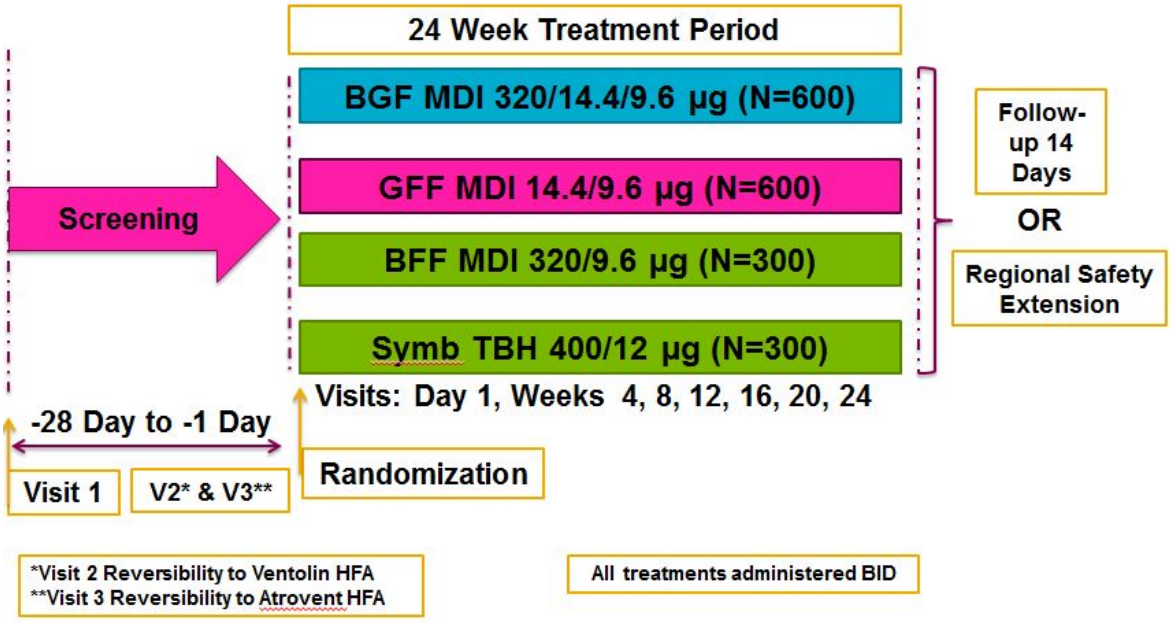
- Note: Subjects who inadvertently took COPD medication(s) within 6 hours of the start of study procedures must be rescheduled as soon as is practical but within the specified visit window. In addition, before the in-clinic dose is administered, the site must confirm the subject met all other protocol specified requirements (e.g., FEV_1 baseline stability and eDiary compliance).
- All post-randomization visits will be scheduled relative to Visit 4 (Day 1). Visits 5, 6, 7, 8, 9, and 10a will be scheduled 4, 8, 12, 16, 20 and 24 Weeks (± 2 days) of Visit 4, respectively. Sites should make every effort to maintain subjects within the scheduled visit window. If a visit falls outside the expected visit window the subsequent visit should still be scheduled as planned relative to Visit 4.
- Subjects must not ingest xanthine and/or xanthine analogue (caffeine)-containing foods, medications, 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.
- 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 4 for all treatment visits (± 2 hours) but no later than 10:00 AM and will be required to remain at the clinic until completion of all protocol-defined assessments.
- Sites should make every effort to ensure that the in-clinic dosing time is before 10:00 AM and within 12±2 hours of the prior at home evening dosing time.
- The in-clinic dosing time for study drug (BGF MDI, GFF MDI, and BFF 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 and remind the subject of the following:
  - To take their last dose the evening before the scheduled visit;
  - To bring their study medications and eDiary with them to the clinic and to withhold all COPD medications (locally available products, if applicable) for at least 6 hours prior to PFTs;
  - To refrain from ingesting xanthine (caffeine)-containing foods, beverages, or medications for at least 6 hours prior to each study visit and for the duration of each study visit;
  - To 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 the 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.

- Subjects completing Visit 10a may be invited to participate in a safety extension study in Japan (Study PT010007) to evaluate the long-term safety of BGF MDI, BFF MDI, and GFF MDI for an additional 28 weeks. All subjects from Japan who volunteer to participate in the extension study will complete Visit 10a (Final Study Visit) and Visit 10b (Safety Extension Study Entry Visit) (refer to the protocol for Study PT010007 for additional details).
- Subjects not participating in the safety extension study (Study PT010007) will complete all Visit 10a (Final Study Visit) assessments and will be scheduled for a post study follow-up telephone call at least 14 days from Visit 10a.

An overall study design is summarized and displayed in Figure 1.

Figure 1. Study Design



4.2 Rationale of Study Design

This Phase III study is designed to assess the long-term efficacy and safety of BGF MDI compared with GFF MDI, BFF MDI, and Symbicort TBH on lung function, subject-reported symptom outcomes, exacerbations and health status over 24 weeks. While studies of shorter duration (e.g., 8 to 12 weeks) may be sufficient for the assessment of bronchodilators, Pearl has chosen to characterize efficacy and safety of the aforementioned investigational products for at least 24 weeks to fully characterize the ICS benefit compared with GFF MDI and to fully characterize the LAMA benefit compared with BFF MDI to allow for global registration of BGF MDI.

Consistent with feedback from global regulatory agencies, this study will evaluate a patient population that remains symptomatic despite treatment with 2 or more inhaled maintenance medications.

Due to the duration of the Study, a randomized, double-blind (other than the open-label active control), parallel-group design was adopted in order to minimize bias in treatment allocation and to allow unbiased comparisons of treatment groups.

BGF MDI, GFF MDI, and BFF MDI will be randomly assigned in a double-blind fashion, while Symbicort TBH is included as an open-label treatment arm to allow for safety and efficacy comparisons relative to an approved ICS/LABA dual combination.

In order to place the efficacy and safety of BGF MDI into context, BFF MDI, GFF MDI and Symbicort TBH are included in the study. It is important to ensure that subjects only receive the inhaled treatment assigned at randomization. Those subjects on oral phosphodiesterase inhibitors (e.g., roflumilast, theophylline) may continue to use these medications as prescribed. When necessary, subjects will be allowed to use sponsor-provided Ventolin (albuterol sulfate) HFA or a locally available and comparable rescue product.

No currently approved treatment prevents death or irreversible morbidity by influencing the course of disease.

4.3 Rationale of Dose/Regimen and Duration of Treatment

The safety and efficacy of the individual components, budesonide, glycopyrronium, and formoterol fumarate are well characterized, and all 3 components are components (alone or in combination) of approved inhalation products for the treatment of patients with COPD.

The doses of the glycopyrronium and formoterol fumarate components of BGF MDI and BFF MDI match the doses utilized in the GFF MDI development program. The GFF MDI clinical program consisted of 12 clinical studies to support the dose selection of glycopyrronium and formoterol fumarate for the dual combination GFF MDI, as well as its components GP MDI and FF MDI, in subjects with moderate to very severe COPD. Based on the data obtained through this Phase II program, a dose of GFF MDI 14.4/9.6 μg BID was selected for progression into Phase III. Two Phase III pivotal efficacy and safety studies, and one long-term extension study, have recently completed which evaluated the efficacy and

safety of GFF MDI, GP MDI, and FF MDI as bronchodilator treatments in subjects with moderate to very severe COPD.

In order to select the appropriate budesonide dose for Phase III studies, Pearl Therapeutics has conducted 2 Phase I PK and safety studies. Pearl Therapeutics has conducted an initial Phase I, single-dose, PK and safety study in healthy adult subjects (Study PT010001) with 3 doses of the triple combination product, BGF MDI, compared with 2 doses of Symbicort MDI and a single dose of the Pearl dual combination product GFF MDI. The study demonstrated that formoterol and glycopyrrolate plasma concentrations following administration of all BGF MDI doses were similar to those following GFF MDI administration, and budesonide plasma concentrations were comparable between BGF MDI and Symbicort MDI. All treatments were well tolerated with a low frequency of AEs, and no untoward safety signals were observed. The results of Study PT010001 supported the evaluation of BGF MDI 320/14.4/9.6 µg and lower doses in further clinical studies, and suggested that the addition of budesonide to GFF MDI does not impact the systemic levels of either component.

Pearl Therapeutics also conducted a randomized, double-blind, single-dose crossover study (Study PT010002) to evaluate the safety and PK of BGF MDI (320/14.4/9.6 µg), BFF MDI (320/9.6 µg), and Symbicort TBH (400/12 µg) in healthy adult subjects. Study PT010002 was conducted to investigate the PK comparability of BGF MDI and BFF MDI to Symbicort TBH. The budesonide component of BGF MDI was nearly identical on Cmax with a GMR of 1.02 and 90% confidence interval (CI) of (0.81, 1.30), but AUC_{0-12} was approximately 25% higher than Symbicort TBH. Similar results were obtained for the comparison of BFF MDI to Symbicort TBH. Study PT010002 also investigated the potential for a DDI by comparing the budesonide and formoterol 12-hour PK profiles following a single dose of BGF MDI or BFF MDI. No DDI was observed as both budesonide and formoterol C_{max} and AUC_{0-12} were similar, following administration of either BGF MDI or BFF MDI.

Based on results from Studies PT010001 and PT010002 and given that higher doses of budesonide are approved in many countries for asthma, it is reasonable to progress to the 320 µg budesonide as the highest dose of BGF MDI and BFF MDI in this study.

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

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:

a. Non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal)
b. Childbearing 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 the Final Visit):
   - Complete abstinence from intercourse (when it is preferred and usual lifestyle of the patient); 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, inserted by a qualified physician, with published data showing that the highest expected failure rate is less than 1% per year; or
   - Estrogenic vaginal ring; or
   - Percutaneous contraceptive patches.

4. COPD Diagnosis: Subjects with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) (Celli, 2004) or by locally applicable guidelines e.g., JRS Guidelines (JRS, 2013) characterized by:
   - Progressive airflow limitation associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.
5. Tobacco Use: Current or former smokers with a history of at least 10 pack-years of cigarette smoking. (Number of pack-years = [number of cigarettes per day/20] x number of years smoked [e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years represent 10 pack-years]).
6. COPD Severity: Subjects with an established clinical history of COPD and severity defined as:
   - At Visit 1, FEV_1/FVC ratio must be <0.70 and FEV_1 must be <80% predicted normal value calculated using NHANES III reference equations (Or reference norms applicable to other regions, e.g., for Japan, use JRS reference equations; [JRS, 2013]).

- At Visit 2, post-bronchodilator FEV_1/FVC ratio of <0.70 and post-bronchodilator FEV_1 must be ≥25% to <80% predicted normal value, calculated using NHANES III reference equations (Or reference norms applicable to other regions, e.g., for Japan, use JRS reference equations [JRS, 2013]).
- At Visit 4, the average of the 60 min and 30 min pre-dose FEV_1 assessments must be <80% predicted normal value, calculated using NHANES III reference equations (Or reference norms applicable to other regions, e.g., for Japan, use JRS reference equations [JRS, 2013]).
- Symptomatic (CAT ≥10) at Screening (Visit 2).

7. Required COPD Maintenance Therapy:
   - All Subjects must have been on two or more inhaled maintenance therapies for the management of their COPD for at least 6 weeks prior to Screening. Scheduled SABA and/or scheduled SAMA are considered inhaled maintenance therapies
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 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, except in countries with restrictive radiology assessment practice where only subjects who have had a chest X-ray or CT scan (thorax) performed outside of the study in the last 6 months are allowed to be enrolled. Alternatively, in these countries an MRI may be used instead of a CT scan or chest X-ray, as per local practice assessment.
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 who meet any of the following criteria will be excluded from the study.

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 that, in the opinion of the Investigator, have a current diagnosis of asthma.
b. Alpha-1 Antitrypsin Deficiency: Subjects who have alpha-1 antitrypsin deficiency as the cause of COPD.
c. Other Respiratory Disorders: Subjects who have other active pulmonary disease such as active tuberculosis, lung cancer, bronchiectasis (High Resolution CT evidence of

bronchiectasis that cause repeated acute exacerbations), sarcoidosis, idiopathic interstitial pulmonary fibrosis (IPF), primary pulmonary hypertension, or 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 6 months of Visit 1.
e. Hospitalization: Subjects who have been hospitalized due to poorly controlled COPD within 3 months prior to Visit 1 (Screening) or during the Screening Period (Visit 1 to Visit 4).
f. Poorly Controlled COPD: Subjects who have poorly controlled COPD, defined as acute worsening of COPD that requires treatment with oral corticosteroids or antibiotics within 6 weeks prior to Visit 1 (Screening) with less than a 4 week washout of corticosteroids and/or antibiotics prior to Visit 1 or during the Screening Period (Visit 1 to Visit 4). Note: Subjects who are steroid dependent and maintained on an equivalent of 5 mg prednisone per day or 10 mg every other day for at least 3 months prior to Visit 1 are eligible for enrollment providing the dose of oral steroids remains stable during the Screening Period Visit 1 through Visit 4.
g. Lower Respiratory Tract Infection: Subjects who had lower respiratory tract infections that required antibiotics within 6 weeks prior to Visit 1 (Screening) with less than a 4 week washout of antibiotics prior to Visit 1 (Screening)
h. Upper Respiratory tract infections (URTI) that have not resolved at least 7 days prior to Screening
i. Chest x-ray (frontal and lateral) with suspicion of pneumonia or other condition/abnormality that will require additional investigation/treatment, or put the subject at risk because of participation in the study.
j. Risk factors for pneumonia: immune suppression (HIV) severe neurological disorders affecting control of the upper airway or other risk factors that in the opinion of the Investigator would put the subject at substantial risk of pneumonia
k. Pneumonia not clinically resolved within 14 days of Visit 1.
l. 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 FEV_1 during at least 1 of the pre-bronchodilator assessments at Visit 2 (60 minute or 30 minute) and at the post-bronchodilator assessment at Visit 2.
   - FEV_1 Baseline Stability: Subjects who cannot meet protocol-specified baseline stability criteria. FEV_1 baseline stability is defined as the average of the 60 minute and 30 minute pre-dose FEV_1 assessments at Visit 4 being within ±20% or 200 mL of the mean of the pre-bronchodilator FEV_1 assessments obtained at the 2 preceding visits (average of pre-dose FEV_1 assessments obtained at Visit 2 and Visit 3).
m. Oxygen: Subjects receiving long-term-oxygen therapy (LTOT) or nocturnal oxygen therapy required for greater than 15 hours a day. Note: As needed oxygen use is not exclusionary.

n. Subject use of any non-invasive positive pressure ventilation device.
Note: Subjects using continuous positive airway pressure or bi-level positive airway pressure for Sleep Apnea Syndrome are allowed in the study if not used for ventilatory support.
o. 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 4).
p. 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 Screening Period. Subjects who are in the maintenance phase of a pulmonary rehabilitation program are not to be excluded.
q. Subjects who have initiated or altered the dose regimen of intranasal corticosteroids, intranasal antihistamines, or a combination thereof within 7 days prior to Visit 1 or during the Screening Period (Visit 1 to Visit 4).
4. Cardiac disease
a. Subjects who have unstable ischemic heart disease, left ventricular failure, or documented myocardial infarction within 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 4), 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 Type 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. 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 5 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 narrow-angle glaucoma that, in the opinion of the Investigator, has 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, timolol) and prostaglandin analogues.
11. Drug Allergy: Subjects who have a history of hypersensitivity to β2 agonists, budesonide or any other corticosteroid components, glycopyrronium or other muscarinic anticholinergics, or any component of the MDI or dry powder inhaler (DPI).
12. Substance Abuse: Subjects who in the opinion of the Investigator significantly abuse alcohol or drugs (refer to Exclusion Criterion 1).

13. Medication prior to spirometry: Subjects who are medically unable to withhold their short-acting bronchodilators for the 6-hour period required prior to spirometry testing at each study visit will be excluded.
14. Prohibited Medications: Subjects who, in the opinion of the Investigator, would be unable to abstain from protocol-defined prohibited medications during the Screening Period and treatment phases of this study (refer to Section 5.4).
15. 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.
    Note: Nebulized albuterol is acceptable, but requires a minimum 6 hours washout prior to Visit 1 and must be discontinued at Visit 1 and throughout the study.
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 non-compliance with diary completion (i.e., <70% subject completion of diary assessments in the last 7 days preceding Visit 4).
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 4).
21. Investigational Drugs or Devices: Treatment with investigational study drug or device in another clinical Study within the last 30 days or 5 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 require the use of a spacer device to compensate for poor hand-to-breath coordination with a MDI. Note: Use of a nebulizer to deliver maintenance COPD medications is prohibited throughout the Study.
23. Previous Participation: Subjects who were previously enrolled in any previous PT009 or PT010 study. However, subjects will be permitted to participate in any supplemental or extension study to this study (PT010006).

5.3 Subject Identification

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

5.4 Prior, Concomitant, and Prohibited Medications

All prescription and over-the-counter (OTC) medications taken by the subject within 30 days before Visit 1 (Screening) will be recorded on the prior/concomitant medications eCRF. Any additions, deletions, or changes in the dose of these medications while in the study should be

entered on the eCRF. Any current ongoing medications, including OTC drugs and herbal supplements, will be allowed provided they are not prohibited by the protocol (refer to Section 5.4.1) and are approved by the Investigator. Subjects should also be instructed to contact the Investigator if they develop any illnesses.

All concomitant medications taken during the study will be recorded on the Concomitant Medications eCRF with indication, dose, dose regimen, and dates of drug administration.

5.4.1 Allowed Medications to Treat a COPD Exacerbation

Medications to treat an exacerbation should not be used for more than 14 days. Recent data have suggested that treatment with systemic steroids for shorter periods of time results in similar outcomes with less systemic steroid exposure. Therefore, it is recommended that subjects are treated with a 5 day course of steroids (Leuppi, 2013) and no longer than 14 days. During a COPD exacerbation, it is important for subjects to be treated as deemed appropriate by the treating health care provider. However, subjects should return to their pre-exacerbation medication regimen as soon as practical.

5.4.2 Pneumococcal and Annual Influenza Vaccination

All subjects should be vaccinated per local guidelines [current global recommendation per local policies, availability, and affordability: GOLD, 2016]. For subjects that have been previously vaccinated with pneumococcal vaccine, the investigator should assess whether a booster vaccination is required. Annual influenza vaccine should also be administered per local guidelines. Pneumococcal and/or annual influenza vaccine can be given at Visit 1 or at any other visit throughout the study at the discretion of the investigator; however, administration should occur after obtaining all requisite PFT assessments for that specific test day. There should be at least 7 days between vaccination and subsequent PFT assessments.

5.4.3 Prohibited COPD Medications and Required Washout Period Prior to Visit 2

Subjects who meet the screening criteria at Visit 1 that are being treated with any of the medications listed in Table 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, unless meeting conditions described in Section 5.4.1.

Table 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 Aclidinium: 7 days Glycopyrronium: 7 days Umeclidinium: 7 days
Short-acting muscarinic antagonists (SAMA) [a]	6 hours
LABAs (inhaled)	7 days (14 days for indacaterol and olodaterol)
Fixed-combinations of LABA/LAMA	7 days (14 days for indacaterol/glycopyrronium and olodaterol/tiotropium)
Fixed-combinations of LABA/ICS	7 days
Fixed-combinations of SABAs and SAMAs	6 hours
SABAs [b]	6 hours
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 β2 agonist; LAMA=long acting muscarinic antagonist;

SABA=short-acting β2 agonist; SAMA=short-acting muscarinic antagonist

Note: Roflumilast (or any PDE4 inhibitor) is allowed provided the subject has 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 (≤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 4-week washout prior to Screening (Visit 1). Any subject that requires systemic corticosteroids during the Screening Period (Visit 1 to Visit 4) will be screen failed.

Note:

- Subjects who are steroid dependent and maintained on an equivalent of up to 5 mg oral prednisone per day or up to 10 mg oral prednisone every other day for at least 3 months prior to Visit 1 are eligible for enrollment, provided the dose of oral steroids remains consistent and does not exceed this threshold for the last two weeks prior to randomization (Visit 4).
- During the Treatment Period (Visit 4 to Visit 10a), subjects may be treated with systemic corticosteroids if required.

Subjects who meet all entry criteria but are using 1 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 Study and be switched to Sponsor provided Atrovent HFA administered 4 times daily (QID) and Sponsor provided Ventolin HFA to be administered up to 4 times per day, as needed, for control of symptoms during the Screening Period.
- Subjects receiving a maintenance dose of an ICS as part of a fixed-dose combination therapy containing fluticasone and salmeterol, mometasone and formoterol, budesonide and formoterol or fluticasone and formoterol or other approved fixed dose ICS/LABA combinations 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 up to QID, as needed, to control 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, vilanterol, olodaterol), or currently-marketed LAMA (tiotropium, aclidinium, glycopyrronium, umeclidinium) administered alone, as a loose combination, or as a fixed combination (e.g., umeclidinium/vilanterol, Glycopyrronium/indacaterol, aclidinium bromide/formoterol fumarate) will have these medications discontinued and replaced with Sponsor-provided Atrovent HFA administered QID, and Sponsor-provided Ventolin HFA to be administered up to QID, as needed for control of symptoms during the Screening Period.

  Note: All adjusted maintenance therapy for COPD, including ICS will be stopped at randomization.

It is preferred that Atrovent and Ventolin be US-sourced products. In cases where it is not possible for the US-sourced product to be used, a locally available product will be provided by the Sponsor. The EU-sourced Symbicort TBH must be used for the active control, and a locally available product cannot be substituted for the sponsor-provided Symbicort TBH.

Subjects receiving the following respiratory medications must discontinue these medications at the initial Screening Visit (Visit 1). The minimum cessation period must be met prior to returning for Visit 2. These medications are not permitted during the study (Table 2).

Table 2. Other Respiratory/Nasal Medications and Required Washout Periods Prior to Visit 2

Class of Medication	Minimum Washout 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

5.4.4 Other Prohibited Medications

Table 3 lists certain non-COPD medications that can be used under the stated conditions during this study. Each concomitant drug must be individually assessed against all exclusion criteria. If in doubt, the Investigator should contact Pearl's Medical Monitor before randomizing a subject or allowing a new medication to be started:

Table 3. Non COPD Medications Allowed Under Certain Conditions

Medications Allowed Under Certain Conditions	Condition
SSRIs or SNRIs or NaSSAs	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 Screening (Visit 1) and during the Screening Period

Abbreviations: COPD=chronic obstructive pulmonary disease; SNRI=serotonin–norepinephrine reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors; NaSSAs=noradrenergic and specific serotonergic antidepressants

Note: Use of cutaneous topical medications, including cutaneous topical corticosteroids, is permitted provided these medications are not applied to more than 20% of the subject's body surface area.

Subjects requiring medications presented in Table 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. 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 randomized treatment, resume the appropriate COPD maintenance therapy, and be encouraged to complete the remaining study visits.

Table 4. Prohibited Medications

Prohibited Medications	Minimum Cessation Period Prior to Screening (Visit 1)
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 β-blocking agents [a]	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 [b]	Allowed if stable dose for at least 3 months and free of seizures for 1 year
Tricyclic antidepressants [c]	14 days
Monoamine oxidase inhibitors	14 days
Anti-tumor necrosis factor 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 [d]	30 days or 5 half-lives, whichever is longer
Antipsychotic drugs [c]	30 days
Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors, and cimetidine	30 days
Systemic anticholinergics [e]	7 days
Chinese complementary and alternative bronchodilatory medicines (CAM), ie, herbal therapies (eg, *Astragalus membranaceus [*huáng qí], *Panax ginseng [ginseng products]* and *Cordyceps sinensis. A. membranaceus [ghost moth caterpillar fungus])* [f]	10 days

Note: Benzodiazepines are not exclusionary.

[a] Carvedilol is allowed for the treatment of Class I/II congestive heart failure where use of this medication is appropriate

[b] Anticonvulsants for conditions other than seizure disorders may be started and stopped at any time throughout the study

[c] Antipsychotic agents and tricyclic antidepressants used for previously diagnosed underlying medical conditions are allowed if, in the opinion of the Investigator, there are no concerns regarding patient safety, and if the patient has been on a stable dose for at least 6 weeks prior to Visit 1

[d] Investigators should contact the Medical Monitor to determine the appropriateness and safety of continuing study drug on a case by case basis (eg, XOLAIR® [omalizumab] will not be allowed, whereas a monoclonal antibody for another indication, such as osteoporosis, may be allowed after consultation with the Medical Monitor)

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

[f] Requires case-by-case review by the Investigator to determine appropriate wash-out period, if needed.

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 the Follow-up TC or to whenever the subject withdraws from 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 at the discretion of the investigator. 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 in the PK sub-study are encouraged to refrain from consuming grapefruits or grapefruit juice during the last 4 weeks of the study (i.e., between Visit 9 and Visit 10a). After the screening visit (Visit 1), subjects must not ingest xanthine and/or xanthine analogue (caffeine)-containing foods or beverages or caffeine containing medications, 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 4) will result in a screen failure. Smoking status changes during the 24-week Treatment Period will be captured in the eCRF, but the subject will be permitted to continue in the study. Subjects will be required to refrain from smoking (including medical marijuana and electronic cigarettes) for at least 4 hours prior to each study visit after the Screening Visit, and throughout the duration of each study visit. Study participants may utilize various nicotine replacement treatments such as chewing gum and patches, as needed, in accordance with recommendations from the Investigator during the entire study visit.

Note: For this study, the use of electronic cigarettes will be treated in the same manner as smoking.

5.7 Reasons for Treatment Discontinuation or Study Withdrawal

5.7.1 Reasons for Treatment Discontinuation

The subject may voluntarily discontinue treatment at any time without prejudice to further treatment.

If a subject experiences any of the changes of concern listed below, a repeat assessment should be obtained, and if confirmed, the subject should be discontinued from randomized treatment and continued in the study. The changes of concern include:

- Calculated QTcF intervals >500 msec, and have increased by 60 msec or more over test day baseline value.
- Hepatic impairment defined as abnormal liver function test of AST, ALT or total bilirubin ≥3 times upper limit of normal on repeat testing.

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 randomized treatment of the study. The changes of concern include:

- Following dosing, a heart rate increase of >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 blood pressure increase of >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 ≤30 mL/minute using CKD-EPI formula or a clinically relevant change from baseline as determined by the Investigator.

If a subject requires any of the following prohibited medications, they should be discontinued from randomized treatment (see Section 8.7):

- Initiation of maintenance therapy with any prohibited medications as listed in Section 5.4.3.
- Initiation of maintenance therapy with a LABA (e.g., salmeterol, formoterol, indacaterol, vilanterol, olodaterol) administered alone or in combination with an ICS or a LAMA (e.g., tiotropium, aclidinium, glycopyrronium, umeclidinium).
- Change inhaled maintenance therapy during the course of the study.

NOTE: Subjects who suffer a COPD exacerbation (regardless of severity) will remain in the study and continue to take their assigned study drug unless the Investigator decides that it is in the best interest of the subject to discontinue randomized treatment and/or withdraw from the study (see Section 8).

5.7.2 Reasons for Study Withdrawal

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. A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). For all subjects who withdraw from the study for any reason, they, their family or healthcare providers, will be contacted 24 weeks post randomization to determine vital status, and if applicable, cause of death (Section 8.10).

If a female subject becomes pregnant during the course of the study, the subject will be withdrawn from the study and the pregnancy will be followed through delivery or final outcome (see Sections 7.2.4.4 and 7.5.12).

6 LABELING, PACKAGING, STORAGE, DISPENSING, AND RETURN OF CLINICAL SUPPLIES

6.1 Subject Information

Clinical supplies will be packaged to support enrollment of the study. Study personnel will have access to an IWRS to allocate subjects, to assign drug to subjects and to manage the distribution of clinical supplies. Clinical supplies will be packaged according to a component schedule generated by the Sponsor. Each person accessing the IWRS must be assigned an individual unique personal identification number (PIN). They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

6.2 Product Descriptions

Investigational materials will be provided by Pearl as summarized in Table 5.

Atrovent HFA and Ventolin HFA will be supplied as open-label MDIs. Additionally, Symbicort TBH will also be supplied as open-label DPI.

It is preferred that Atrovent and Ventolin be US-sourced products. In cases where it is not possible for the US-sourced product to be used, a locally available product will be provided by the Sponsor. The EU-sourced Symbicort TBH must be used for the active control, and a locally available product cannot be substituted for the sponsor-provided Symbicort TBH.

Table 5. Product Descriptions

Product Name & Dose	Product Strength	Dosage Form/ Fill Count	Administration
Study Drug			
BGF MDI (PT010) 320/14.4/9.6 µg ex-actuator	160/7.2/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
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
BFF MDI (PT009) 320/9.6 µg ex-actuator	160/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
Open-Label Products			
Budesonide and formoterol fumarate inhalation powder (Symbicort Turbuhaler) 400/12 µg[a]	EU Source: Symbicort® Turbuhaler® 200/6 µg per actuation Each metered dose contains: budesonide 200 µg and formoterol fumarate dihydrate 6 µg per inhalation which corresponds to a delivered dose of 160 µg budesonide and 4.5 µg formoterol fumarate dihydrate per inhalation.	DPI/ 60 inhalations	Taken as 2 inhalations BID Supplies are open-label
Albuterol Sulfate inhalation aerosol 90 µg[b] ex-actuator[c]	US source[d]: Ventolin® HFA HFA inhalation aerosol will be the US-supplied product." 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 ex-actuator[e]	US source[d]: Atrovent® HFA will be the US-supplied product. Ipratropium bromide HFA Each inhalation contains 17 µg per actuation	MDI/ 200 actuations	Taken as 2 inhalations QID during Screening Supplies are open-label

BID=twice daily; BGF MDI=Budesonide, Glycopyrronium and Formoterol Fumarate Inhalation Aerosol;

GFF MDI=Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; BFF MDI=Budesonide and Formoterol Fumarate Inhalation Aerosol; HFA=Hydrofluroalkane; MDI=Metered Dose Inhaler; DPI=dry power inhalation;

QID=4 times daily; EU=Europe; US=United States.

[a] Active control. Symbicort Turbuhaler is also known as Symbicort Turbohaler in some countries

Table 5. Product Descriptions

Product Name & Dose	Product Strength	Dosage Form/ Fill Count	Administration

[b] Active control. Albuterol sulfate is also known as salbutamol sulfate in some countries.

[c] Reversibility testing at Visit 2, rescue medication during the study.

[d] US-sourced products are the preferred product. In cases where it is not possible for the US-sourced product to be used, a locally available product will be provided by Pearl.

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

Notes: All study drugs will be administered by oral inhalation. Glycopyrronium 14.4 µg in GFF MDI is equivalent to 18 µg of glycopyrrolate (glycopyrronium bromide).

Note: It is preferred that Atrovent and Ventolin be US-sourced products. In cases where it is not possible for the US-sourced product to be used, a locally available product will be provided by the Sponsor. The EU-sourced Symbicort TBH must be used for the active control, and a locally available product cannot be substituted for the sponsor provided Symbicort TBH.

Open-label Symbicort TBH DPIs will be provided from commercial supplies. Manufacturer's instructions for study drug administration are provided in Appendix 3.

Open-label Atrovent HFA MDIs will be provided from commercial supplies. Manufacturer's instructions for study drug administration are provided in Appendix 4.

Open-label Ventolin HFA with dose counters will be provided from commercial supplies. Manufacturer's instructions for study drug administration are provided in Appendix 5.

6.3 Primary Packaging and Labeling Information

Investigational materials will be packaged by the Sponsor. Symbicort TBH will be supplied as open-label DPI. 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: Symbicort TBH will be supplied as open-label DPI. The DPI actuator will be labeled with a single label. 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. Labels will be printed with black ink and may include the following text: 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 (Box)

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

Table 6. Description of Boxes

Drug Supplies	Individual Box Contents
Blinded	1 MDI
Symbicort Turbuhaler	1 DPI
Atrovent (ipratropium bromide) HFA[a]	1 MDI
Ventolin (albuterol sulfate) HFA[a]	1 MDI

DPI=dry powder inhaler; HFA=Hydrofluoroalkane; MDI=metered dose inhaler

[a] In cases where it is not possible for the US-sourced product to be used, a locally available product will be provided by the Sponsor.

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)

ID=identification; #=number

6.5 Emergency Unblinding of Treatment Assignment

The IWRS should be used in order to unblind subjects and to unmask drug identity. When the Investigator contacts the system to unblind a subject, he/she must provide the requested subject identifying information and confirm the necessity to unblind the subject. Pearl will not provide a disclosure envelope with the clinical supplies.

The Investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject.

Whenever possible, the Investigator must first discuss options with the Medical Monitor or appropriate study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the Investigator must notify Pearl 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 kept in a secured location. BGF MDI, GFF MDI, and BFF MDI should be stored below 25° C (77° F) in a dry place. Excursions permitted up to 30° C (86° F).

Symbicort® Turbuhaler supplies: Do not store above 30°C (84° F). Keep the container tightly closed, in order to protect from moisture.

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 Unites 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 BGF MDI, GFF MDI, BFF MDI

Individual BGF MDI, GFF MDI, and BFF MDI will be packaged in a foil pouch and contained in an individual visit treatment box. Both the visit treatment box and the foil overwrap will have a label with a component ID number. Confirm that the identifier given by IWRS and the component ID number written on the label are the same. The visit treatment box is labeled with a 2 part label. Write the subject number and treatment visit number on each of the 2-part labels. The ‘tear-off’ part of the label is to be placed onto the IWRS confirmation report.

All MDIs must be primed before the first use. Priming involves releasing a certain number of sprays (4) into the air before the first use of the inhaler. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that the inhaler is ready to use.

The MDI must be primed in a separate room, away from the subject treatment area. Each dose will consist of 2 puffs from the MDI. Subjects will be dispensed the MDI and instructed to continue taking study medication twice daily, 2 puffs in the morning and 2 puffs in the evening approximately 12 hours apart, until subject returns to the clinic. The MDI should be stored at room temperature by the subject, to avoid temperature extremes, and the products should not be stored in direct sunlight. Refer to Appendix 2 for instructions on administration and cleaning of BGF MDI, GFF MDI, and BFF MDI.

6.7.2 Symbicort® Turbuhaler

Refer to Appendix 3 for instructions on the administration and cleaning of Symbicort® Turbuhaler®.

6.7.3 Atrovent® HFA (Ipratropium Bromide)

Refer to Appendix 4 for instructions on the administration of Atrovent® HFA.

6.7.4 Ventolin HFA® (Albuterol Sulfate)

Refer to Appendix 5 for the manufacturer's instructions on the administration and cleaning 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 or designee 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 each 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 schedule of events is provided in Table 8. Detailed schedules for pre-and post-dose procedures to be performed at Visit 4 through Visit 10a are provided in Table 9. Detailed schedules for pre-and post-dose procedures at Visit 4 (Day 1) and Visit 10a (Week 24) for subjects participating in the HPA Axis sub-study and Visit 10a (Week 24) for subjects participating in the 12-hour PFT and Week 24 PK profile sub-studies are provided in Table 10.

7.1 Efficacy Assessments

7.1.1 Pulmonary Function Tests

Forced expiratory spirometry maneuvers for derivation of FEV_1, FVC, FEF_{25-75}, and PEFR will be assessed using a spirometer that meets or exceeds minimum performance recommendations of the ATS (Refer to Appendix 6).

The volume accuracy of the spirometer is to be checked daily using a 3 L syringe across 3 flow ranges (i.e., low, medium and high flows), with temperature and barometric pressure correction. The calibration syringe must meet ATS specifications and must not be used beyond the expiry date. Required accuracy is ±3% (i.e., 3.09 L to 2.91 L) (ATS/ERS). The results will be printed and maintained in a calibration log, which will be monitored for compliance during the monitoring visits (Refer to Appendix 7, Spirometry Assessment Criteria).

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

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

At Visit 1, a single spirometry assessment will be conducted.

Note: Spirometry must meet both acceptability and repeatability criteria. (Refer to Exclusion Criteria, Section 5.2).

At Visit 2 and Visit 3, spirometry will be conducted 60 minutes and 30 minutes prior to bronchodilator administration and at 30 min post bronchodilator.

Note: Spirometry must meet both acceptability and repeatability criteria. (Refer to Exclusion Criteria, Section 5.2).

Spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration at Visit 4 through Visit 10a. The mean of the 60 minutes and 30 minutes pre-dose spirometry assessments conducted at Visit 4 will be used to establish baseline FEV_1, FVC, FEF_{25-75}, and PEFR.

At Visit 4 (Day 1) through Visit 10a (Week 24) spirometry will be obtained at 15 and 30 minutes, and 1, 2 and 4 hours post-dosing of study drug. Note: At Visit 4 (Day 1) only, a 5-minute post-dose spirometry assessment will also be obtained.

For subjects participating in the 12-hour PFT sub-study, at Visit 10a (Week 24), additional spirometry assessments will be obtained at 6, 8, 10, 11.5 and 12 hours after dosing.

7.1.1.1 Characterization of Reversibility

Reversibility to Ventolin HFA will be evaluated at Visit 2 and reversibility to Atrovent HFA will be evaluated at Visit 3. The procedures will be as follows:

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

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

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

7.1.1.2 FEV_1 Baseline Stability Criteria

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

7.1.2 Subject Electronic Diary Data Collection

Subjects will be provided with an electronic Diary (eDiary) at screening to be completed twice daily to record time of study medication administration, daily symptoms using the Exacerbations of Chronic pulmonary disease Tool (EXACT) scale (see Section 7.1.4.5), and the use of rescue albuterol (Ventolin HFA) throughout their study participation. The dose indicator reading will be recorded from Visit 4 onwards once daily for subject on blinded study drug. Before issuing the eDiary to the subject, site personnel will be responsible for programming the eDiary and training the subject on its use.

During the screening period (between Visit 1 and Visit 4), subjects will be required to demonstrate acceptable eDiary collections and compliance in order to be eligible for randomization.

Electronic Diary Compliance Requirement: Subject participation may be terminated at any time during the study for the following reasons:

- Chronic failure, in the judgment of the Investigator, to comply with diary compliance, despite documentation at the site of repeated efforts to reinforce compliance. As defined for this study, compliance requires >70% subject completion of diary assessments. Pearl may also instruct a site to discontinue a subject based on consistent noncompliance.
- Subjects who are unable to meet the compliance requirement (>70% subject completion of diary assessments) in the last 7 days preceding the Randomization Visit (Visit 4) will be considered a screen failure.

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

7.1.2.1 Rescue Medication Usage

The subject will record the total number of "puffs" of rescue medication (i.e., albuterol sulfate or locally available equivalent product) used on a daily basis in the eDiary. The number of "puffs" of rescue product will be recorded as the number of actuations on the canister. For example, when rescue product is required and 2 actuations are inhaled, this should be recorded as 2 "puffs." In the event the subject requires 4 actuations, this should be recorded as 4 "puffs". Subjects requiring more than 8 puffs per day on 3 consecutive days with worsening symptoms should contact the site.

7.1.2.2 Medication Compliance

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

7.1.2.3 Major/Minor Symptom Worsening Assessment and Alert System

All major and minor symptoms of a worsening event will be captured once each morning for the purposes of a symptom worsening alert. The purpose of this alert is to notify both the subject and the site of a potential symptom worsening event that warrants contact between the subject and site for further evaluation.

All questions will have a 24-hour recall period. Questions pertaining to the severity of symptoms versus their usual state will have 3 response options (e.g., How breathless have you been in the last 24 hours? Less breathlessness than usual, Usual level of breathlessness, More breathless than usual) whereas questions related to the presence or absence of a symptom will have a dichotomous response (e.g., Have you had a sore throat in the last 24 hours? No, Yes, I had a sore throat).

An alert will be triggered if 2 or more major symptoms (dyspnea, sputum volume, and sputum color) worsen for 2 consecutive days or if 1 major symptom and 1 minor symptom (sore throat, cold, fever without other cause, cough, and wheeze) worsen for at least 2 consecutive days. When either of these criteria is met, the subject will be alerted via the eDiary to contact the site as soon as possible for further evaluation. Likewise, the study site will be alerted to contact the subject within approximately 24 to 72 hours if he/she has not yet contacted the study site for further evaluation.

7.1.3 COPD Exacerbations

A COPD exacerbation will be defined as a change in the subject's usual COPD symptoms that lasts 2 or more days, is beyond normal day-to-day variation, is acute in onset, and may warrant a change in regular medication. The change in symptoms must include at least one major COPD symptom and at least one other major or minor symptom from the list below:

- Major COPD symptoms: dyspnea, sputum volume, and sputum color

- Minor COPD symptoms: cough, wheeze, sore throat, cold symptoms (rhinorrhea or nasal congestion), and fever without other cause

If symptoms are acute or have progressed rapidly and require treatment less than two days from onset of symptoms, the investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF.

If a subject's symptoms and the overall clinical findings support the diagnosis of a COPD exacerbation, but the subject has not experienced a worsening of at least one major COPD symptom and at least one other major or minor symptom, the investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF.

7.1.3.1 Severity of COPD Exacerbation

COPD exacerbations will be classified as mild, moderate or severe based on the following criteria:

Exacerbations will be considered moderate if they result in:

- Use of systemic corticosteroids and/or antibiotics for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids

Exacerbations will be considered severe if they result in:

- An inpatient COPD-related hospitalization (documentation stating that the subject was hospitalized for the COPD exacerbation or a record of the subject being admitted for ≥24 hours to an observation area, the emergency department, or other equivalent healthcare facility depending on the country and healthcare system).
- COPD-related death

Exacerbations will be considered mild if they do not meet the requirements to be classified as moderate or severe but otherwise fulfill the definition of COPD exacerbation.

7.1.3.2 Duration of COPD Exacerbation

For moderate or severe exacerbations, the duration is defined by the length of prescribed treatment, whereas for mild exacerbations, the duration is defined by the length of symptoms.

For moderate or severe COPD exacerbations, the start date will be defined as the start date of prescribed treatment with a systemic corticosteroid or systemic antibiotic and the stop date will be defined as the last day of prescribed treatment with a systemic corticosteroid or systemic antibiotic. In order to ensure that the same event is not counted twice, concurrent moderate or severe COPD exacerbations with start and stop dates equal to or less than 7 days apart will be considered the same event and assigned the maximum severity between the two.

For mild COPD exacerbations, start date will be defined as the onset of worsened symptoms as recorded by the subject in the eDiary, and the stop date will be defined as the last day of worsened symptoms. In order to ensure that the same event is not counted twice, mild COPD exacerbations with start and stop dates equal to or less than 7 days apart will be considered the same event.

7.1.3.3 Approach for Capturing COPD Exacerbations

All moderate or severe COPD exacerbations must be captured using the COPD Exacerbation eCRF. Mild COPD exacerbations will be captured based on symptoms as recorded by the subject in the eDiary. 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).

7.1.3.4 Other Information

Pearl Therapeutics will be using an electronic diary (eDiary) to capture daily symptom reporting. If symptoms meet a specific threshold (i.e., one major COPD symptom and at least one other major or minor symptom for 2 consecutive days), the eDiary generates alerts to the subject and the clinical site. This alert is intended to generate a contact between the subject and the clinical investigator. The clinical investigator makes the decision to escalate or initiate treatment (steroids and/or antibiotics and/or hospitalizations).

Circumstances will occur where symptoms are not captured in the eDiary (e.g. technical difficulties, rapid deterioration, or sudden death). In these cases, the investigator or designee will enter the information into the eCRF to capture the symptoms related to a COPD exacerbation.

7.1.3.5 Investigator-Judged COPD Exacerbations

For events which do not meet the outlined symptom criteria and/or when symptoms have a shorter duration, the investigator can justify the decision for considering the event an exacerbation. Exacerbations could be defined by an investigator when symptoms of COPD warranted urgent treatment due to rapid onset or rapidly progressive symptoms. Such a situation does not allow enough time to strictly fulfill the criteria for symptom duration (≥2 consecutive days). In these cases, the investigator may define such an event as a COPD exacerbation. As clinical presentations may vary among patients with COPD, exacerbations defined by an investigator can be supported by respiratory symptoms that may not strictly fulfill all symptom requirements defined above. Since the investigator will need to document the symptoms that justify his or her decision to begin treatment defining a COPD exacerbation event, all exacerbations in the study will have documented symptoms justifying their clinical relevance.

7.1.4 Subject Questionnaires

The following subject questionnaires will be completed by subjects using the study-supplied electronic questionnaire devices at specified visits throughout the study: CAT, SGRQ, and

EQ-5D-5L. The BDI/TDI will be interviewer-administered to study subjects using the study-supplied questionnaire (electronic version) at specified visits throughout the study. The EXACT questionnaire will be captured via the subject eDiary (see Section 7.1.2). When the BDI/TDI, SGRQ, and/or EQ-5D-5L are obtained at the same visit, it is recommended that the BDI/TDI be collected first, followed immediately by the SGRQ and then the EQ-5D-5L.

7.1.4.1 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 8) 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.

7.1.4.2 Baseline and Transition Dyspnea Indices

Dyspnea is the primary symptom of COPD and its relief is an important goal of therapy. In the evaluation of pharmacotherapy for COPD, several instruments are available to provide a discriminative and evaluative assessment of dyspnea. Among these are the BDI and TDI indices, which assess breathlessness in components related to functional impairment, magnitude of task and magnitude of effort. The reliability and validity of the BDI have been reported (Mahler, 1984). The validity of the BDI/TDI based on its association with other related measures has also been demonstrated (Witek, 2003). The BDI/TDI questionnaire should always be completed before any other assessments are made to avoid influencing the responses. The Interviewer-administered rating of severity of dyspnea at a single state provides a multidimensional measurement of dyspnea based on 3 components that evoke dyspnea in activities of daily living, in symptomatic individuals. The BDI score ranges from 0 (very severe impairment) to 4 (no impairment) for each domain and are summed to determine the BDI focal score (0 to 12) (i.e., the lower the score, the worse the severity of dyspnea). The appropriate language version of the questionnaires will be used. The questionnaire can be found in Appendix 9.

The TDI measures changes in dyspnea severity from the baseline as established by the BDI. TDI components are: Change in Functional Impairment, Change in Magnitude of Task, and Change in Magnitude of Effort. The TDI score ranges from -3 (major deterioration) to +3 (major improvement) for each component. The sum of all components yields the TDI focal score (-9 to +9) (i.e., the lower the score, the more deterioration in severity of dyspnea). The BDI will be completed at Visit 4 (Day 1, prior to study drug administration). The TDI will be completed at each post-randomization visit including the Treatment Discontinuation/Withdrawal Visit.

The BDI/TDI should be completed prior to study drug administration and before administration of SGRQ Questionnaire.

7.1.4.3 St. George Respiratory Questionnaire

The SGRQ 4-week recall tool will be used to provide the health status/health-related quality-of-life measurements in this study (Refer to Appendix 10). The appropriate language version of the questionnaires will be available in each participating country. The subject should complete the questionnaires in a quiet area and be allowed to ask questions; however site staff should take care not to influence the subject's responses. The subject will be instructed to provide the most accurate and best individualized response about how they felt regarding their health status/health-related Quality of Life in the last 4 weeks from the study visit day. The questionnaire will be checked for completeness and collected before the subject leaves the study site. At later visits, subjects are not allowed to review their previous responses.

The SGRQ contains 50 items divided into 3 domains: "Symptoms" concerned with respiratory symptoms, their frequency and severity; "Activity" concerned with activities that cause or are limited by breathlessness; and "Impacts" which covers a range of aspects concerned with social functioning and psychological disturbances resulting from airway disease. A "Total" score combining each domain will be calculated. In each case the lowest possible value is zero and the highest is 100. Higher values correspond to greater impairment of quality of life. Completed questionnaires will be reviewed and examined by the Investigator or designee, before the clinical examination, for responses which may indicate potential AEs or SAEs. The Investigator should review not only the responses to the questions in the questionnaire but also for any unsolicited comments written by the subject. Investigators should not encourage the subjects to change the responses reported in the questionnaire.

The SGRQ will be completed by the subject prior to study drug administration at Visit 4 (Day 1) and at each post-randomization visit including the Treatment Discontinuation/Withdrawal Visit.

7.1.4.4 European Quality-of-Life-5 Dimension Questionnaire

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status [EuroQol, 2014]. The EQ-5D-5L consists of 2 assessments, a descriptive system and a visual analogue scale (VAS). The descriptive system comprises of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 severity levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

The VAS records the respondent's self-rated health on a 20 cm, 0-100 vertical scale with endpoints labeled "the best health you can imagine" and "the worst health you can imagine", with higher scores corresponding to a better health state. This information is used as a quantitative measure of health as judged by the individual respondents.

The EQ-5D-5L (see Appendix 11) will be completed by the subject prior to study drug administration at Visit 4 (Day 1; Randomization) and at each post-randomization visit including the Treatment Discontinuation/Withdrawal Visit.

7.1.4.5 Exacerbations of Chronic Pulmonary Disease Tool (EXACT)

The EXACT is a 14-item patient-reported outcome (PRO) instrument developed to assess the frequency, severity and duration of COPD exacerbations (Jones, 2011). The instrument was developed for daily, at home, administration using a handheld electronic device. Respondents are instructed to complete the diary each evening just prior to bedtime and to answer the questions while considering their experiences "today". The instrument includes assessments of breathlessness (5 items), cough and sputum (2 items), chest symptoms (3 items), and 4 additional items (difficulty with sputum, tired or weak, sleep disturbance, and psychological state).

The daily EXACT total score is computed across the 14 items and has a range of 0-100 with higher scores indicative of greater severity. Total score changes are used to identify the onset and recovery from an EXACT-defined exacerbation event. In identifying event onset and recovery, the EXACT can provide information on event frequency and duration as well as event severity.

The E-RS is an 11-item sub-set of the 14- question EXACT to evaluate the severity of respiratory symptoms of COPD (Jones, 2011). The E-RS was designed to be captured as part of the daily EXACT assessment. On 07 March 2016, the EXACT-Respiratory Symptoms Scale was renamed the Evaluating Respiratory Symptoms (E-RS) measure. When referring specifically to its use in COPD, the proposed context of use for qualification, the full name is now "Evaluating Respiratory Symptoms in COPD (E-RS™: COPD). Summation of E-RS item responses produces a total score ranging from 0 to 40, with higher scores indicating greater severity. In addition to the total score, symptom domain scores can be calculated for breathlessness (5 items; score range: 0–17), cough and sputum (3 items; score range: 0–11) and chest symptoms (3 items; score range: 0–11) by summing the responses of items within a respective domain. As with the total score, higher domain scores indicate greater severity.

The EXACT (see Appendix 12) will be completed daily by the subject as part of the eDiary assessments.

7.2 Safety Assessments

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

7.2.1 Medical/Surgical History and Physical Examination

Medical history, including specific cardiovascular history details, will be collected at Visit 1 (Screening) and updated during the Screening Period (Visit 1 to Visit 4). The number of COPD exacerbations requiring oral steroids and/or oral antibiotics, or hospitalization within 12 months of Visit 1 (Screening) will be collected. A complete physical examination will be

performed at Visit 1 (Screening) and at Visit 10a 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. Weight, assessed in ordinary indoor clothing with shoes removed will be recorded at Visit 1 (Screening) and Visit 10a or Treatment Discontinuation/Withdrawal Visit only. Height will be recorded at Visit 1 (Screening) only.

7.2.2 Vital Sign Measurements

Vital signs, including Heart rate (HR) and systolic and diastolic blood pressure (DBP), and temperature will be assessed as outlined below; assessments may be obtained while the subject is resting for 5 minutes in either the supine or seated position.

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

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

At Visit 4 (Randomization) only, pre-dose vital signs will be obtained two times at least 5 minutes apart within 1 hour prior to dosing. Post-dose vital signs will be obtained 30 minutes and 2 hours post study drug dosing.

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

At Visits 5 through 10a:

- Pre-dose vital signs will be obtained once within 1 hour prior to dosing.
- Post-dose vital signs will be obtained at 30 minutes and 2 hours post study drug dosing at all treatment visits.

For subjects participating in the 12-hour PFT and PK sub-studies at Visit 10a (Week 24), additional vital signs will be obtained at 12 hours post study drug dosing.

7.2.3 12-Lead Electrocardiogram

- A single ECG will be obtained at Visit 1 (Screening) and the Treatment Discontinuation/Withdrawal Visit.

Timed ECGs will be obtained as follows:

- Visit 2 and Visit 3 within 60 minutes pre-bronchodilator and at 30 minutes post-bronchodilator.

- At Visit 4 only, pre-dose ECGs will be obtained twice at least 5 minutes apart within 1 hour prior to dosing.
- Pre-dose ECG will be obtained once within one hour prior to dosing at Visit 5 (Week 4), Visit 7 (Week 12), and Visit 10a (Week 24).
- A post-dose ECG will be obtained at 30 minutes and 2 hours post study drug dosing at Visit 4 (Day 1), Visit 5 (Week 4), Visit 7 (Week 12), and Visit 10a (Week 24).

For subjects participating in the 12-hour PFT sub-study, an additional post-dose ECG will be obtained at 12 hours after study drug dosing at Visit 10a (Week 24).

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

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

QT intervals and calculated QTcF intervals will be reviewed and checked for gross inaccuracies by the Investigator or designated ECG reviewer. If the calculated QTcF intervals are >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.

7.2.4 Clinical Laboratory Tests

Clinical safety laboratory tests will be analyzed by a central laboratory according to standardized, validated assays. The laboratory will supply detailed instructions and all containers for blood and urine investigations. Blood sample volumes will meet the laboratory's specification. All clinical laboratory tests will be obtained at Visit 1 (Screening) and prior to dosing at Visit 4 (Day 1), Visit 5 (Week 4), Visit 7 (Week 12) and Visit 10a (Week 24) and the Treatment Discontinuation/Withdrawal Visit.

A Basic Metabolic Panel (BMP) will be obtained at 30 minutes and 2 hours post-dosing at Visit 4 (Day 1), Visit 5 (Week 4), Visit 10a (Week 24).

7.2.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured at Visit 1 (Screening) and prior to dosing at Visit 4 (Day 1), Visit 5 (Week 4), Visit 7 (Week 12) and Visit 10a (Week 24), or the Treatment Discontinuation/Withdrawal Visit.

7.2.4.2 Clinical Chemistry

Albumin, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, total cholesterol, magnesium, phosphate, sodium, potassium, chloride, creatinine, gamma-glutamyl transferase, blood glucose, total protein, triglycerides, bicarbonate, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) will be measured at Visit 1 (Screening) and prior to dosing at Visit 4 (Day 1), Visit 5 (Week 4), Visit 7 (Week 12) and Visit 10a (Week 24), or the Treatment Discontinuation/Withdrawal Visit.

Refer to Table 7 for a list of study-associated laboratory tests. The central laboratory will supply procedures for the preparation and collection of these samples.

Table 7. 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	Albumin
Aspartate aminotransferase	Blood Urea Nitrogen (BUN)
Alkaline phosphatase	Calcium[a]
Bilirubin, total	Chloride[a]
Gamma-glutamyl transferase	Cholesterol

Table 7. Clinical Laboratory Tests

	Bicarbonate
	Creatinine[a]
	Glucosea
	Magnesium
	Potassium[a]
	Phosphate
	Protein, total
	Sodium[a]
	Triglycerides
Urinalysis	
Macroscopic examination including specific gravity, pH, protein, glucose, ketones, blood, and urobilinogen.	
Other Tests:	
Pregnancy test (women of childbearing potential only): serum hCG at Visit 1 (Screening), and Final Visit (Visit 10a) or Treatment Discontinuation Visit; urine hCG at Visit 7 (Week 12). Creatinine clearance will be estimated by the CKD-EPI formula [Levey, 2009].	

Abbreviations: CKD EPI=Chronic Kidney Disease Epidemiology Collaboration; hCG=human chorionic gonadotropin

[a] Parameters included in the Basic Metabolic Panel.

7.2.4.3 Urinalysis

Routine macroscopic urinalysis for specific gravity, pH, protein, glucose, ketones, blood, and urobilinogen will be measured. A microscopic examination will be performed if warranted based on macroscopic results.

Urinalysis will be measured at Visit 1 (Screening) and prior to dosing at Visit 4 (Day 1), Visit 5 (Week 4), Visit 7 (Week 12) and Visit 10a (Week 24) or the Treatment Discontinuation/Withdrawal Visit.

7.2.4.4 Pregnancy Test

A serum pregnancy test will be performed at the central laboratory in pre-menopausal women who are not surgically sterile at Visit 1 (Screening) and Visit 10a (Week 24), or the Treatment Discontinuation/Withdrawal Visit. A urine pregnancy test will be performed on-site at Visit 7 (Week 12).

7.3 Pharmacokinetic Sub-Study Assessments

Pharmacokinetic assessments will be obtained in a subset of PFT sub-study subjects randomized to each treatment arm (BGF MDI:BFF MDI:GFF MDI) at Visit 10a (Week 24). Sample collections will be scheduled for the nominal time point and actual collection times will be recorded in the source documents (Refer to Table 8).

7.3.1 Procedure for Blood Sample Collection and Schedule

Pre-Dose Administration Sample Collection - Week 24 (Visit 10a): Approximately 10 mL of whole blood will be collected within 30 minutes before administration of study drug.

Post-Dose Administration - Week 24 (Visit 10a): Approximately 10 mL of whole blood will be collected at 2, 5, and 20 minutes, and at 1, 2, 4, 8, 10, and 12 hours post-dose.

Blood will be collected by direct venipuncture or may be obtained from an indwelling intravenous cannula (per the study site's Standard Operating Procedure [SOP] after review by Pearl's Medical Monitor or designee) using a vacuum collection tube (e.g., Vacutainer™ plasma collection tube) containing ethylenediaminetetraacetic acid (EDTA) tripotassium. Refer to the Laboratory Manual for details of plasma collection, storage, and handling.

7.3.1.1 Procedure for Shipping Blood Samples

Samples are to be shipped frozen by overnight courier to the central laboratory for analysis. Plasma levels of budesonide, glycopyrrolate (the bromide salt of glycopyrronium), and formoterol will be determined using a validated High Performance Liquid Chromatography tandem Mass Spectrometry methodology. Instructions for sample handling, storage, and shipping will be provided in the Laboratory Manual.

7.4 HPA Axis Sub-Study Assessments

Blood samples to measure serum cortisol will be obtained in a subset of PFT sub-study subjects over 24 hours between Visits 3 and 4 prior to dosing at Randomization and Visit 10a (Week 24). It is recommended that subjects provide samples starting 24 hours prior to Randomization. However, the subject can complete the 24-hour blood draws any day between Visits 3 and 4.

Samples will be collected at the following time points: 30 minutes pre-dose, and 1, 2, 4, 8, 10, 12, 14, 16, 20, 22, and 24 hours post-dose. Samples will be sent to the central laboratory and analyzed for cortisol levels. These data will also be categorized as normal/abnormal.

Those subjects participating in the HPA Axis sub-study will also participate in the Week 24 PK profile sub-study (see Section 7.3).

7.5 Adverse Events

7.5.1 Performing Adverse Event Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's case report form and on the AE Reporting Form. If the AE is "alarming," the Investigator must report the AE immediately to Pearl. In addition, certain AEs (as described in Section 7.5.10) 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 AE, the Investigator and the Medical Monitor may discontinue the subject from treatment prematurely.

7.5.2 Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the US Code of Federal Regulations (21 CFR 312.32) and EU 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 (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Adverse events include, but are not limited to:

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

An AE does not include:

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

7.5.3 Pre-Randomization Adverse Events

Adverse events that occur between the time subject signs the ICF for the study and the time when that subject is randomized will be summarized as medical history and not as an adverse event unless the event meets the definition of an SAE as defined in Section 7.5.10.

7.5.4 Severity

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

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

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

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

7.5.5 Relationship

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

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

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

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

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

7.5.6 Chronic Obstructive Pulmonary Disease Exacerbations

All moderate or severe COPD exacerbations must be captured using the COPD Exacerbation eCRF. Mild COPD exacerbations will be captured based on symptoms as recorded by the subject in the eDiary. 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.

7.5.7 Adverse Events of Special Interest

Certain AEs have been identified as adverse events of special interest (AESIs) due to the class of drugs being studied. These adverse events will be captured through spontaneous reporting and the reporting of these AESIs will be described in the SAP. Some events are described below but this is not a comprehensive list of all AESIs.

7.5.7.1 LABA and LAMA Effects

Known effects of LAMAs and LABAs include cardiovascular effects, ocular disorders, urinary retention, gastrointestinal disorders, and anticholinergic effects for LAMAs and cardiovascular and tremor effects for LABAs.

7.5.7.2 Local Steroid Effects

Local steroid effects include oral candidiasis, hoarseness candidiasis, oropharyngeal candidiasis, dysphonia, and throat irritation.

7.5.7.3 Pneumonia

In order to adequately assess and characterize the risk of pneumonia in patients in a non-biased manner, an external, independent Clinical Endpoint Committee (CEC), as described in the Pneumonia Clinical Endpoint Adjudication Charter, will review all adverse events reported as pneumonia to ensure appropriate pre-defined and clinically consistent pneumonia criteria are met.

To standardize the diagnosis of pneumonia a clinically consistent definition of pneumonia will be implemented, which will require the following:

1. Clinical diagnosis of pneumonia by the Investigator
2. Documentation of chest imaging obtained within 14 days of the diagnosis of pneumonia that is compatible with the diagnosis of pneumonia
3. Treatment with antibiotics (and/or if appropriate antiviral and/or antifungal agents)
4. At least 2 of the following clinical signs, symptoms, or laboratory findings:
    - Increased cough
    - Increased sputum purulence or production
    - Adventitious breath sounds on auscultation
    - Dyspnea or tachypnea
    - Fever

- Elevated white blood cell counts
- Hypoxemia

The CEC will be empowered to request any additional information, including copies of chest X-rays or CT scans if needed, to confirm the pneumonia diagnosis.

Radiographs will be evaluated locally and the results (infiltrate compatible with pneumonia (yes/no) will be entered in the eCRF. If the Investigator becomes aware that a diagnosis of pneumonia was made without a chest image having been performed, he or she should obtain a chest image (frontal and lateral) up to 10 to 14 days after the date of pneumonia diagnosis.

7.5.7.4 Paradoxical Bronchospasm

Monitoring for paradoxical bronchospasm will occur at each visit during the Treatment Period (Visits 4 through 10a) at 15 and 30 minutes post-dose. In this study, paradoxical bronchospasm is defined as a reduction in FEV_1 of >20% from baseline (i.e., the mean FEV_1 values obtained 60 and 30 minutes prior to study drug administration) that occurs within 30 minutes post-dosing with associated symptoms of wheezing, shortness of breath, or cough.

7.5.8 Major Adverse Cardiovascular Events

Due to the prevalence of cardiovascular diseases in patients with COPD, MACE will be evaluated according to pre-defined criteria as described in the Cardiovascular and Cerebrovascular Clinical Endpoint Adjudication Charter. The CEC will review potential clinical endpoints to determine if the events meet the following MACE criteria:

- Cardiovascular death
- Non-fatal myocardial infarction (MI)
- Non-fatal stroke

The Clinical Endpoint Adjudication Charters will be established to govern these processes as described in Section 7.5.16 Clinical Endpoint Committee.

7.5.9 Clinical Laboratory Adverse Events

Many laboratory abnormalities observed during the course of a study will be included under a reported AE describing a clinical syndrome (e.g., elevated BUN and creatinine in the setting of an AE of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). Isolated laboratory abnormalities should be reported as AEs if they are considered to be clinically significant by the Investigator.

Criteria for a "clinically significant" laboratory abnormality are:

- A laboratory abnormality that leads to a dose-limiting toxicity (e.g., an abnormality that results in study drug dose reduction, suspension, or discontinuation)

- A laboratory abnormality that results in any therapeutic intervention (i.e., concomitant medication or therapy)
- Other laboratory abnormality judged by the Investigator to be of any particular clinical concern (e.g., significant fall in hemoglobin not requiring transfusion)

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

7.5.10 Serious Adverse Events

An AE is considered "serious" if, in the view of the Investigator or Sponsor, it results in any of the following outcomes:

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

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

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

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

An AE or suspected adverse reaction is considered unexpected if it is not listed in the current Investigator brochure or is not listed at the specificity or severity that has been observed.

7.5.10.1 Reporting of 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 Therapeutics no later than 24 hours after the Investigator recognizes/classifies the event as an SAE. At a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report using the appropriate form (e.g., SAE Report Form). After the initial report, as necessary, the Investigator must provide any additional information on a SAE to Pearl Pharmacovigilance within 2 working days after he/she receives that information. This follow-up information will be a detailed written report that may include copies of hospital records, case reports, and autopsy reports, and other pertinent documents.

Post-study SAEs following the last dose of study drug must be reported to Pearl as described in Section 7.5.10.3.

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

7.5.10.2 Supplemental Investigations of SAEs

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

7.5.10.3 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.

7.5.10.4 Notification of Post-Study Serious Adverse Events

Investigators are not obligated to actively follow subjects after the completion of the study. However, if the Investigation becomes aware of a post-study SAEs occurring up to 14 days following the last dose of study drug must be reported to Pearl, 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.

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

The Investigator is responsible for promptly notifying her/his Investigational Research Board/Independent Ethics Committee (IRB/IEC) of all SAEs, including any follow-up information, occurring at her/his site and any SAE regulatory report, including any follow-up reports that he/she receives from Pearl. 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 ICF or other measures based on its review of an SAE report.

7.5.10.6 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.

7.5.11 Overdose

An overdose is defined as a dose greater than the high dose level evaluated in this study as described in Section 6.2 (Product Descriptions) that results in clinical signs and symptoms. In the event of an overdose of study medication, the Investigator should use clinical judgment in treating the overdose and contact the study Medical Monitor. The Investigator should refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drug(s) being used in this study. Such document may include, but not be limited to, the Investigator's Brochure for BGF MDI, BFF MDI, GFF MDI, and approved product labeling for open-label products.

7.5.12 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 Report 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.

7.5.13 Paternal Exposure

Male subjects who are sexually active must agree to use a double barrier method of contraception (condom with spermicide) from the first dose of randomized treatment until 2 weeks after their last dose, and must not donate sperm during their study participation period. If a male subject's partner becomes pregnant during the course of the study, it must be reported to the Sponsor within 24 hours of the investigator learning of its occurrence.

7.5.14 Hy's Law

Cases where a subject shows an AST or ALT ≥ 3x Upper Limit of Normal (ULN) and Total Bilirubin (TBL) ≥ 2x ULN may need to be reported as SAEs. Please refer to Appendix 13 for further instructions in cases of combined increase of aminotransferase and TBL.

7.5.15 Use of Steroids During the Study

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

Subjects treated with oral, intramuscular, or intravenous corticosteroids for other indications will follow their visit schedule. If a subject requires intraocular corticosteroids, this should be fully documented and the Investigator should make a determination as to the suitability of the subject continuing on randomized treatment.

7.5.16 Clinical Endpoint Committee

An external CEC will be established for this study. The committee will provide systematic and unbiased assessment of pre-defined, Investigator reported adverse events. The committee will consist of experts who will provide a centralized review functioning independently of Pearl. Three Clinical Endpoint Adjudication Charters will outline the clinical endpoints for adjudication.

- Cardiovascular and Cerebrovascular (CCV) Clinical Endpoint Adjudication Charter
- Cause-Specific Mortality Clinical Endpoint Adjudication Charter
- Pneumonia Clinical Endpoint Adjudication Charter

Further details are provided in the Adjudication Committee Charters.

7.5.16.1 Cardiovascular and Cerebrovascular Clinical Endpoint Adjudication Charter

A Cardiovascular and Cerebrovascular Clinical Endpoint Adjudication Charter will be referenced for the review and assessment of non-fatal serious CCV events and classification of Major Adverse Cardiovascular Event (MACE). The CEC will review potential clinical endpoints to determine if the event meets MACE criteria.

7.5.16.2 Cause-Specific Mortality Clinical Endpoint Adjudication Charter

A Cause-Specific Mortality Clinical Endpoint Adjudication Charter will be referenced for the review and assessment of the cause of deaths. The CEC will review fatal reports to determine if the event meets MACE criteria. Cardiovascular deaths will be classified as MACE.

7.5.16.3 Pneumonia Clinical Endpoint Adjudication Charter

A Pneumonia Clinical Endpoint Adjudication Charter will be referenced for the review and assessment of all pneumonia-related events to ensure appropriate pre-defined and clinically consistent pneumonia criteria are met.

7.5.17 Data Monitoring Committee

An external Data Monitoring Committee (DMC) will be set up to provide systematic and unbiased assessment of safety for Study PT010006. Members of the DMC will review data at predetermined intervals. If significant safety issues arise in between scheduled meetings, ad hoc meetings will be scheduled to review the data. Based on the safety implications of the data, the DMC may recommend modification or termination of the study.

7.6 Health Care Resource Utilization

The number of days missed from work, days that primary caregivers of subjects missed work as a result of the subject's COPD, telephone calls to health care providers or general practitioners (GPs), visits to health care providers or GPs, Emergency Room (ER) visits, days in the hospital, days in Intensive Care Units (ICU), days in Coronary Care Units (CCU), and use of ambulance transport will be assessed at Visit 5 (Week 4), Visit 6 (Week 8), Visit 7 (Week 12), Visit 8 (Week 16), Visit 9 (Week 20), Visit 10a (Week 24), and the telephone follow up call or Treatment Discontinuation/Withdrawal Visit.

7.7 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' wellbeing.

8 STUDY ACTIVITIES

A schedule of events is provided in Table 8. Detailed schedules for pre-and post-dose procedures to be performed at Visit 4 through Visit 10a are provided in Table 9. Detailed schedules for pre-and post-dose procedures at Visit 4 (Day 1) and Visit 10a (Week 24) for subjects participating in the HPA Axis sub-study and Visit 10a (Week 24) for subjects participating in the 12-hour PFT and Week 24 PK profile sub-studies are provided in Table 10.

Table 8. Schedule of Events

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

Table 8. Schedule of Events

	Screening Period				Treatment Period						Follow-Up TC
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10a	14 days Post-Dose
Study Day/Week[a]	Day -28 to -9	Day -21 to -2	Day -19 to -1	Day 1	Week 4 ±2 Days[a]	Week 8 ±2 Days[a]	Week 12 ±2 Days[a]	Week 16 ±2 Days[a]	Week 20 ±2 Days[a]	Week 24 ±2 Days[a]	
SGRQm				X	X	X	X	X	X	X[s]	
EQ-5D-5L Questionnaire[m]				X	X	X	X	X	X	X[s]	
12-hr PFTs (sub-study)										X	
PK Profile (sub-study)										X	
HPA Axis (sub-study)[n]			X							X	
eDiary Dispense/Collect[o]	X									X[s]	
Review of eDiary[p]		X	X	X	X	X	X	X	X	X	
HCRU					X	X	X	X	X	X[s]	
Telephone Contact[q]		X	X	X	X	X	X	X	X		X
Vital Status Check[r]										X	

BDI/TDI=Baseline Dyspnea Index/Transition Dyspnea Index; CAT=COPD Assessment Test; COPD=Chronic obstructive pulmonary disease; eDiary=electronic diary; ECG=electrocardiogram; EQ-5D-5L=European Quality-of-Life-5 Dimensions EXACT=Exacerbations of Chronic Pulmonary Disease Tool – Patient Reported Outcomes; HCRU=Healthcare Resource Utilization; HFA=Hydrofluoroalkane ; HPA Axis=hypothalamic-pituitary-adrenal axis; Inc/Exc=Inclusion/Exclusion; LABA=long acting β2 agonist; MDI=metered dose inhaler; MRI=Magnetic resonance imaging; PFTs=pulmonary function tests; PK=pharmacokinetic; Rand=randomization; SGRQ=St. George Respiratory Questionnaire; TC=Telephone call

Note: When data collection time points are concurrent, it is recommended that variables be collected in the following order: BDI/TDI, SGRQ, EQ-5D-5L, vital signs, ECG, clinical laboratory assessments, PK, and spirometry.

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

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

[c] Subjects will complete the CAT (see Appendix 8) at Visit 2 as an entry criterion.

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

[e] Refer to Section 7.1.1 and Table 9 for spirometry assessments and specific time points for these assessments to be performed at each treatment visit.

[f] Includes evaluation of weight at Visit 1 (Screening) and Visit 10a and evaluation of height at Visit 1 (Screening) only.

[g] Refer to Section 7.2.2 and Table 9 for vital signs assessments and specific time points for these assessments to be performed at each treatment visit.

[h] Refer to Section 7.2.3 and Table 9 for ECG assessments and specific time points for these assessments to be performed at each treatment visit.

[i] Refer to Section 7.2.4 and Table 9 for clinical laboratory assessments (hematology, chemistry and urinalysis) and specific time points for these assessments to be performed at each treatment visit. Serum pregnancy test will be performed at Visit 1 (Screening) and at Visit 10a (Week 24) or at the Treatment Discontinuation/Withdrawal Visit. At Visit 7 (Week 12), a urine pregnancy test will be performed. Note: A Basic Metabolic Panel (BMP) will be obtained at 30 minutes and 2 hours post-dosing at Visit 4 (Day 1), Visit 5 (Week 4), Visit 10a (Week 24)

[j] Obtain a new chest x-ray (frontal and lateral) at Visit 1 if a chest x-ray or CT performed within the 6 months prior to Visit 1 (Screening) is not available, except in countries with restrictive radiology assessment practice, where only subjects who have had a chest x-ray or CT scan (thorax) performed outside of the study in the last 6 months are allowed to be enrolled. Alternatively, in these countries, an MRI should be used instead of a CT scan or chest x-ray as per local practice assessment.

[k] At Visit 1 (Screening), stop prohibited COPD medications and change COPD medications as specified in Section 5.4.1 (i.e., Sponsor provided Atrovent HFA with or without ICS). At the end of Visit 10a, return subject to pre-study or other appropriate inhaled maintenance COPD.

[l] Sponsor-provided Atrovent HFA or Ventolin HFA is dispensed 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).

[m] When BDI/TDI and SGRQ are obtained at the same visit, it is recommended that the BDI/TDI should be collected first, followed immediately by the SGRQ and then the EQ-5D-5L. The BDI/TDI, SGRQ, and EQ-5D-5L should be completed by the subject prior to any other visit procedures.

[n] It is recommended that subjects provide these samples 1 day prior to Randomization (see Section 7.4)

[o] Issue and train subjects on eDiary use, only after a subject is determined to qualify to proceed to Visit 2. Retraining will be done if necessary at Visits 2 and 3.

[p] Refer to Section 7.1.2 for details on eDiary review. Subjects will be asked to maintain a daily record of their study drug dosing and rescue medication use. EXACT will be reviewed at each visit as part of the e Diary review.

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

[r] Vital status check for all subjects. For subjects that discontinue, the vital status check will be conducted 24 weeks after randomization.

[s] These are the minimum procedures that should be completed at a Treatment Discontinuation/Withdrawal Visit.

Table 9. Timed Assessments at Each Treatment Visit (Visit 4 to Visit 10a)

Clinical Variable[a]	Pre-dosing		Post-dosing					
	-60 minutes	-30 minutes	5 minutes	15 minutes	30 minutes	1 hour	2 hours	4 hours
BDI/TDI[b]	X							
SGRQ[b]	X							
EQ-5D-5L Questionnaire[b]	X							
Review of eDiary[b]	X							
Vital Signs[c]	X				X		X	
12-Lead ECG[d]	X				X		X	
Clinical Laboratory Testing[e]	X				X[f]		X[f]	
Spirometry (FEV_1, FVC, FEF_{25-75},PEFR) [g]	X	X	X[h]	X	X	X	X	X
Study Drug Collection[i]	X							
Study Drug Dispensing		X						

BDI/TDI=Baseline Dyspnea Index/Transition Dyspnea Index; eDiary=electronic diary; ECG=electrocardiogram; EQ-5D-5L=European Quality-of-Life-5 Dimensions EXACT=Exacerbations of Chronic Pulmonary Disease Tool; FEF_{25-75}=Forced expiratory flow from 25% to 75%; FEV_1=forced expiratory volume in 1 second; FVC=Forced vital capacity; HFA=Hydrofluoroalkane; PEFR=Peak expiratory flow rate; SGRQ=St. George Respiratory Questionnaire

Note: When data collection time points are concurrent, it is recommended that variables be collected in the following order: BDI/TDI, SGRQ, EQ-5D-5L, vital signs, ECG, clinical laboratory assessments, PK, and spirometry.

[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 assessments for FEV_1, FVC, and PEFR will be conducted as close to the specified time points as possible (i.e., FEV_1, FVC, and PEFR assessments need to be conducted within ±15 minutes of specified time prior to study drug administration; ±5 minutes of specified time point for the first 60 minutes post study drug administration; ±15 minutes of specified time point for assessments obtained thereafter).

[b] 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.

[c] At Visit 4 only, pre-dose vital signs will be collected twice, at least 5 minutes apart within 1 hour prior to dosing. Vital signs will be obtained within 1 hour pre-dosing and at 30 minutes and 2 hours post-dose at all treatment visits. Temperature will be obtained pre-dose; no further temperature assessments are required unless clinically indicated.

[d] At Visit 4 only, pre-dose ECGs will be collected twice, at least 5 minutes apart. An ECG will be obtained pre-dose and at 30 minutes and 2 hours post-dose Visit 4 (Day 1), Visit 5 (Week 4), Visit 7 (Week 12) and Visit 10a (Week 24).

[e] Clinical laboratory tests ((hematology, chemistry and urinalysis) will be obtained prior to dosing at Visit 4 (Day 1), Visit 5 (Week 4), Visit 7 (Week 12), and Visit 10a (Week 24) only. Serum pregnancy test will be performed at Visit 10a (Week 24) and a urine pregnancy test will be performed at Visit 7 (Week 12).

[f] A Basic Metabolic Panel (BMP) will be obtained at 30 minutes and 2 hours post-dosing at Visit 4 (Day 1), Visit 5 (Week 4), Visit 10a (Week 24).

[g] The baseline FEV_1 at Visit 4 must be within ±20% or 200 mL of the mean of the pre dose FEV_1 obtained at the 2 preceding visits (average of pre-dose FEV_1 obtained at Visit 2 and Visit 3). At Visit 4, if the pre-dose FEV_1 average is outside of the ±20% or 200 mL range, but the 30 min assessment is within ±22% or 220 mL, then another

assessment may be conducted 30 minutes later. If the last 2 assessments meet the FEV_1 baseline stability requirements (i.e., within ±20% or 200 mL), the initial 60 minute pre-dose assessment will not be used and the last 2 assessments will be used to establish the eligibility criteria. If the test day FEV_1 is not within ±20% or 200 mL, the subject will not be randomized and will be considered a screen failure.

[h] 5-minute spirometry assessment post-dose at ONLY Visit 4 (Day1)

[i] At the start of each treatment visit, subject must have withheld all COPD medications, including study medication, and rescue Ventolin HFA, for at least 6 hours prior to start of the test day procedures.

Table 10. Timed Assessments at Visit 10a (Week 24) for 12-hour PFT, PK-Profile and HPA Axis Sub-studies

	Pre-dosing		Post-dosing																	
	Minutes		Minutes					Hours												
Clinical Variable[a]	**-60**	**-30**	**2**	**5**	**15**	**20**	**30**	**1**	**2**	**4**	**6**	**8**	**10**	**11.5**	**12**	**14**	**16**	**20**	**22**	**24**
Vital Signs	X						X		X						X					
12-Lead ECG	X						X		X						X					
Spirometry (FEV_1, FVC, FEF_{25-75}, PEFR)	X	X		X	X		X	X	X	X	X	X	X	X	X					
PK Sample Collection		X	X	X		X		X	X	X		X	X		X					
HPA Axis		X						X	X	X		X	X		X	X	X	X	X	X
Study Drug Collection	X[b]																			

ECG=electrocardiograph; FEF_{25-75}=forced expiratory flow from 25% to 75%; FEV_1=Forced expiratory volume in 1 second; FVC=Forced vital capacity; PEFR=Peak expiratory flow rate; PK=pharmacokinetic

Note: At the start of Visit 10a, subject must have withheld all COPD medications, including study medication and rescue Ventolin HFA for at least 6 hours prior to start of the test day procedures.

Note: When data collection time points are concurrent, it is recommended that variables be collected in the following order: BDI/TDI, SGRQ, EQ-5D-5L, vital signs, ECG, clinical laboratory assessments, PK, and spirometry.

[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 assessments for FEV_1, FVC, and PEFR will be conducted as close to the specified time points as possible (i.e., FEV_1, FVC, and PEFR assessments need to be conducted within ±15 minutes of specified time prior to study drug administration; ±5 minutes of specified time point for the first 60 minutes post study drug administration; ±15 minutes of specified time point for assessments obtained thereafter).

[b] 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.

8.1 Visit 1 (Screening Period)

- Obtain informed consent prior to conducting any study procedure.
- Register subject in IWRS to obtain subject screening number.
- Obtain demographic data, including age, race, smoking history, medical/surgical history (including cardiovascular risk factors and history), and age of onset of COPD.
- Review inclusion/exclusion criteria.
- Obtain medication history, including prior concomitant and COPD medications.
- Conduct a complete physical examination (general appearance, skin, head, eyes, ears, nose, throat, neck [including thyroid], lymph nodes, chest, heart, abdomen, extremities, and nervous system).
- Record COPD exacerbations and AEs (if any).
  Note: Adverse events that occur during the Screening Period (Visit 1 to Visit 4, before study drug dosing) will be summarized as medical history and not as a study AE, unless the event meets the definition of an SAE.
- Obtain height, weight, and vital signs (heart rate and blood pressure after being supine or seated for 5 minutes, and oral or tympanic temperature).
- Obtain a 12-lead ECG.
- Conduct 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.
- For those subjects participating in a sub-study (12-hour PFT, Week 24 PK profile, and/or HPA Axis) provide consent, as applicable.
- Conduct spirometry assessments.
- Confirm subject's ability to use MDI correctly (provide training as needed).
- If the subject qualifies to continue to Visit 2 perform the following:
  - Obtain laboratory samples (hematology, chemistry and urinalysis)
  - 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 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, except in countries with restrictive radiology assessment practice (e.g., Germany) where only subjects who have had a chest x-ray or CT scan (thorax) performed outside of the study in the last 6 months are allowed to be enrolled. Alternatively, in these countries an MRI may be used instead of a CT scan or chest x-ray, as per local practice assessment.
  - Stop prohibited COPD medications and change concurrent COPD medications, as specified in protocol (refer to Section 5.4.3).
  - Obtain subject assignment information of Atrovent HFA and Ventolin HFA from IWRS.
  - Dispense and train subject on eDiary use.

- In order to allow for 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.
- Schedule Visit 2.
- It is recommended that sites call subjects on the day before their scheduled Visit 2 and remind them of these expectations for the upcoming visit.
  - Subjects will be instructed to bring their eDiary, Sponsor-provided Ventolin HFA and Atrovent HFA to the next scheduled clinic visit.

8.2 Visit 2 (Screening Period)

- Review smoking status
- Review subject eDiary entries and retrain subject if he/she has not met the eDiary compliance requirement of >70% subject completion of eDiary assessments.
  - Review EXACT for completion as part of the eDiary review.
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, Visit 2 must be rescheduled).
- Review inclusion/exclusion criteria and confirm subject's eligibility to continue.
- If not previously reviewed, review clinical laboratory results from Visit 1. Please note whether the results are clinically significant and include comments where applicable.
- Record COPD exacerbations and AEs (if any).
  Note: Adverse events that occur during the Screening Period (Visit 1 to Visit 4, before study drug dosing) will be summarized as medical history and not as a study AE, unless the event meets the definition of an SAE.
- Have the subject complete the CAT questionnaire
- Review all prior medications and ensure adherence to COPD regimen.
- Obtain vital signs and 12-lead ECG 60 minutes pre-bronchodilator and 30 minutes post-bronchodilator administration
- Conduct spirometry 60 and 30 minutes prior to bronchodilator administration and at 30 minutes post-bronchodilator administration
- Perform reversibility test to Ventolin HFA (refer to Section 7.1.1.1 for instructions) and confirm subject continues to meet entry criteria based on pre- and post dose spirometry quality (refer to Exclusion Criterion 3 in Section 5.2), and post dose spirometry values.
- Schedule Visit 3.
  Note: Visit 3 can be scheduled a minimum of 1 day after Visit 2 and no later than 27 days after Visit 1 (Screening).
- Ensure subject has adequate supply of Sponsor-provided Atrovent HFA and Sponsor provided rescue Ventolin HFA.
- It is recommended that sites call subjects on the day before their scheduled Visit 3 and remind them of these expectations for the upcoming visit

- Subjects will be instructed to bring their eDiary, Sponsor-provided Atrovent HFA, and Sponsor-provided Ventolin HFA to the next scheduled clinic visit.

8.3 Visit 3 (Screening Period)

- Review inclusion/exclusion criteria and confirm subject's eligibility to continue
- Review smoking status
- Review subject diary entries and retrain subject if subject has not met the eDiary compliance requirement of >70% subject completion of diary assessments.
  - Review EXACT for completion as part of the eDiary review.
- 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 AEs (if any).
  Note: Adverse events that occur during the Screening Period (Visit 1 to Visit 4, before study drug dosing) will be summarized as medical history and not as a study AE, unless the event meets the definition of an SAE.
- Review all prior medications and ensure adherence to COPD regimen.
- Obtain vital signs and 12-lead ECG 60 minutes pre-bronchodilator and 30 minutes post-bronchodilator administration.
- Conduct spirometry 60 and 30 minutes pre- bronchodilator and 30 minutes post-bronchodilator administration
- Perform reversibility test to Sponsor-provided Atrovent HFA (refer to Section 7.1.1.1 for instructions).
- If participating in HPA Axis sub-study, obtain serum sample over 24 hours between Visits 3 and 4 prior to dosing at Randomization (Visit 4). Refer to Section 7.4 and Table 10 for sample collection schedule and details.
  Note: It is recommended that subjects provide the samples starting 24 hours prior to Randomization. However, he/she can do the 24-hour blood draws any day between Visits 3 and 4.
- Schedule Visit 4 (Randomization Visit, Day 1).
  Note: Visit 4 (Randomization Visit, Day 1) can be scheduled at minimum 1 day after Visit 3 and no later than 28 days after Visit 1 (Screening).
- Ensure subject has adequate supply of Sponsor-provided Atrovent HFA and Sponsor provided rescue Ventolin HFA.
- It is recommended that sites call subjects on the day before their scheduled Visit 4 and remind them of these expectations for the upcoming visit
  - Subjects will be instructed to bring their eDiary, Sponsor-provided Atrovent HFA, and Sponsor provided Ventolin HFA to the next scheduled clinic visit.

8.4 Visit 4 (Randomization)

- Review inclusion/exclusion criteria and confirm subject's eligibility to continue.

- Review smoking status
- Review subject diary entries and screen fail subject if subject has not met the diary compliance requirement of >70% subject completion of diary assessments.
  - Review EXACT for completion as part of the eDiary review.
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, Visit 4 must be rescheduled).
- Complete BDI questionnaire followed by SGRQ questionnaire before any other study procedures are performed.
- Have the subject complete the EQ-5D-5L.
- Record COPD exacerbations and AEs (if any).
- Review all concomitant medications and ensure adherence to COPD regimen.
- Collect Sponsor-provided Atrovent HFA and Sponsor-provided Ventolin HFA dispensed during the Screening Period.
- Subjects treated with an ICS during screening must discontinue ICS use prior to randomization and throughout the study.
- Perform all pre-dose assessments (refer to Table 9)
  - Obtain vital signs and 12-lead ECG two times each at least 5 minutes apart 1 hour prior to dosing
  - Obtain clinical laboratory samples
  - Spirometry to be conducted 60 and 30 minutes pre-dose
- To be randomized, all subjects must meet the FEV_1 baseline stability criteria. Refer to Section 7.1.1.2 for additional details. If the FEV_1 baseline stability entry criteria are not met at Visit 4 (Randomization) the subject will not be eligible to be randomized and will be screen failed.
- Obtain subject randomization number and treatment assignment information from IWRS. Note: The subject is to be considered randomized after receiving a randomization number.
- To allow for proper preparation of study drug, it is recommended that the seal around the study day treatment box is opened 15 to 30 minutes prior to dosing and the instructions for administration of study drug followed:
  - Refer to Appendix 2 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
  - Record/document the dose indicator reading. The dose indicator count recorded by the site staff will be the dose indicator count observed after priming but prior to subject dosing. For new MDIs, the recorded count will be the count following the priming of the device but before the subject dose. Refer to Appendix 1 for more details.
- Subject will administer first dose of newly assigned study drug at the clinic.
- Perform all post-dosing assessments (Refer to Table 9)
  - Conduct spirometry 5, 15 and 30 minutes and 1, 2, and 4 hours post-dose.
  - Obtain vital signs, ECG, and BMP 30 minutes and 2 hours post-dose

- Return eDiary to subjects and provide retraining if appropriate.
- Subjects will be instructed to track study drug dosing in their eDiary between study clinic visits.
- Schedule Visit 5 and ensure subject has adequate supply of study drug including a replacement MDI kit and rescue Ventolin HFA
- It is recommended that sites call subjects on the day before their scheduled Visit 5 and remind them of these expectations for the upcoming visit.
  - Subjects will be instructed to bring their eDiary and all study medication (including used study drug, replacement MDI kit and rescue Ventolin HFA) to the next scheduled clinic visit.

8.5 Visits 5 to 9 (Treatment Period)

- Confirm subject eligibility to continue.
- Review subject diary and EXACT questionnaire for data collection compliance.
- Review smoking status
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, the visit must be rescheduled).
- Confirm the subject took their last dose of randomized study medication as scheduled the prior evening. If the time of dosing was not in accordance with the protocol, then the visit must be rescheduled.
- Complete TDI questionnaire (Visits 5 to 9) followed by SGRQ questionnaire before any other study procedures are performed.
- Have the subject complete the EQ-5D-5L
- Collect HCRU information.
- Record COPD exacerbations and AEs (if any).
- Review all concomitant medications and ensure adherence to COPD regimen.
- Perform all pre-dose assessments (Refer to Table 9)
  - Conduct spirometry 60 and 30 minutes pre-dose.
  - Obtain vital signs once within 1 hour of dosing.
  - Obtain a 12-lead ECG within 1 hour of dosing at Visit 5 and Visit 7.
  - Obtain clinical laboratory samples at Visit 5 and Visit 7.
  - Perform a urine pregnancy test at Visit 7.
- Prior to dosing, site personnel will use IWRS to assign subjects a new kit of study drug for in-clinic dosing and to continue dosing at home until the next scheduled visit.
- Refer to Appendix 2 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
- Perform all post-dose assessments (Refer to Table 9)
  - Obtain vital signs 30 minutes post-dose and 2 hours post-dose.

  - Obtain a 12-lead ECG 30 minutes and 2 hours post-dose at Visit 5 and Visit 7.
  - Obtain BMP samples 30 minutes and 2 hours post-dose at Visit 5.
  - Obtain spirometry 15 and 30 minutes, and 1, 2, and 4 hours post-dose.
- Subjects will be instructed to track study drug dosing in their eDiary between study clinic visits.
- Return eDiary to subjects and provide retraining if appropriate.
- Subjects assigned to blinded study drug will be instructed to dose while at home from the site-primed MDI only, unless all of the following replacement conditions are met:
  - Dose indicator is in the red zone (Refer to Appendix 1 for dose indicator reading instructions)
  - The dose indicator registers ≤10 puffs remaining, and
  - Their next scheduled study clinic visit is not the following day.
- If these replacement conditions are met, subjects will be instructed to open their replacement kit, prime the MDI and start using for at-home dosing until the next scheduled study clinic visit.
- Schedule next visit and ensure subject has adequate supply of study drug including a replacement MDI kit and Sponsor-provided rescue Ventolin HFA.
- It is recommended that sites call subjects on the day before their scheduled visit and remind them of these expectations for the upcoming visit.
  - Subjects will be instructed to bring their eDiary and all study medication (including used study drug, replacement MDI kit and Sponsor-provided rescue Ventolin HFA) to the next scheduled clinic visit.

8.6 Visit 10a (Week 24; Final Visit)

- Review subject eDiary and EXACT questionnaire for data collection compliance.
- Perform physical examination (including weight) and review smoking status
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, the visit must be rescheduled).
- Confirm the subject took their last dose of randomized study medication as scheduled the prior evening. If the time of dosing was not in accordance with the protocol, then the visit must be rescheduled.
- Have subject complete TDI questionnaire followed by SGRQ questionnaire before any other study procedures are performed.
- Have subject complete the EQ-5D-5L.
- Collect HCRU information.
- Record COPD exacerbations and AEs (if any).
- Review all concomitant medications and ensure adherence to COPD regimen.
- Perform all pre-dose assessments (Refer to Table 9)
  - Obtain vital signs and 12-lead ECG 1 hour prior to study dosing
  - Obtain central laboratory samples and conduct a serum pregnancy test (as applicable).

- Obtain spirometry 60 and 30 minutes pre-dose

- **If subjects are participating in the PK and/or 12-hour PFT sub-studies**, perform additional assessments at Visit 10a (refer to Table 10).
- **If subjects are participating in the HPA Axis sub-study**, perform additional assessments at Visit 10a (refer to Table 10)
- Prior to dosing, site personnel will use IWRS to assign subjects a new kit of study drug for in-clinic dosing.
- Refer to the appendices for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
- Record/document the dose indicator readings of the used MDI and the replacement MDI.
  - For the new MDI, the recorded count will be the count following the priming of the device but before the subject doses.
- Administer in-clinic study drug dose from the new kit assigned at the visit.
- Perform all post-dose assessments (Refer to Table 9)
  - Obtain spirometry 15 and 30 minutes and 1, 2, and 4 hours post-dose
  - Obtain vital signs and 12-lead ECG 30 minutes and 2 hours post dose
  - Obtain BMP samples 30 minutes and 2 hours post-dose.
- Collect subject eDiary.
- Collect all study medication including Sponsor-provided Ventolin HFA and Atrovent HFA

Subjects not participating in the Extension Study (All Subjects):

- At completion of all assessments at Visit 10a, return subject to appropriate maintenance COPD medications.
- Inform subject about reporting all SAEs up to 14 days following the last dose of study drug.
- Schedule the follow-up telephone call at least 14 days from Visit 10a.

Subjects who choose to participate in the extension study (Subjects in Japan only):

- Subjects who volunteer to participate in the 28-week extension study will complete Visit 10a procedures and be scheduled for the first study visit in the extension study (Visit 10b).

8.7 Procedures for Treatment Discontinuation and Study Withdrawal Subjects

Subjects who discontinue study treatment prior to Week 24 (Visit 10a) will be encouraged to remain in the study to complete all remaining study visits during the 24 week treatment period. Subjects who agree to continue to be followed post treatment discontinuation will

sign an ICF addendum. All subjects who agree to continue study participation beyond treatment discontinuation will complete a Treatment Discontinuation/Withdrawal Visit (refer to Table 8) prior to transitioning back to regularly scheduled study visits. Subjects participating in a sub-study who choose to discontinue from treatment will only complete regular scheduled visits and not complete any remaining sub-study assessments. Treatment discontinuation subjects will return to appropriate maintenance COPD medications, per the investigators discretion. For subjects recorded as Treatment Discontinuations that do not complete at least one post-treatment data collection a telephone follow-up call is required at least 14 days after last study drug dose.

If a subject chooses not to continue with study assessments, at a minimum the subject will complete the Treatment Discontinuation/Withdrawal Visit (refer to Table 8). These subjects will return to appropriate maintenance COPD medications, per the investigators discretion. A follow-up telephone call will be performed at least 14 days after the last study drug dose. In the event the Treatment Discontinuation/Withdrawal Visit is performed >14 days post last study drug dosing, a follow-up TC will not be required. These subjects will be followed for vital status at 24 weeks post randomization in accordance with the informed consent.

8.8 Unscheduled Visit and Treatment Discontinuation/Withdrawal Visit

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

Treatment Discontinuation/Withdrawal Visits will be captured as unscheduled visits. The following minimum procedures will be completed for these types of visits:

- Complete TDI questionnaire first; followed by SGRQ questionnaire before any other study procedures are performed.
- Have subject complete the EQ-5D-5L.
- Collect HCRU information.
- Record COPD exacerbations and AEs (if any).
- Review concomitant medications.
- Conduct a physical examination, including vital signs.
- Perform spirometry assessment (subject should have withheld all COPD medications, including study medication and rescue Ventolin HFA, for at least 6 hours prior to the start of procedures)
- Perform ECG and collect blood samples for hematology, chemistry and urinalysis.
- Collect a blood sample for pregnancy test for women of child-bearing potential.
- Collect subject eDiary.
- Collect all study drugs, including rescue medications.
- Return subject to pre-study or appropriate maintenance COPD medications.
- Inform subject about reporting all SAEs up to 14 days following the last dose of study drug.
- Capture the reason for subject discontinuation.

8.9 Telephone Follow-up

Subjects will be followed-up within 14 days after the last study drug dosing. The following information will be requested:

- Review previously on-going COPD exacerbations and AEs/SAEs (if any)
- Review concomitant medications

Note: For subjects who withdraw consent, schedule a follow-up TC at least 14 days after the last study drug dosing unless the visit is performed >14 days post last study drug dosing, a follow-up TC will not be required. For Treatment Discontinuation Subjects, a telephone follow-up call is not required as long as at least one post treatment study visit is completed.

8.10 24-Week Post-Randomization Vital Status Confirmation

All subjects who discontinue study treatment prior to 24 weeks post- randomization will have their vital status confirmed at 24 weeks post-randomization.

To confirm the vital status and cause of death, if appropriate, the following attempts will be made:

- The first and second attempts may be conducted as telephone follow-up call to the subject within 2 weeks after 24 weeks post-randomization
- The third attempt will be by certified mail to the subject's address provided at the time of informed consent within 3 weeks after 24 weeks post-randomization.
- The fourth attempt will be made as a telephone follow-up call to the next of kin/emergency contact provided at the time of informed consent within 4 weeks after 24 weeks post-randomization
- A fifth attempt will be made through a certified letter to the next of kin/emergency contact provided at the time of informed consent within 5weeks after 24 weeks post-randomization
- After the fifth attempt, the study site will contact the national death registries (if available in that country) to confirm date and cause of death.

8.11 Completion of Study

The Investigator will document the completion or the reason for a subject's early withdrawal from the study in the eCRF. The following categories should be used to describe these events in the eCRF:

- Subject discretion (document reason)
- Investigator considers it to be in the best interest of the subject
- Adverse events(s)
- Administrative reasons (e.g., early termination of the study)

- Subject lost-to-follow-up
- Lack of efficacy
- Major protocol deviation
- Death
- Completion of the study
- Protocol-specified criteria (Refer to Section 5).

9 PLANNED STATISTICAL METHODS

9.1 Introduction

This study will be conducted as a double-blind, active-control (open-label), and parallel-group study evaluating the following treatments in approximately 1800 subjects:

- BGF MDI (320/14.4/9.6 μg BID)
- GFF MDI (14.4/9.6 μg BID)
- BFF MDI (320/9.6 μg BID)
- Symbicort Turbuhaler (400/12 μg BID)

Approximately 1800 subjects with moderate to very severe COPD will be randomized to provide approximately 1600 subjects to complete the study.

The primary objective of this study is to compare the effects of treatment with BGF MDI relative to GFF MDI, BFF MDI, and Symbicort TBH on lung function in subjects with moderate to very severe COPD.

This study will include a 24 week Treatment Period, preceded by a Screening Period and followed by either enrollment into a 28-week extension study or a 2-week follow-up telephone call.

The primary endpoints, comparisons of interest, and time frames for analyses may differ by country or region due to local regulatory agency requirements. The 3 different registration approaches will be called: (1) Japan/China, (2) EU/Canada, and (3) US. Countries not specifically mentioned will be decided by regulatory requirements and included in one of the three defined registration approaches. The impact of these approaches is delineated in each of the relevant sections below. Where not specified, a common approach will be used for all regions.

The registration requirements also impact controls for multiplicity; these multiplicity controls will be delineated by approach.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

All efficacy assessments are relative to pre-dose baseline obtained at or prior to Visit 4 (Section 3).

9.2.2 Safety Endpoints

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

9.3 Study Populations

The following analysis populations are defined in this study:

- The **Intent-To-Treat Population** is defined as all subjects who are randomized to treatment and used any amount of the study treatment. Subjects will be analyzed according to the treatment they were assigned to at randomization. Data obtained after discontinuation of treatment, but prior to withdrawal from the study, will be included
- The **Modified Intent-to-Treat (mITT) Population** is a subset of the ITT Population, defined as all subjects with post randomization data obtained prior to discontinuation from treatment. Any data collected after completion of or discontinuation from randomized study medication will be excluded from the mITT analysis but will still be included in the ITT analysis. Subjects will be analyzed according to randomized treatment group. (Note that a subject who used a study treatment, but took less than one full dose of treatment will qualify for this population). Data obtained after treatment discontinuation will be excluded. The mITT Population will be the primary population for all efficacy analyses except for the non-inferiority analyses. Note: The knowledge that a subject did not have a COPD exacerbation constitutes an efficacy assessment.
- The **Rescue Ventolin User Population** is defined as all subjects in the ITT Population with mean baseline rescue Ventolin use of ≥1.0 puff/day.
- The **Per-Protocol (PP) Population** is a subset of the ITT Population, defined as all subjects with post-randomization data obtained prior to any major protocol deviations. Data obtained after any major protocol deviation or discontinuation from treatment will be excluded. Since receiving the wrong treatment will be a major protocol deviation, subjects in the PP population will be analyzed as randomized (which for this population if identical to analysis by the actual treatment received). Any evaluability criteria with a potential impact on efficacy results will be identified in a blinded fashion from review of data listings prior to unblinding. Major protocol deviations (protocol violations), therefore, can result in exclusion of all data from a particular subject from the PP population or require exclusion of data from a specific time point and/or subsequent time points for an endpoint.
- The **Safety Population** is similar to the ITT Population (all subjects who are randomized to treatment and receive at least one dose of the study treatment). However, subjects will be analyzed according to treatment received rather than randomized. If a subject received more than 1 randomized treatment, they will be analyzed and included in summaries according to the treatment they received the most. Subjects receiving no study treatment

will be excluded, as will subjects who have no post-dose safety assessments. (Note that a subject who used a study treatment, but took less than 1 full dose of treatment will qualify for this population). Note: The statement that a subject had no AEs also constitutes a safety assessment

- The **PK Population** is defined as all randomized and treated subjects who have sufficient data to reliably calculate at least 1 PK parameter. Subjects will be analyzed according to treatment received rather than randomized.
- The **HPA Axis Population** consists of subjects who participated in the HPA axis sub-study and is a subset of the ITT Population without protocol deviations which could affect the serum cortisol endpoint and whose serum samples did not have confounding factors that would affect the interpretation of the results

Analyses will be performed as follows:

Demographics will be summarized for the mITT, PP, Safety, and Non-randomized Populations. Extent of exposure will be summarized for the Safety Population. The Safety Population will be used to summarize safety. Efficacy Analyses will be performed for the ITT, mITT, and PP Populations. The mITT Population using only on-treatment data will be considered the primary population for these analyses, with the ITT and PP populations being considered supportive.

9.4 Efficacy Analyses

9.4.1 Estimands

The primary estimand of interest is called the efficacy estimand and is the effect of the randomized treatments in all subjects assuming continuation of randomized treatments for the duration of the study regardless of actual compliance. There are three additional estimands of interest. One is called the attributable estimand and is the effect of treatment in subjects attributable to the randomized treatment. For this estimand, discontinuation of randomized medication for reasons such as tolerability or lack of efficacy is considered a bad outcome. Another estimand of interest is called the treatment policy estimand. This estimand is the effect of randomized treatment over the study period regardless of whether randomized treatment is continued. The final estimand of interest is called the per protocol estimand. This estimand is the effect of treatment on subjects who are compliant with the protocol (i.e. no major protocol deviations), including the use of randomized medication.

The primary analysis for the efficacy estimand will be conducted using the mITT Population where only data obtained prior to subjects discontinuing from randomized treatment will be utilized. This assumes that efficacy observed on treatment is reflective of what would have occurred after discontinuation of randomized treatment had they remained on treatment.

The second estimand of interest is the attributable estimand. Analyses of the attributable estimand will be conducted in the mITT Population, but data that are missing due to treatment discontinuation will be imputed based on the 95th percentile of the reference arms' distribution if the reason is reasonably attributable to tolerability or lack of efficacy. The 95th

percentile applies to an endpoint for which a higher value is a worse outcome; however, the 5th percentile applies to an endpoint for which a higher value is a better outcome. More detail about the computation of the attributable estimand will be provided in the SAP.

The third estimand of interest is the treatment policy estimand. Analyses of the treatment policy estimand will be conducted in the ITT Population, in which all observed data will be utilized regardless of whether subjects remain on randomized treatment. The treatment policy estimand will be provided as a supporting analysis for all primary and secondary endpoints.

Finally, the last estimand of interest is the per protocol estimand. Analysis of this estimand will use the PP Population. This estimand will serve as primary for the non-inferiority comparison of BFF MDI to Symbicort TBH. It will be supportive for all other comparisons of interest.

9.4.2 Primary Efficacy Analyses

For the primary comparisons, the null hypothesis for each pair-wise comparison will be that the mean treatment difference is zero (mean treatment effects are equal). The alternative hypothesis is that the mean treatment difference is greater (less than) zero (mean treatment effects are not equal).

All comparisons will be for superiority except that the comparison of BFF MDI to Symbicort TBH will be for non-inferiority and will use margins (δ's) of 50 mL for trough FEV_1 and 75 mL for post-dose FEV_1 measures. P-values will be reported as 2-sided.

9.4.2.1 Change from Baseline in Morning Pre-dose Trough FEV_1

The primary analysis will be conducted using the efficacy estimand. The change from baseline in morning pre-dose trough FEV_1 will be analyzed using a linear model with repeated measures (RM). The model will include treatment, visit, treatment, treatment by visit interaction, and ICS use at Screening as categorical covariates and baseline FEV_1, percent reversibility to Ventolin HFA, and baseline eosinophil counts as continuous covariates. Baseline FEV_1 is defined as the average of the non-missing 60 minute and 30 minute values obtained prior to dosing at Visit 4, and baseline eosinophil count is defined as the average of non-missing eosinophil counts prior to treatment. An unstructured covariance matrix will be used to model correlation within a subject. If this model fails to converge, a first-order autoregressive structure will be used instead; for this model, subject will be included as a random effect. Contrasts will be used to obtain estimates of the treatment differences over 24 weeks (primary for EU/Canada; secondary for Japan/China; secondary for the US), over Weeks 12 to 24 (primary for Japan/China), and at Week 24 (primary for US). Two-sided p values and point estimates with 2-sided 95% CIs will be produced for each treatment difference. The primary analysis will be for the efficacy estimand. Secondary analyses will be produced for the attributable estimand. The non-inferiority comparison of BFF MDI to Symbicort TBH will be based on the per-protocol estimand.

Supportive analyses will:

- repeat the above analysis using the treatment policy estimand
- provide estimates of the change from baseline at individual time points from the primary RM model

Subgroup analyses for morning pre-dose trough FEV_1 will be performed for the Japanese region versus the remaining regions combined. Additional subgroup analyses may be defined in the Statistical Analysis Plan (SAP) as appropriate.

Sensitivity analyses to evaluate the robustness of the primary analyses to the nature of the missing data are discussed in Section 9.15.

9.4.2.2 FEV_1 AUC_{0-4}

Change from baseline in FEV_1 AUC_{0-4} over 24 weeks will be analyzed in a similar manner as for morning pre-dose trough FEV_1. Area under the curve will be calculated using the trapezoidal rule and will be normalized by dividing by the time in hours from dosing to the last measurement included (typically 4 hours). Only 1 non-missing, post dose value is required for the calculation of AUC. Actual time from dosing will be used if available; otherwise scheduled time will be used.

9.4.3 Analysis of Secondary Endpoints

The following variables appear as secondary for 1 or more registration approaches: peak FEV_1, TDI focal score over 24 weeks, rescue Ventolin HFA usage over 24 weeks, SGRQ total score over 24 weeks, percentage of subjects achieving an MCID of 4 units or more in SGRQ total score at Week 24, RS-total score over 24 weeks, time to CID, the rate of moderate or severe COPD exacerbations, and time to onset. Multiplicity will be controlled for the secondary variables as described in Section 9.4.5. The main analysis for secondary endpoints and other endpoints will use the efficacy estimand. The attributable estimand and treatment policy estimand will be estimated as sensitivity analyses for the secondary endpoints with the exception of time of onset on Day 1. The attributable estimand will impute missing data due to lack of efficacy and tolerability punitively, whereas all other missing data will be imputed using the observed data model. Details of imputation will be described in the SAP. The treatment policy estimand will include all post-treatment discontinuation data.

9.4.3.1 Transition Dyspnea Index

Assessments of dyspnea will be obtained using the BDI/TDI. The BDI/TDI questionnaire is presented in Appendix 9.

At Visit 4, the severity of dyspnea at baseline will be assessed using the BDI. At subsequent visits (as per Schedule of Events, Table 8) change from baseline will be assessed using the TDI. The difference between treatment groups in TDI focal score over 24 weeks will be evaluated using a similar RM approach as for the primary endpoint, but using BDI instead of baseline FEV_1 in the model, and adding baseline post-bronchodilator percent predicted FEV_1

as a continuous covariate. Scoring and handling of missing items will be conducted in accordance with the user's guide for the TDI score. Two-sided p values and point estimates with 2-sided 95% CIs will be produced for each treatment difference. The comparison of BFF MDI to Symbicort TBH will be for non inferiority rather than superiority and will use a margin of 0.75.

The above analyses of the TDI focal score will be repeated over Weeks 12 to 24 as secondary efficacy for Japan/China.

The difference between treatments at each of the individual visits will be evaluated and summarized, both for the focal score as well as for the individual components of the TDI: functional impairment, magnitude of task, and magnitude of effort. Responder analyses will be performed, where responders are defined as a response of 1.0 point or more (corresponding to at least a minor improvement) on average over 24 weeks, and separately over Weeks 12 to 24. Logistic regression will be used to compare the treatment groups with BDI, baseline eosinophil count, post-bronchodilator percent predicted FEV_1, and percent reversibility to Ventolin HFA as continuous covariates, and treatment, and ICS use at Screening as categorical covariates. P-values and odds ratios with 95% CIs will be produced for each treatment comparison.

9.4.3.2 Peak FEV_1

The peak change from baseline in FEV_1 within 2 hours post-dosing over 24 weeks, over Weeks 12 to 24, and at Week 24 will be analyzed in a similar way to morning pre-dose trough FEV_1.

9.4.3.3 St. George Respiratory Questionnaire

The SGRQ is presented in Appendix 10. The difference between treatment groups in the change from baseline in SGRQ over 24 weeks and over Weeks 12 to 24 will be evaluated using a similar RM approach as for the TDI focal score, but adding country as a covariate, and with baseline SGRQ replacing BDI in the model. Scoring and handling of missing items will be conducted in accordance with the user's guide for the SGRQ. Each response is to be given a unique empirically derived weight between 0 and 100, the weights of all responses are then summed up and divided by the maximum possible score and expressed as a percentage. Missing data of the SGRQ total score will not be imputed. Two-sided p-values and point estimates with 2-sided 95% CIs will be produced for each treatment difference.

As supportive analyses, the difference between treatments at each of the individual visits will be evaluated and summarized. Individual domains of the SGRQ also will be analyzed in a similar fashion as the overall score. A responder analysis will be performed where responders are defined as an improvement of 4.0 points or more on average at 24 weeks, over 24 weeks, over Weeks 12-24, and at each post-randomization assessment time-point. Logistic regression will be used to compare the treatment groups with baseline SGRQ using a similar approach as the TDI responder analyses - with baseline eosinophil count, baseline post-bronchodilator percent predicted FEV_1, and reversibility to Ventolin HFA as continuous

covariates, and treatment, country, and ICS use at Screening as categorical covariates. P-values and odds ratios with 95% CIs will be produced for each treatment comparison.

9.4.3.4 Rescue Ventolin HFA Use

The number of puffs of rescue Ventolin HFA taken in the previous 12 hours will be recorded in the subject diary in the morning and evening. The mean daily number of puffs of rescue Ventolin HFA will be calculated overall and for each of the 4-week intervals during the Treatment Period. Diary data recorded during the last 7 days of the Screening Period will be used to calculate the baseline. For every interval of time over which the mean number of puffs of rescue will be calculated for both overall as well as 4-week intervals, records with missing values will be ignored in both the numerator and denominator. As such, the denominator will be adjusted based on the number of days (including half days) with non-missing values.

The difference between treatment groups in the change from baseline in rescue Ventolin HFA usage over 24 weeks will be evaluated using a similar RM approach as for the TDI. Instead of visit, the number of the relevant 4-week interval (Interval 1 to Interval 6) will be used as a categorical covariate in the model. As supportive analyses, the treatment difference for each 4 week interval and over Weeks 12 to 24 will be evaluated and summarized. Additionally as supportive analyses, daytime rescue Ventolin HFA use and night-time rescue Ventolin HFA usage will be evaluated and summarized in a similar fashion. Two sided p values and point estimates with 2-sided 95% CIs will be produced for each treatment difference.

9.4.3.5 RS-Total Score

The EXACT is a 14-item PRO daily diary which will be used to measure the effect of treatment on exacerbations, and on the severity of respiratory symptoms. The RS-total utilizes the 11 respiratory symptom items contained in the 14-item EXACT. The RS-Total score represents respiratory symptom severity, overall. The mean change from baseline in: the RS-Total Score will be calculated over each 4-week interval of the 24-week Treatment Period. The last 7 days of the Screening Period will be used to calculate the baseline. The mean change from baseline in the RS-Total Score will be analyzed using a similar model as for the TDI to estimate treatment effects over 24 weeks, but using the baseline mean score instead of the BDI as a covariate, and baseline post-bronchodilator percent predicted FEV_1 as a continuous covariate. Instead of visit, the number of the relevant 4-week interval (Interval 1 to Interval 6) will be used as a categorical covariate in the model. This analysis will be secondary for the EU only.

9.4.3.6 COPD Exacerbations

Secondary Endpoint Analysis:

The rate of moderate or severe COPD exacerbations will be analyzed using negative binomial regression. Chronic obstructive pulmonary disease exacerbations will be considered separate events provided that 7 or more days are between the recorded stop date

of the earlier event and start date of the latter. Time at risk of experiencing an exacerbation will be used as an offset variable in the model. Time during an exacerbation or in the 7 days following an exacerbation will not be included in the calculation of time at risk. For moderate or severe COPD exacerbations, the start date is be defined as the start date of prescribed treatment with a systemic corticosteroid or systemic antibiotic and the stop date will be defined as the last day of prescribed treatment with a systemic corticosteroid or systemic antibiotic. Treatments will be compared adjusting for country, baseline post-bronchodilator percent predicted FEV_1, baseline COPD exacerbation history, baseline eosinophil count, and ICS use at Screening.

Other endpoints:

The rate of COPD exacerbations of any severity and the rate of severe COPD exacerbations will be analyzed in a similar manner.

The time to first moderate or severe COPD exacerbation, the time to the first COPD exacerbation of any severity, and the time to the first severe COPD exacerbation will each be analyzed using Cox regression model. The model will include treatment; baseline percent predicted FEV_1, baseline COPD exacerbation history, baseline eosinophil count, and ICS use at Screening. Estimated adjusted hazard ratios relative to the comparator will be displayed along with the associated Wald 2-sided 95% CIs and p-values. Time to first moderate or severe COPD exacerbation as well as the time to first COPD exacerbation of any severity will be displayed graphically for each treatment group using a Kaplan-Meier curve. Subjects who did not experience a COPD exacerbation will be censored at the Week 24 visit. Subjects who withdrew from the study without experiencing a COPD exacerbation will be censored at the date of withdrawal.

Duration of COPD Exacerbation

For moderate or severe exacerbations, the duration is defined by the length of prescribed treatment, whereas for mild exacerbations, the duration is defined by the length of symptoms.

For moderate or severe COPD exacerbations, the start date will be defined as the start date of prescribed treatment with a systemic corticosteroid or systemic antibiotic and the stop date will be defined as the last day of prescribed treatment with a systemic corticosteroid or systemic antibiotic. In order to ensure that the same event is not counted twice, concurrent moderate or severe COPD exacerbations with start and stop dates equal to or less than 7 days apart will be considered the same event and assigned the maximum severity between the two.

For mild COPD exacerbations, start date will be defined as the onset of worsened symptoms as recorded by the subject in the eDiary, and the stop date will be defined as the last day of worsened symptoms. In order to ensure that the same event is not counted twice, mild COPD exacerbations with start and stop dates equal to or less than 7 days apart will be considered the same event.

In addition, in order to not double count exacerbations that are moderate or severe, eDiary data from dates within 7 days of a moderate or severe exacerbation will not be included as

additional mild COPD exacerbations. This implies that continuing worsened symptoms that meet the definition of a mild exacerbation would need to be present at least 2 days prior to the 7-day period immediately preceding the start date of a moderate or severe COPD exacerbation in order to be considered a separate event. Similarly, worsened symptoms would need to be present for at least 2 days after the 7-day period immediately following a moderate or severe COPD exacerbation to be considered a separate event.

Analyses of each severity of exacerbation will account for the time that subjects are at risk of having an exacerbation of that severity or greater. Time during or immediately following an exacerbation will not be considered as part of the time that the subject was at risk. However, time during or immediately following an exacerbation of lower severity will be included since, for example, a subject experiencing a mild exacerbation is still at risk of the event increasing in severity and becoming a moderate exacerbation.

9.4.3.7 Time to Clinically Important Deterioration

CID is defined as a ≥ 100 mL decrease (from baseline) in trough FEV_1, or ≥ 4 points increase (from baseline) in SGRQ total score, or a TDI focal score of -1 point or less, or treatment-emergent moderate-or-severe COPD exacerbation occurring up to Week 24. Sustained CID is defined as ≥ 100 mL decrease (from baseline) in trough FEV_1, or ≥ 4 points increase (from baseline) in SGRQ total score, or a TDI focal score of -1 point or less, any of which is occurring on two consecutive analysis visits or for ≥ 50% of all available subsequent analysis visits, or a treatment emergent moderate-or-severe COPD exacerbation occurring up to Week 24.

Time to CID analysis will be performed using the Cox regression model. The model will include baseline post-bronchodilator percent predicted FEV_1, baseline eosinophil count, baseline COPD exacerbation history (0, 1, ≥2), country, and ICS use at Screening (yes/no). Time to a CID event will be based on the component event which occurs first. Subjects who do not have a CID event will be censored at the earliest day among the component censoring times. COPD exacerbations happening after Week 24 will not be counted as CID events. Estimated adjusted hazard ratios will be displayed along with associated 95% CI and p-values. Time to CID will be displayed for each treatment group using a Kaplan-Meier curve. Time to CID will be presented for the efficacy, the attributable, the treatment policy, and per-protocol estimands.

The analyses will be repeated for time to sustained CID as an ‘other’ endpoint for the efficacy estimand.

9.4.3.8 Time to Onset of Action

The onset of action will be determined for each treatment using the post dosing FEV_1 assessments from Day 1. The onset of action for each product (BGF MDI, GFF MDI, and BFF MDI) will be defined as the first time point where the mean change from baseline exceeds 100 mL. Supportive analyses may be conducted using alternatively definitions of onset of action.

9.4.4 Analysis of Other Endpoints

All exploratory endpoints will be presented for the efficacy estimand only. These will not be presented for the attributable, treatment policy, or per-protocol estimands.

9.4.4.1 Other Spirometry Endpoints

The analysis of the other between-treatment comparisons for changes in morning pre-dose trough FEV_1 at each post-dose time point has already been described in Section 9.4.2.1. Treatment differences in the change from baseline in FEV_1, morning pre-dose trough FVC, PEFR, and FEF_{25-75} will be evaluated in a similar manner to the primary endpoint.

9.4.4.2 12-Hour Pulmonary Function Tests

FEV_1 AUC_{0-12} will be measured in a subset of subjects at the 12 week visit. Area under the curve will be calculated using the trapezoidal rule and transformed into a weighted average by dividing by the time in hours from dosing of the last measurement included (typically 12 hours). Only 1 non-missing post dose value is required for the calculation of AUC. The per protocol estimand is primary for the non-inferiority comparison of BFF vs. Symbicort. Actual time from dosing will be used if available; otherwise scheduled time will be used. The differences between treatment groups in FEV_1 AUC_{0-12} at Week 12 will be evaluated using an ANCOVA with baseline FEV_1, baseline eosinophil count, and percent reversibility to Ventolin HFA as continuous covariates, and treatment, and ICS use at Screening as categorical covariates. Two-sided p-values and point estimates with 2-sided 95% CIs will be produced for each treatment difference. The comparison of BFF MDI to Symbicort TBH will be for non-inferiority rather than superiority and will use a margin of 75 mL.

As additional supportive analyses, FEV_1 AUC_{0-4}, FEV_1 AUC_{0-6}, FEV_1 AUC_{6-12}, FVC AUC_{0-4}, FVC AUC_{0-4}, PEFR AUC_{0-12}, PEFR AUC_{0-4}, and FEF_{25-75} AUC_{0-12}, FEF_{25-75} AUC_{0-4} will be calculated and analyzed for the efficacy estimand only, in a similar fashion as the efficacy estimand for FEV_1 AUC_{0-12}.

9.4.4.3 Percentage of Days with No Rescue Ventolin HFA Use over the Treatment Period

As a supportive analysis, the percentage of days with ‘no rescue Ventolin HFA use’ over 24 weeks will be analyzed. A ‘day with no rescue use’ is defined as any day where the subject reported zero puffs of rescue Ventolin HFA. The rescue Ventolin HFA usage diary data from days where rescue Ventolin HFA usage data is non-missing will be used to ascertain the days with “no rescue Ventolin HFA use”. The percentage of days with ‘no rescue Ventolin HFA use’ will be summarized by treatment and analyzed using ANCOVA with baseline average daily rescue Ventolin HFA use instead of baseline FEV_1 as a covariate, and baseline post-bronchodilator percent predicted FEV_1 as a continuous covariate.

9.4.4.4 Time to Treatment Discontinuation

Treatment discontinuation will be defined as a moderate or severe COPD exacerbation or discontinuation from treatment for any reason. The time to treatment discontinuation will be analyzed using a Cox regression model. The model will include treatment, baseline post-bronchodilator percent predicted FEV_1, baseline eosinophil count, baseline COPD exacerbation history, and ICS use at Screening. Estimated adjusted hazard ratios will be displayed along with associated 95% CIs and p-values. Time to treatment discontinuation will be displayed graphically for each treatment group using a Kaplan-Meier curve. Subjects who did not experience a treatment discontinuation will be censored at Week 24.

9.4.4.5 Exacerbations of Chronic Pulmonary Disease Tool

The EXACT (please note new name Section 7.1.4.5) is a 14-item PRO daily diary which will be used to measure the effect of treatment on exacerbations, and on the severity of respiratory symptoms. The severity of respiratory systems will be measured using the E-RS:COPD, which is an 11-item subset of the EXACT. The analysis of the RS-Total score is already described under secondary endpoints. Mean change from baseline in: the daily EXACT Total Score, and the 3 subscale scores of the E-RS:COPD (i.e. RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms) will be calculated over each 4-week interval of the 24-week Treatment Period and analyzed using a similar approach as the RS-Total score. The last 7 days of the Screening Period will be used to calculate the baseline.

9.4.4.6 European Quality-of-Life-5 Dimension-5 Level Questionnaire

The European Quality-of-Life-5 Dimension-5 Level Questionnaire (EQ-5D-5L) data will be weighted to calculate an index score based upon subjects responses to the 5 dimensions. The visual analogue scale will be scored from 0 (worst imaginable health state) through 100 (best imaginable health state) to represent the subject's self-report concerning how bad or how good their health was during that day. The percentage of subjects' categorical responses to each of the 5-dimensions will be summarized. Descriptive statistics for the index score and VAS will be presented by treatment group. VAS scores over 24 weeks may be analyzed using a similar RM model as is used for the TDI, but using baseline EQ-5D-5L VAS score as a covariate instead of BDI.

The compliance of completing the EQ-5D-5L questionnaires will be described at each assessment time-point, by the number and percentage of subjects who filled out a questionnaire (per subject, at least 1 question answered).

9.4.5 Control of Type I Error

There are 3 separate plans for control of Type I error, corresponding to each of the 3 registration approaches for Japan/China, EU/Canada, and US. Each of the plans will test the primary endpoint (s) using the efficacy estimand first for superiority comparisons, followed by the attributable estimand as the first secondary. Additional secondary endpoints will only be tested using the efficacy estimand for Type I error control. Non-inferiority comparisons will be made using the per-protocol estimand. Additional details, including non-inferiority

margins, will be described in detail in the SAP. All secondary endpoints with the exception of time to onset are included in the Type I error control plans described below.

9.4.5.1 Japan/China Approach:

The comparisons of interest for the Japan/China approach are BGF MDI versus BFF MDI and BGF MDI versus GFF MDI, both for superiority, and BFF MDI versus Symbicort TBH for non-inferiority.

Strong control of the Type I error rate will be maintained at the 2-sided 0.05 level for the primary endpoint across key treatment comparisons using a sequential approach across comparisons, and then for the secondary measures. Type I error control will be maintained within comparison using a combination of sequential and simultaneous approaches as detailed below. Based on positive dependence of the test statistics (Sarkar, 2008; Sarkar and Chang 1997), simultaneous control of Type I error for the relevant secondary measures will be achieved using the Hochberg procedure (Hochberg, 1988).

The following 3 between-treatment comparisons will be conducted, in the order stated, for morning pre-dose trough FEV_1 over Weeks 12 to 24: BGF MDI versus BFF MDI, BGF MDI versus GFF MDI, using the efficacy estimand, and BFF MDI versus Symbicort TBH (non-inferiority) using the per-protocol estimand. Each comparison will be made only if the preceding comparison in the sequence is statistically significant.

If the comparisons for BGF MDI versus BFF MDI and BGF MDI versus GFF MDI are both statistically significant at a 2-sided alpha level of 0.05, testing will proceed to comparison of the respective attributable estimands in the same order. If the comparisons of the attributable estimands are also significant, then the remaining secondary measures within each comparison will be tested using the efficacy estimand. Type I error will be controlled at 0.05 within each comparison (BGF MDI versus BFF MDI, BGF MDI versus GFF MDI) for the secondary endpoints through simultaneous testing under the Hochberg procedure with a 2-sided alpha of 0.05.

If non-inferiority is established for the comparison of trough FEV_1 between BFF MDI and Symbicort TBH, then tests of the additional secondary measures for this comparison will be interpreted without any additional control of Type I error.

9.4.5.2 EU/Canada Approach

The comparisons of interest for the EU/Canada approach are: BGF MDI versus GFF MDI, BGF MDI versus BFF MDI, and BGF MDI versus Symbicort TBH, all for superiority, and the comparison of BFF MDI vs. Symbicort for non-inferiority. All comparisons are evaluated over 24 weeks unless stated otherwise.

Strong control of the Type I error rate will be maintained at the 2-sided 0.05 level for the key comparisons using a sequential approach for the primary endpoints and then for the secondary measures Type I error control will be maintained within comparison using a combination of sequential and simultaneous approaches as detailed below.

The following 4 comparisons will be conducted first, in the order they appear below:

- FEV_1 AUC_{0-4} for BGF MDI versus BFF MDI using the efficacy estimand
- Trough FEV_1 for BGF MDI versus GFF MDI using the efficacy estimand
- FEV_1 AUC_{0-4} for BGF MDI versus BFF MDI using the attributable estimand
- Trough FEV_1 for BGF MDI versus GFF MDI using the attributable estimand

All subsequent comparisons below will use only the efficacy estimand.

If the comparison of FEV_1 AUC_{0-4} between BGF MDI and BFF MDI using the attributable estimand above is statistically significant, testing will proceed to the secondary comparison of BGF MDI versus BFF MDI for change in morning pre-dose trough FEV_1 using a 2-sided 0.05 level test. If this test is also significant, testing will proceed to the remaining secondary endpoints. BGF MDI versus BFF MDI will be simultaneously compared among these secondary endpoints using the Hochberg procedure with a 2-sided alpha of 0.05.

If the comparison of BGF MDI versus GFF MDI for change in morning pre-dose trough FEV_1 using the attributable estimand is statistically significant, testing will proceed to the remaining secondary endpoints for BGF MDI vs. GFF MDI using the efficacy estimand. BGF MDI versus GFF MDI will be simultaneously compared among the secondary endpoints using the Hochberg procedure with a 2-sided alpha of 0.05.

If the comparison of FEV_1 AUC_{0-4} for BGF MDI versus BFF MDI is statistically significant using the attributable estimand, testing will also proceed to a comparison of BGF MDI versus Symbicort TBH for of FEV_1 AUC_{0-4} using the efficacy estimand. If statistically significant, the remaining secondary endpoints for BGF MDI versus Symbicort TBH will be simultaneously compared among the secondary endpoints using the Hochberg procedure with a 2-sided alpha of 0.05.

Finally, if the comparison of FEV_1 AUC_{0-4} over 24 weeks for BGF MDI versus BFF MDI is statistically significant, testing will proceed to the non-inferiority comparisons of BFF MDI versus Symbicort TBH. If non-inferiority is established, tests of the additional secondary measures for this comparison will be interpreted without any additional control of Type I error.

9.4.5.3 US Approach

The comparisons of interest for the US approach are: BGF MDI versus GFF MDI and BGF MDI versus BFF MDI, both for superiority, and at Week 24 unless stated otherwise. Statistical significance for nominal comparisons will be at alpha=0.05.

Strong control of the Type I error rate will be maintained at the 2-sided 0.05 level for the key comparisons using a sequential approach for the primary endpoints and then for the secondary measures Type I error control will be maintained within comparison using a combination of sequential and simultaneous approaches as detailed below .

The following 4 comparisons will be conducted first, in the order they appear below:

- FEV_1 AUC_{0-4} for BGF MDI versus BFF MDI using the efficacy estimand
- Trough FEV_1 for BGF MDI versus GFF MDI using the efficacy estimand
- FEV_1 AUC_{0-4} for BGF MDI versus BFF MDI using the attributable estimand
- Trough FEV_1 for BGF MDI versus GFF MDI using the attributable estimand

If the comparison of FEV_1 AUC_{0-4} between BGF MDI versus BFF MDI using the attributable estimand is statistically significant, the secondary endpoints for BGF MDI versus BFF MDI will be compared simultaneously using the efficacy estimand, and using the Hochberg procedure with a 2-sided alpha of 0.05.

If the comparison of trough FEV_1 AUC_{0-4} between BGF MDI versus GFF MDI for the attributable estimand is statistically significant, the remaining secondary endpoints for BGF MDI versus GFF MDI will be simultaneously compared using the Hochberg procedure with a 2-sided alpha of 0.05.

9.5 Subgroup Analyses

Subgroup analyses for primary and secondary endpoints will be performed for the Japanese region versus the remaining regions combined as well as for Chinese and Asian subgroups. Additional subgroup analyses will be defined in the SAP as appropriate.

9.6 Safety Analyses

9.6.1 Adverse Events

The version of the Medical Dictionary for Regulatory Activities (MedDRA) that is current at the time of database lock will be used to code verbatim terms for AEs for final analysis of the data. The number and incidence of adverse events, serious adverse events, adverse events of special interest by category, confirmed AEs of pneumonia, and study drug discontinuations due to adverse events will be summarized by treatment group. They will be tabulated at the level of the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and the MedDRA system organ class. Tabulations will be broken down by severity, by relationship to study drug, and AEs leading to treatment discontinuation. No hypothesis tests will be performed.

9.6.2 Cardio- and Cerebrovascular Events Determined by Clinical Endpoint Committee

The CEC will review and adjudicate serious CCV events as MACE. MACE events are defined as the following:

- Cardiovascular death
- Non-fatal myocardial infarction (MI)

- Non-fatal stroke

The CEC will review and assess these non-fatal serious CCV events and all deaths as to whether or not they fulfill criteria (based on CEC working practices) for MACE.

MACE events will be summarized by treatment group.

9.6.3 Pneumonia Events Determined by Clinical Endpoint Committee

All AEs/SAEs with preferred terms that could relate to pneumonia will be adjudicated to provide a more complete assessment of all physician-reported pneumonias. The assessment of pneumonia events will include the overall rates of pneumonia.

In order to account for specific patient risk factors, time to first pneumonia will be compared between treatments using Cox proportional hazards. Specific patient risk factors that have will be evaluated for inclusion.

9.6.4 Clinical Laboratory Measurements

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

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

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

9.6.5 Vital Signs

Summary statistics (mean, median, standard deviation and range) for absolute values and change from baseline values will be tabulated for each treatment and assessment time. For vital signs, baseline values will be defined as the average of the values prior to dosing at the randomization visit (Visit 4). Potentially clinically significant values for vital signs will be defined in the SAP and the percentage of subjects with PCS values will be summarized. No hypothesis tests will be performed.

9.6.6 Electrocardiograms

Summary statistics (mean, median, standard deviation and range) for raw values and change from baseline values in Heart Rate, PR Interval, QRS Axis, QRS Interval, QT Interval and QTcF interval will be calculated, where baseline is defined as the average of the pre-dose measurements taken prior to the start of treatment at the randomization visit (Visit 4). The QTcF (Fridericia Corrected QT) is defined as (QT/[RR1/3]). Heart rate (bpm) is estimated as 60,000/RR. These assessments will be tabulated for each treatment and assessment time. Potentially clinically significant values for ECG parameters will be defined in the SAP, and the percentage and number of subjects with PCS ECG values will be tabulated. No hypothesis tests will be performed.

9.6.7 Exposure

The duration of exposure to study medication (in days), the person-years of exposure, the mean number of doses, and number and percentage of subjects who are compliant will be summarized by treatment group. All exposure summaries will be generated for the safety population by actual treatment received.

9.7 Pharmacokinetic Analyses

Non-compartmental parameter estimates for budesonide, glycopyrronium, and formoterol AUC_{0-12} and C_{max} will be natural-log transformed and analyzed using mixed effect models. Additional analyses will estimate bioavailability of BGF MDI relative to GFF MDI, BFF MDI, or Symbicort TBH. Separate mixed models with fixed effects for treatment, visit and treatment-by-visit interaction and a random effect for subject will be fit for each analyte.

9.8 HPA Axis

The primary analysis will performed on the log transformed ratio from baseline of the serum cortisol weighted mean (0-24 h) for subjects in the HPA Axis Population. Baseline was defined as the weighted mean 0-24 h from Day -1/1. An analysis of covariance (ANCOVA) model was fitted with baseline (log transformed), gender, age, and treatment group as terms in the model and the following comparisons will be made: BGF MDI versus GFF MDI, BGF MDI versus BFF MDI, and Symbicort TBH versus GFF MDI. The change from Screening (Visit 3) to Visit 10a (Week 24) in the 0- to 24-hour weighted mean SC at Week 24 will also be summarized by treatment group. Serum cortisol profiles over 24 hours will be graphically presented by treatment group using box plots over time, at baseline and at Week 24.

The percentage of subjects observing a 30% or greater reduction from baseline in the 0-24 hour weighted mean SC will be summarized.

9.9 Health Care Resource Utilization

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

9.10 Randomization

Subjects will be randomized in a 2:2:1:1 scheme. Approximately 600 subjects each will be randomized to the BGF MDI and GFF MDI treatment groups, and 300 subjects each will be randomized to the BFF MDI and Symbicort TBH treatment groups. Randomization will be stratified by reversibility (yes/no) to Ventolin HFA, country, and disease severity as determined by post-bronchodilator percent predicted FEV_1 (≥50%=moderate versus <50%=severe or very severe) to ensure even distribution of treatment arms within each stratum.

9.11 Experimental Design

This study is a multi-center, double-blind, parallel-group, active-controlled (open-label Symbicort TBH) design.

9.12 Sample Size

It is estimated that a sample size of 1800 subjects (600 per arm in the BGF MDI and GFF MDI groups and 300 per arm in the BFF MDI and Symbicort TBH groups) will provide the following power estimates, all assuming Type I error control at a 2-sided alpha level of 0.05 unless specified otherwise: 99% power to detect a difference of 75 mL between BGF MDI and BFF MDI in FEV_1 AUC_{0-4} over 24 weeks; 96% power to detect a difference of 35 mL between BGF MDI and GFF MDI in morning pre-dose trough FEV_1 over 24 weeks and approximately 92% power over Weeks 12 to 24; 97% power to detect a difference of 50 mL between BGF MDI and BFF MDI in morning pre-dose trough FEV_1 over Weeks 12 to 24; and 96% power to demonstrate non-inferiority of BFF MDI to Symbicort TBH in morning pre-dose trough FEV_1 over 24 weeks and approximately 92% power over Weeks 12 to 24 based on a margin of 50 mL (one-sided, alpha=0.025) assuming no true difference.

Assumptions regarding variability for the primary endpoint are based on Pearl's experience with Phase IIb and III clinical studies. A composite value standard deviation (SD) of 200 mL for the change from baseline at each visit has been assumed for trough FEV_1 and 220 mL for FEV_1 AUC_{0-4}. Dropout is anticipated to be approximately 12% by the end of the study. Based on the repeated measures analysis, an effective SD for the change over 24 weeks of 157 mL and 173 mL for trough FEV_1 and FEV_1 AUC_{0-4}, respectively, is assumed. For Weeks 12 to 24, an effective SD for trough FEV_1 of 171 mL is assumed.

9.13 Data Validation and Transformation

In general the distribution of spirometry measures is well-approximated by a normal distribution. Under some circumstances, however, (for example during a COPD exacerbation, unrelated to treatment) extreme and atypical values can arise. Such values have high influence on estimation of variance parameters and on standard errors of fixed effect estimates. The distribution and potential influence of outliers will be evaluated and additional sensitivity analyses will be conducted if warranted to demonstrate the robustness of the primary and secondary results.

9.14 Analysis Plan

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

9.15 Handling of Missing Data

All observed values will be included in the treatment policy estimand. All observed values recorded prior to treatment discontinuation will be included in the efficacy estimand. As a maximum likelihood method, RM is valid for missing-at-random (MAR) data (Little and Rubin, 2002). Additional sensitivity analyses will be performed using multiple imputations under varying assumptions about treatment effects in the unobserved data to explore the impact of missing data. Further details are provided in the SAP.

Change from baseline in morning pre-dose trough FEV_1 at each visit is defined as the average of the 60 and 30 minute pre-dose values minus baseline. In subjects missing either of these pre-dose assessments, the value will be calculated from the single measurement. In subjects missing both pre-dose values, morning pre-dose trough FEV_1 at that visit will not be calculated.

Peak FEV_1 and FEV_1 AUC_{0-4} will be included in the efficacy, attributable, treatment policy, and per-protocol estimands as long as there is at least 1 non-missing post-dose value during the first 4 hours post-dose.

For the subset of subjects included in the 12-hour spirometry assessment at Visit 10a (Week 24), the efficacy estimand will use all available data with the trapezoidal rule to calculate AUC_{0-12} (AUC_{0-6} and AUC_{6-12}) using change from baseline values. The determination of peak change from baseline in FEV_1 requires at least 1 non-missing FEV_1 value during the first 2 hours post-dose.

9.16 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 or Independent Ethics Committee 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 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 ICF, and any other information that will be presented to potential subjects (eg, advertisements or information that supports or supplements the ICF) are reviewed and approved by the appropriate IRB/IEC. The Investigator agrees to allow the IRB/IEC direct access to all relevant documents. The IRB/IEC must be constituted in accordance with all applicable regulatory requirements.

Pearl 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 (i.e., 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 SOPs to ensure that Studies 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 FDA Form 1572 or the locally accepted alternate Investigator Statement form, 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

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

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

1. **Responsibility:** Each Principal Investigator is responsible for the accuracy and completeness of all data from their site. Pearl (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.
2. **Authorship and Publication Committee:** The Sponsor, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE and the International Society for Medical Publication Professionals. It is anticipated that a publication committee will be formed to assume oversight of these activities. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
3. **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be

submitted at least 30 days prior to submission for publication or presentation to Pearl for review, approval, and to ensure consistency with the policy in this protocol. Pearl will have the right to request appropriate modification to correct facts and to represent its opinions, or the opinions of the publication committee, if these differ with the proposed publication.

4. **Confidentiality:** Investigators will conduct all interactions with Pearl and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of nonclinical studies, or chemical formulae) may still need to remain confidential.
5. **Medical Journal Review:** Consistent with the intention of Pearl to publish the study in a fair and accurate manner, Pearl supports diligence in the publication review process of medical journals. Accordingly, upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, e.g., protocol and amendments, data tabulations. The journal and reviewers will need to make arrangements to maintain the confidentiality of such supplemental information, where relevant, and Pearl will make suitable arrangements to ensure that the identity of journal reviewers is kept confidential. Records will be maintained of reviewers and the respective documents and datasets that were reviewed by each of them.
6. **Reporting of Clinical Trial Results:** To provide transparency in the conduct and reporting of randomized clinical trials, Pearl reports clinical findings based on the guidance of The CONSORT (Consolidated Standards of Reporting Trials) Statement (CONSORT, 2010) and a 25 item checklist which is intended to improve the reporting of a randomized controlled Study, and to facilitate reader understanding of the Study design, conduct, analysis and interpretation, and to support their ability to assess the validity of its results.
7. **Internet Clinical Trial Listing:** In addition, also consistent with the recommendations of the ICMJE, Pearl will make available appropriate information regarding the study via the internet. This will include registration and listing of the study on www.clinicaltrials.gov, the US National Institutes of Health listing of clinical trials, and other clinical trial listings as appropriate (e.g., EUdraCT; https://eudract.ema.europa.eu). Per AstraZeneca policy, Pearl posts clinical study protocols for public viewing when a manuscript is published in a medical journal. Prior to being made public, the protocol is reviewed by AstraZeneca Intellectual Property.

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12 APPENDICES

Appendix 1 Dose Indicator Reading

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

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

Appendix 2 Subject Instructions for Use of BGF MDI, GFF MDI, and BFF MDI

How do I store the inhaler?

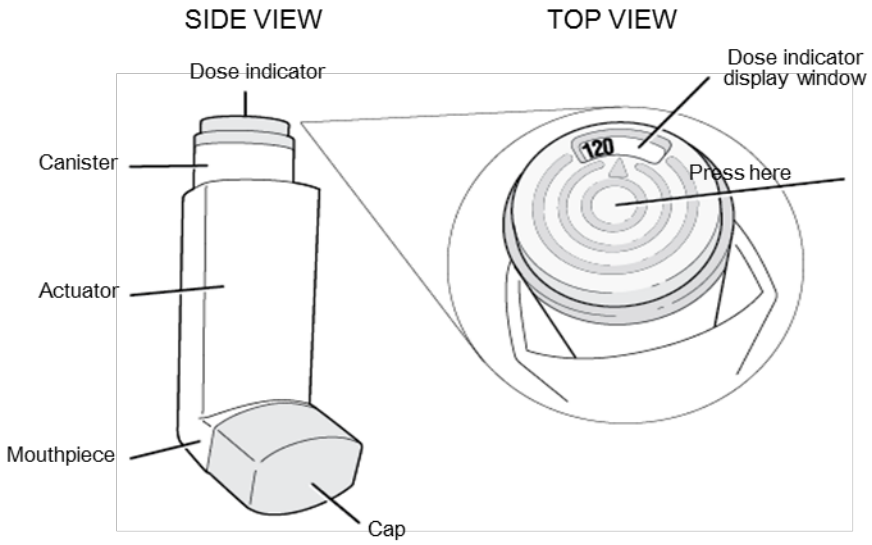
- The inhaler should be stored below 25°C (77°F) in a dry place. Excursions permitted up to 30°C (86°F).
- The contents of the canister are under pressure. Do not puncture or throw the canister into a fire or incinerator. Do not use or store it near heat or open flame. Storage above 120ºF may cause the canister to burst.
- Keep the product and all medicines out of the reach of children.

For Oral Inhalation Only

Parts of the Inhaler:

- The parts of your inhaler are seen in **Figure 1**.

Figure 1



- The **Dose indicator** lets you know about how many puffs are left in your inhaler and is the part of the inhaler that is pressed to dispense a puff of medication. **See Figure 1**.
- The **Dose indicator** should be pointing just to the right of 120 when your inhaler is new. **See Figure 1**.
- The **Dose indicator** has numbers for every 20 puffs. The **Dose indicator** display will move after every tenth puff.

- For example, if the **Dose indicator** is pointing to 120 (**see Figure 2a**) and you take 10 puffs it will move between 120 and 100. This means that there are 110 puffs of medicine left (**see Figure 2b**). After 10 more puffs are used, the **Dose indicator** pointer will move to the number 100. This means that there are 100 puffs of medicine left (**see Figure 2c**).
- The **Dose indicator** number will continue to change after every 20 puffs.
- When the number in the **Dose indicator** window changes to 20 and the color behind the number changes to red, this means that there are only 20 puffs left in your inhaler. **See Figure 2d**.

Figure 2

Figure 2a
120 puffs

Figure 2b
110 puffs

Figure 2c
100 puffs

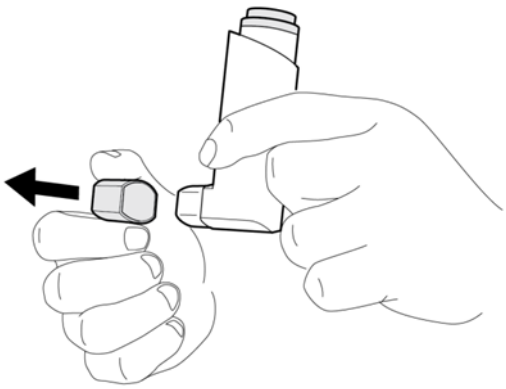
Figure 2d

Preparing the Inhaler for Use:

The inhaler comes in a foil pouch that contains a drying packet (desiccant).

- Take the inhaler out of the foil pouch.
- Throw away the pouch and the drying packet. Do not eat or inhale the contents of the drying packet.
- Remove the Cap from the Mouthpiece as shown in **Figure 3**.

Figure 3



Prime the inhaler before you use it for the first time.

Priming the Inhaler:

- Check inside the **Mouthpiece** for objects before use.
- Hold the **Actuator** with the **Mouthpiece** pointing away from you and others as shown in **Figure 4a**.
- Shake the inhaler well before each puff.
- Push down fully on the center (not 'off center') of the **Dose indicator** on top of the **Canister (see Figure 1)** until the **Canister** stops moving in the **Actuator** to release a puff from the **Mouthpiece as shown in Figure 4b**. Note: It is normal to hear a soft click from the dose indicator as it counts down during use.
- Repeat this priming step 3 more times for a total of 4 times, shaking the inhaler each time before you press it.
- After completing the 4 priming puffs, your inhaler is now primed ready to use for the first time.

You must re-prime your inhaler again if you have not used it in more than 7 days. Take the cap off the mouthpiece and shake and spray the inhaler 2 times into the air away from your face.

Figure 4

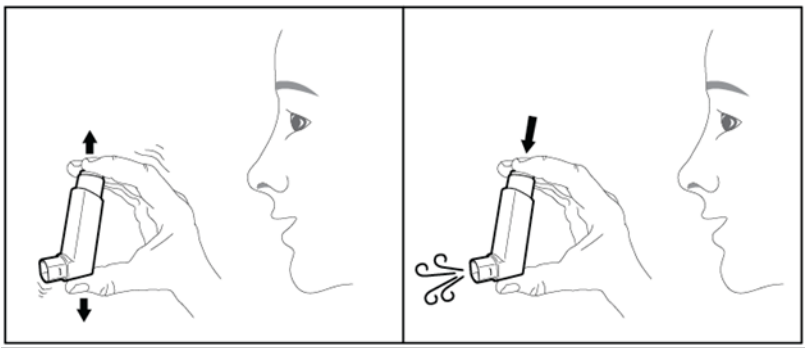


Figure 4a Figure 4b

Using the Inhaler:

Your dose of medicine comes from **2 puffs** from the inhaler.

Refer to **Figure 5** for Step 1 through Step 8.

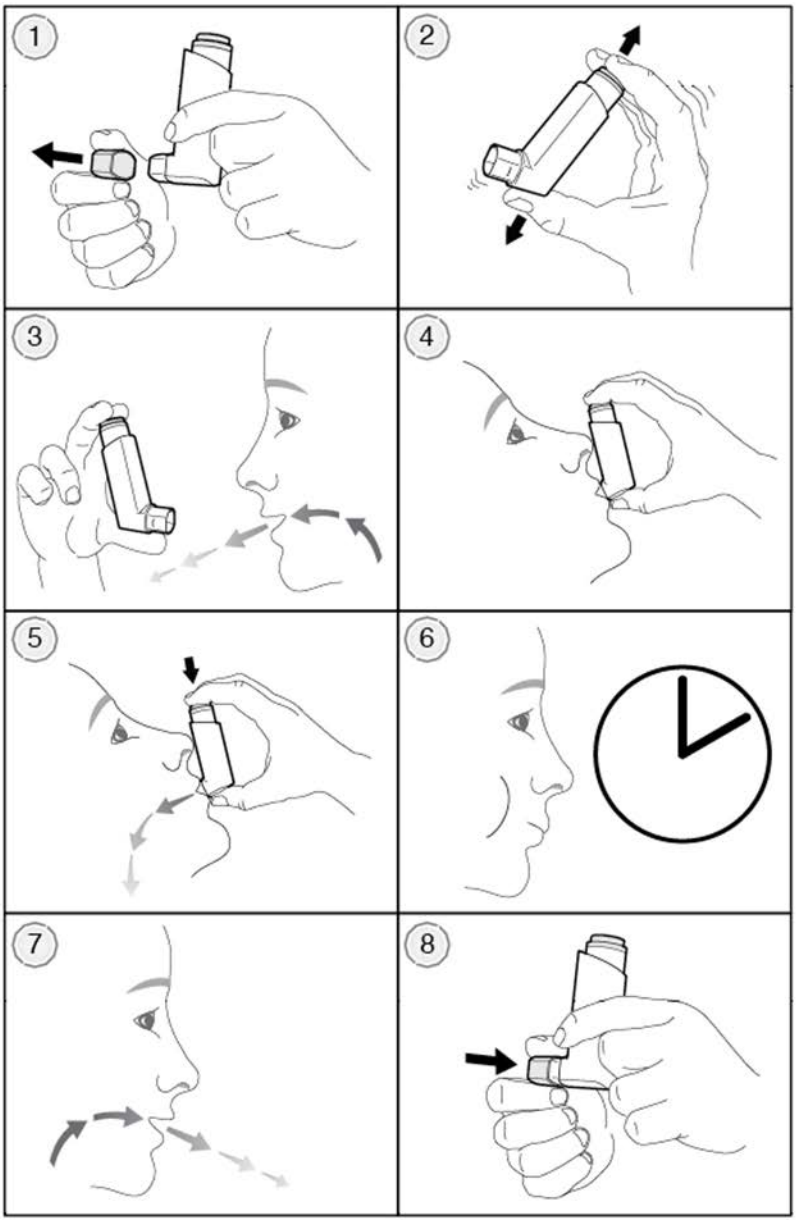
- **Step 1**: Remove the **Cap** from the **Mouthpiece**.
- **Step 2**: Shake the inhaler well before each puff.
- **Step 3**: While holding the inhaler with the **Mouthpiece** pointing towards you breathe out through your mouth to empty as much air from your lungs as possible.

- **Step 4**: Close your lips around the **Mouthpiece** and tilt your head back slightly to make sure your tongue is away from the **Mouthpiece**.
- **Step 5**: Take a deep breath in (inhale) slowly through your mouth while pressing down firmly on the center (not 'off center') of the **Dose indicator** until the **Canister** stops moving in the **Actuator** and a puff has been released. Then, stop pressing the **Dose indicator**.
- **Step 6**: When you have finished breathing in, remove the **Mouthpiece** from your mouth and hold your breath for 10 seconds or as long as comfortable.
- **Step 7**: Then, breathe out normally.

Take your second puff of medicine by repeating Step 2 through Step 7.

- **Step 8**: Replace the **Cap** back on the **Mouthpiece**.

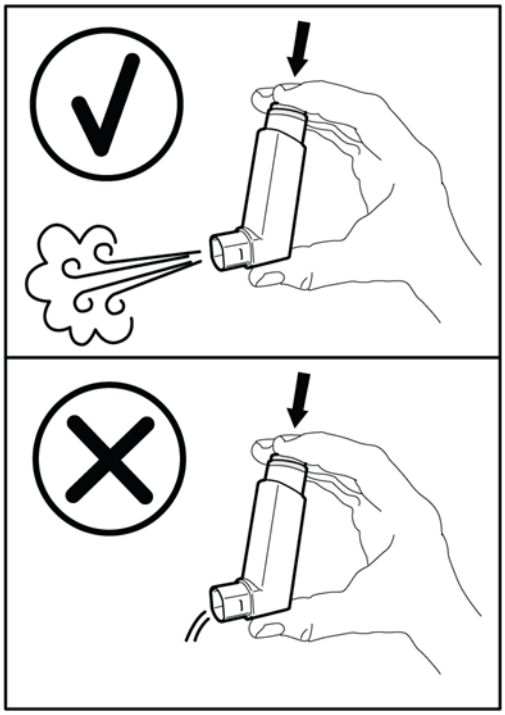
Figure 5



How to clean the Inhaler:

It is very important to keep your inhaler clean so medicine will not build-up and block the spray through the **Mouthpiece. See Figure 6**.

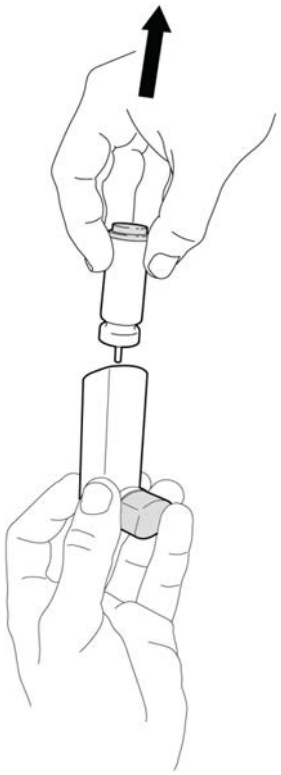
Figure 6



The **Canister** should be gently pulled from the top of the **Actuator** once a week and the **Actuator** cleaned. **Do not clean the Canister or let it get wet**.

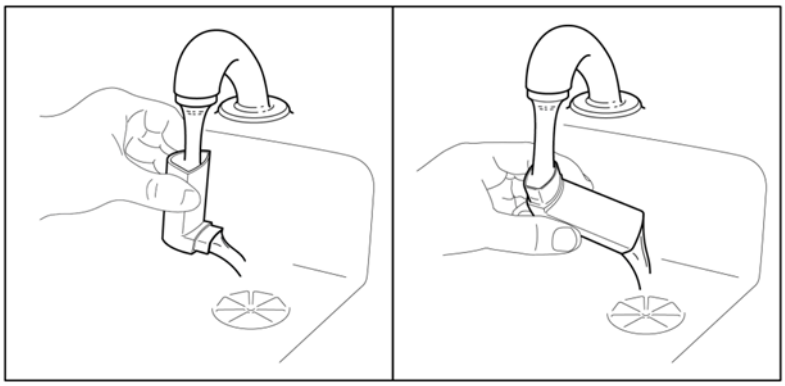
- **Step 1:** Pull the **Canister** out of the **Actuator** as shown in **Figure 7**.

Figure 7



- **Step 2**: Set the **Canister** aside where it will not get wet.
- **Step 3**: Take the **Cap** off the **Mouthpiece**.
- **Step 4**: Rinse the **Actuator** through the top with warm running water for 30 seconds. Then rinse the actuator again through the **Mouthpiece** (**see Figure 8**).

Figure 8

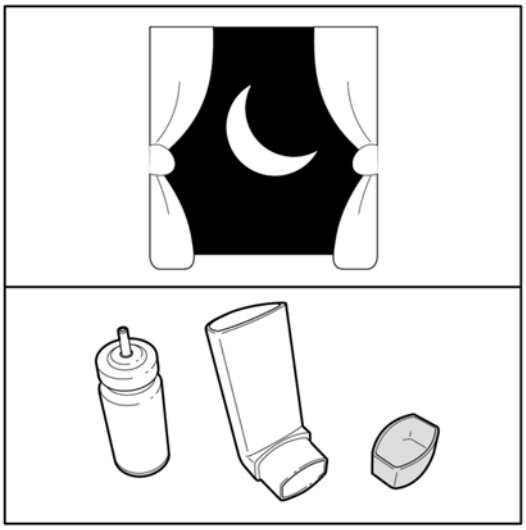


- **Step 5**: Shake all of the water droplets out of the **Actuator**.
- **Step 6**: Look in the **Actuator** and the **Mouthpiece** to make sure it is clean and clear.

Repeat **Step 4** through **Step 6**, until the **Actuator** and the **Mouthpiece** are clean and clear.

- **Step 7**: Let the **Actuator** dry completely, such as overnight as shown in **Figure 9**. **Do Not** put the **Canister** back into the **Actuator** if it is still wet.

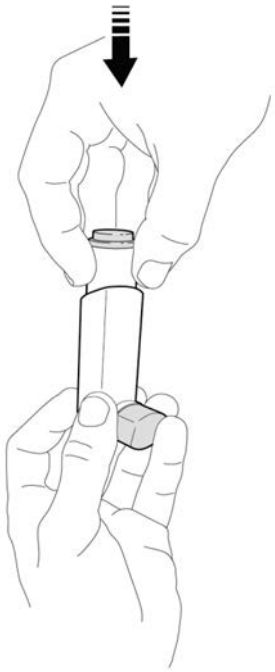
Figure 9



Reassembly of the Inhaler and Instructions for Use after Cleaning:

- After the **Actuator** is completely dry, gently press the **Canister** down in the **Actuator** as shown in **Figure 10**. It is not necessary to press down on the **Canister** hard enough to cause a puff to be released.

Figure 10



- Re-prime your inhaler 2 times after each cleaning.
- Hold the **Actuator** with the **Mouthpiece** pointing away from you and others as shown in **Figure 4**.
- Shake the inhaler well before each puff.
- Push down fully on the center (not 'off center') of the **Dose indicator** on top of the **Canister** until the **Canister** stops moving in the **Actuator** to release a puff from the **Mouthpiece**.
- Repeat this re-priming step 1 more time for a total of 2 times.
- After re-priming your inhaler 2 times, your inhaler is now ready to use.

Appendix 3 Instructions for Use of Symbicort® Turbuhaler® Inhalation Powder Device

Preparing your new Symbicort Turbohaler

Before using your **new** Symbicort Turbohaler **for the first time**, you need to prepare it for use as follows:

- Unscrew the cover and lift it off. You may hear a rattling sound.
- Hold your Turbohaler upright with the red grip at the bottom.
- Turn the red grip as far as it will go in one direction. Then turn it as far as it will go in the other direction (it does not matter which way you turn it first). You should hear a click sound.

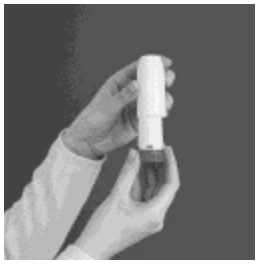
- Do this again, turning the red grip in both directions.
- Your Turbohaler is now ready for use.

How to take an inhalation

Every time you need to take an inhalation, follow the instructions below.

1. Unscrew the cover and lift it off. You may hear a rattling sound.
2. Hold your Turbohaler upright with the red grip at the bottom.
3. Do not hold the mouthpiece when you load your Turbohaler. To load your Turbohaler with a dose, turn the red grip as far as it will go in one direction. Then turn it as far as it will go in the other direction (it does not matter which way you turn it first). You should hear a click sound. Your Turbohaler is now loaded and ready to use. Only load your Turbohaler when you need to use it.
4. Hold your Turbohaler away from your mouth. Breathe out gently (as far as is comfortable). Do not breathe out through your Turbohaler.
5. Place the mouthpiece gently between your teeth. Close your lips. Breathe in as deeply and as hard as you can through your mouth. Do not chew or bite on the mouthpiece.

6. Remove your Turbohaler from your mouth. Then breathe out gently.
   The amount of medicine that is inhaled is very small. This means you may not be able to taste it after inhalation. If you have followed the instructions, you can still be confident that you have inhaled the dose and the medicine is now in your lungs.



7. If you are to take a second inhalation, repeat steps 2 to 6.
8. Replace the cover tightly after use.
9. Rinse your mouth with water after your daily morning and/or evening doses, and spit it out.

Do not try to remove or twist the mouthpiece. It is fixed to your Turbohaler and must not be taken off. Do not use your Turbohaler if it has been damaged or if the mouthpiece has come apart from your Turbohaler.

Cleaning your Turbohaler

Wipe the outside of the mouthpiece once a week with a dry tissue. Do not use water or liquids.

How to store Symbicort Turbohaler

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date that is stated on the carton or on the label of your inhaler after EXP. The expiry date refers to the last day of that month.
- Do not store above 30°C.
- Keep the container/cap tightly closed, in order to protect from moisture.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Appendix 4 Instructions for Use of Atrovent® HFA Inhalation Aerosol Device

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 2**), between your thumb and first 2 fingers. Put the mouthpiece in your mouth and close your lips.
   - Keep your eyes closed so that no medicine will be s prayed 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 1

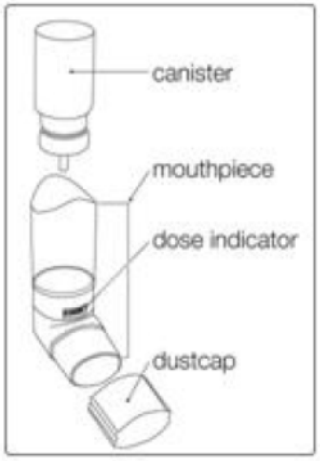
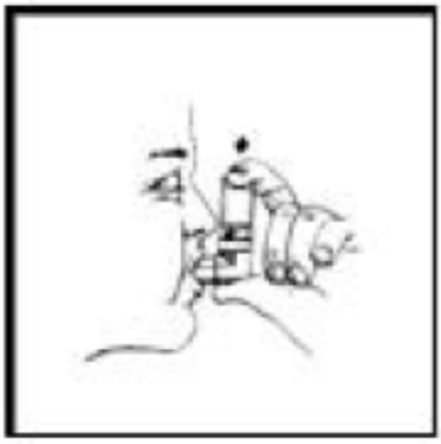


Figure 2

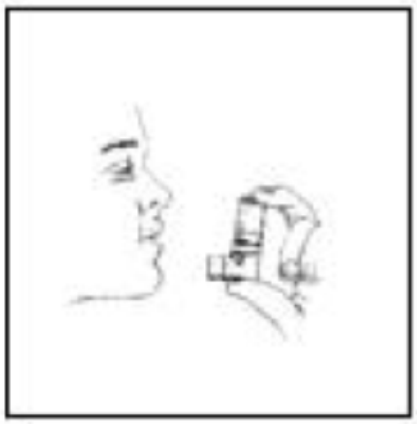
4. Breathe in (inhale) slowly through your mouth and at the same time spray the ATROVENT HFA into your mouth.
   - To spray ATROVENT HFA firmly press the canister against the mouthpiece 1 time (**See Figure 3**). Keep breathing in deeply.

Figure 3



5. Hold your breath for ten seconds and then take the mouthpiece out of your mouth and breathe out slowly (**See Figure 4**).

Figure 4



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 5**). Do not use anything other than water to wash the mouthpiece.

Figure 5

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

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

Step E. Replace the green protective dust cap.

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

This product does not contain any chlorofluorocarbon (CFC) propellants.

The contents of ATROVENT HFA are under pressure. Do not puncture the canister. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw the container into a fire or incinerator. Keep ATROVENT HFA and all medicines out of the reach of children.

Store ATROVENT HFA at Room Temperature [77°F (25°C)]. Short-term exposure to higher or lower temperatures [from 59°F (15°C) to 86°F (30°C)] is acceptable.

Appendix 5 Instructions for Use of Ventolin HFA Inhalation Aerosol Device

Instructions for Use
For Oral Inhalation Only
Your VENTOLIN HFA inhaler

- The metal canister holds the medicine. See **Figure A**.

Figure A

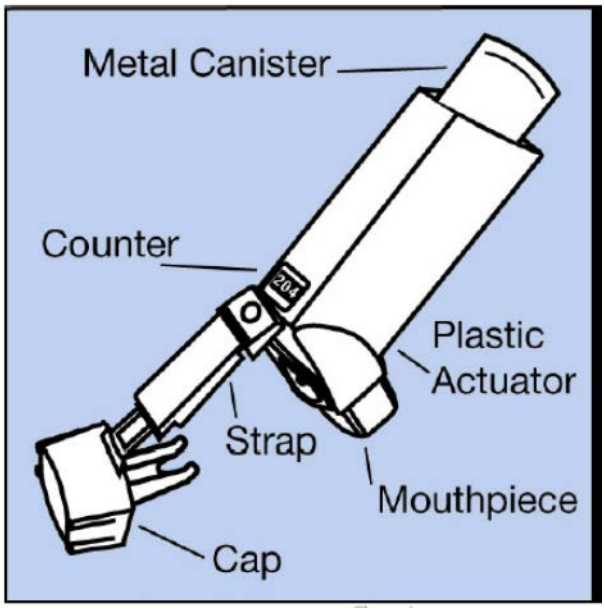


Figure A

The canister has a counter to show how many sprays of medicine you have left. The number shows through a window in the back of the actuator. See **Figure B**.

Figure B

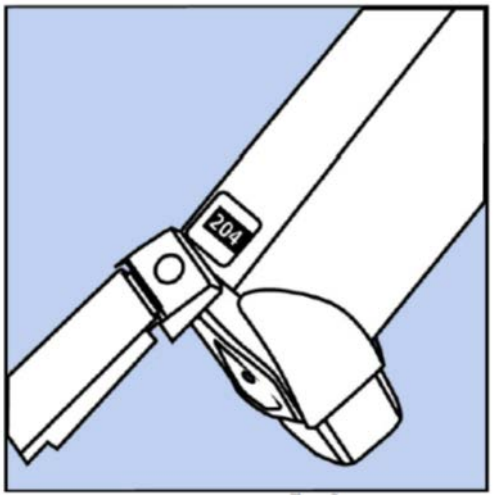


Figure B

- The counter starts at either **204 or 064**, depending on which size inhaler you have. The number will count down by 1 each time you spray the inhaler. The counter will stop counting at **000**.
- Do not try to change the numbers or take the counter off the metal canister. The counter cannot be reset, and it is permanently attached to the canister.
- The blue plastic actuator sprays the medicine from the canister. The actuator has a protective cap that covers the mouthpiece. See **Figure A**. Keep the protective cap on the mouthpiece when the canister is not in use. The strap keeps the cap attached to the actuator.
- **Do not** use the actuator with a canister of medicine from any other inhaler.
- **Do not** use a VENTOLIN HFA canister with an actuator from any other inhaler.

Before using your VENTOLIN HFA inhaler

Before you use VENTOLIN HFA for the first time, you must prime the inhaler so that you will get the right amount of medicine when you use it.

To prime the inhaler, take the cap off the mouthpiece and shake the inhaler well. Then spray the inhaler 1 time into the air away from your face. **See Figure C. Avoid spraying in eyes.**

Figure C

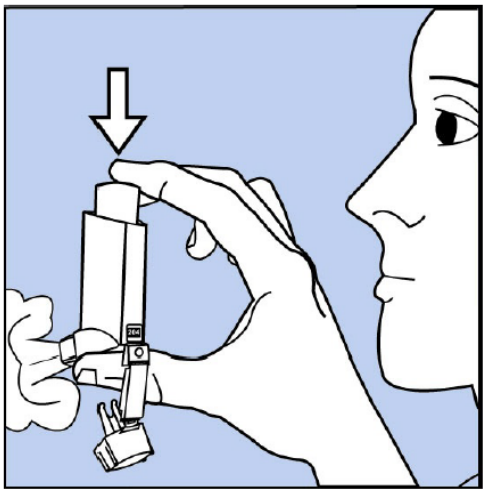


Figure C

- Shake and spray the inhaler like this 3 more times to finish priming it. The counter should now read **200 or 060**, depending on which size inhaler you have. **See Figure D**.

Figure D

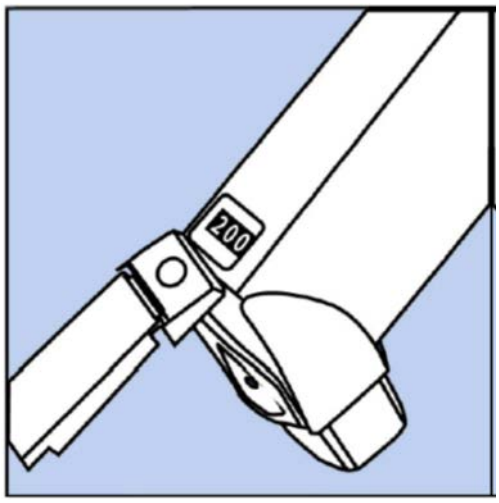


Figure D

You must prime your inhaler again if you have not used it in more than 14 days or if you drop it. Take the cap off the mouthpiece and shake and spray the inhaler 4 times into the air away from your face.

How to use your VENTOLIN HFA inhaler

Follow these steps every time you use VENTOLIN HFA.

Step 1. Make sure the canister fits firmly in the actuator. The counter should show through the window in the actuator.

Shake the inhaler well before each spray.

Take the cap off the mouthpiece of the actuator. Look inside the mouthpiece for foreign objects, and take out any you see.

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

Figure E

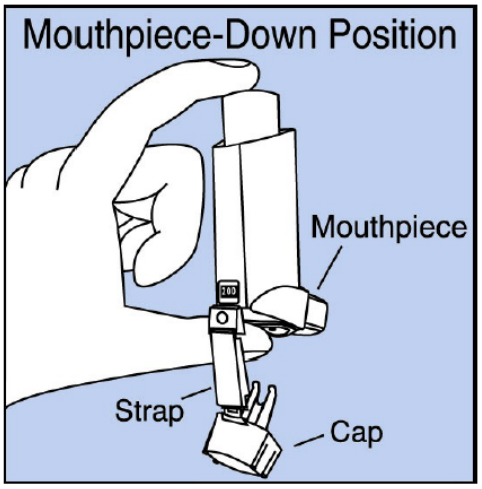


Figure E

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**.

Figure F

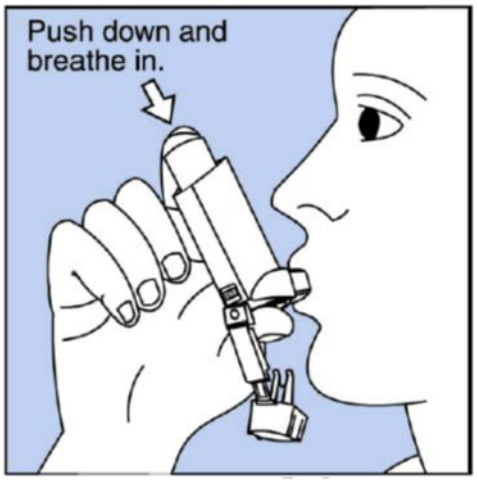


Figure F

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. 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 for about 10 seconds, or for as long as is comfortable. **Breathe out slowly as long as you can.**

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 it snaps firmly into place.

Cleaning your VENTOLIN HFA inhaler

Clean your inhaler at least 1 time each week. You may not see any medicine build-up on the inhaler, but it is important to keep it clean so medicine build-up will not block the spray. **See Figure G.**

Figure G

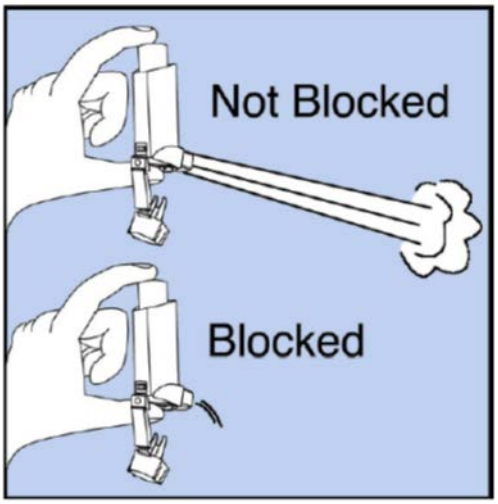


Figure G

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 H

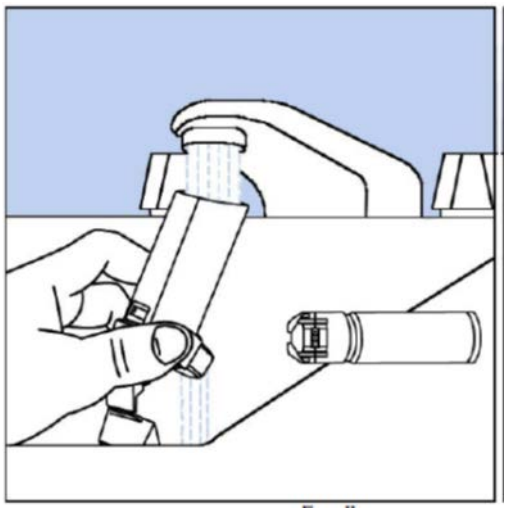


Figure H

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

Figure I

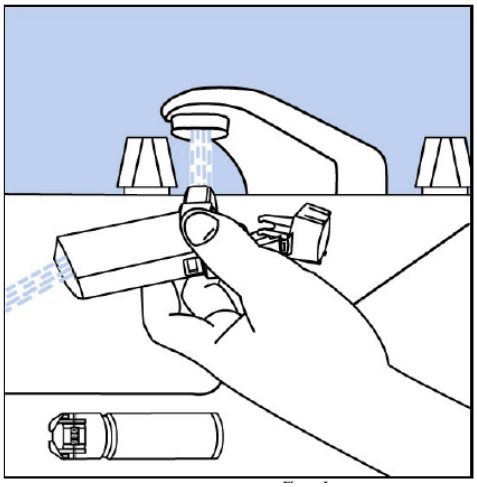


Figure I

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.

Step 12. Let the actuator air-dry overnight. **See Figure J**.

Figure J

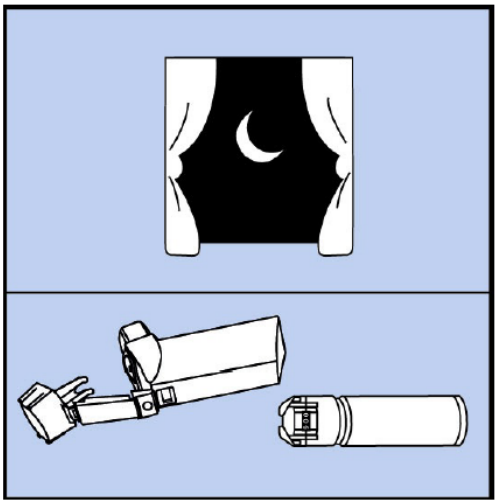


Figure J

Step 13. When the actuator is dry, put the protective cap on the mouthpiece and then put the canister in the actuator and make sure it fits firmly. Shake the inhaler well, remove the cap,

and spray the inhaler 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 cap on the mouthpiece and then put the canister in the actuator and make sure it fits firmly.
- Shake the inhaler well and spray it 1 time into the air away from your face.
- Take your VENTOLIN HFA dose as prescribed.
- Follow cleaning Steps 8 through 13 above.

Appendix 6 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.

FEV_1 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 +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 cmH_2O L-1s-1 (0.15 kPa L-1s-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 8 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 Studys, 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 >10 mm L^{-1} (BTPS). For a screen display, 5 mm L^{-1} is satisfactory (Table A1-1).

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

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

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

The time scale should be >20 mm-s^{-1}, and larger time scales are preferred (>30 mm-s^{-1}) when manual measurements are made. When the volume–time plot is used in conjunction with a flow–volume curve (i.e., both display methods are provided for interpretations and no hand measurements are performed), the time scale requirement is reduced to 10 mm-s^{-1} from the usually required minimum of 20 mm-s^{-1} (Table A1-1). The rationale for this exception is that the flow–volume curve can provide the means for quality assessment during the initial portion of the FVC maneuver. The volume–time curve can be used to evaluate the latter part of the FVC maneuver, making the time scale less critical.

Validation

It is strongly recommended that spirometry systems should be evaluated using a computer-driven mechanical syringe or its equivalent, in order to test the range of exhalations that are likely to be encountered in the test population. Testing the performance of equipment is not part of the usual laboratory procedures.

Quality Control

Attention to equipment quality control and calibration is an important part of Good Laboratory Practice. At a minimum, the requirements are as follows: 1) a log of calibration results is maintained; 2) the documentation of repairs or other alterations which return the equipment to acceptable operation; 3) the dates of computer software and hardware updates or changes; and 4) if equipment is changed or relocated (eg., industrial surveys), calibration checks and quality-control procedures must be repeated before further testing begins.

Key aspects of equipment quality control are summarized in Table A1-2.

Table A1-2. Summary of Equipment Quality Control

Test	Minimal Interval	Action
Volume	Daily	Calibration check with a 3 L syringe
Leak	Daily	2 cm H_2O (0.3 kPa) constant pressure for 1 minute
Volume Linearity	Quarterly	1 L increments with a calibrating syringe measured over the entire volume range
Flow Linearity	Weekly	Test at least 3 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., +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 +0.5% of the full scale (15 mL for a 3-L syringe), and the manufacturer must provide recommendations concerning appropriate intervals between syringe calibration checks. Users should be aware that a syringe with an adjustable or variable stop may be out of calibration if the stop is reset or accidentally moved. Calibration syringes should be periodically (eg, monthly) leak tested at more than one volume up to their maximum; this can be done by attempting to empty them with the outlet corked. A dropped or damaged syringe should be considered out of calibration until it is checked.

With regard to time, assessing mechanical recorder time scale accuracy with a stopwatch must be performed at least quarterly. An accuracy of within 2% must be achieved.

Quality Control for Volume-Measuring Devices

The volume accuracy of the spirometer must be checked at least daily, with a single discharge of a 3-L calibrated syringe. Daily calibration checking is highly recommended so that the onset of a problem can be determined within 1 day, and also to help define day-to-day laboratory variability. More frequent checks may be required in special circumstances, such as: 1) during industrial surveys or other studies in which a large number of subject maneuvers are carried out, the equipment's calibration should be checked more frequently than daily; and 2) when the ambient temperature is changing (eg, field studies), volume accuracy must be checked more frequently than daily and the BTPS correction factor appropriately updated.

The accuracy of the syringe volume must be considered in determining whether the measured volume is within acceptable limits. For example, if the syringe has an accuracy of 0.5%, a reading of +3.5% is appropriate.

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

Volume-type spirometer systems must be evaluated for leaks every day. The importance of undertaking this daily test cannot be overstressed. Leaks can be detected by applying a constant positive pressure of >3.0 cmH_2O (0.3 kPa) with the spirometer outlet occluded (preferably at or including the mouthpiece). Any observed volume loss of 30 mL after 1 minute indicates a leak and needs to be corrected.

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

Quality Control for Flow-Measuring Devices

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

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

VC Maneuvers

Equipment

For measurements of VC, the spirometer or flow meter must comply with the requirements for FVC (as described previously) and be capable of accumulating volume for >30 s. Expiratory maneuvers 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 A1-3, but must meet the recommendations for those that are measured. Accuracy and repeatability recommendations apply over the entire volume range of the instrument.

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

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

FEVt: forced expiratory volume in t seconds

BTPS correction

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

Appendix 7 Spirometry Assessment Criteria

Acceptable Versus Usable Tests

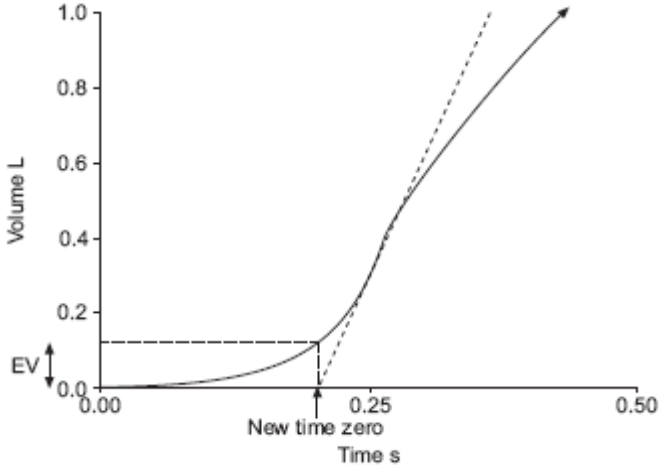
***Acceptable* Tests must meet the following 7 Criteria:**

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, i.e., the volume-time curve shows no change in volume (<0.025 L) for ≥1 second, 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 Studys with observed limitations.

Figure A2-1. Example of a Usable Spirogram



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

Between-Maneuver Reproducibility Criteria

After 3 acceptable spirograms have been obtained, apply the following tests

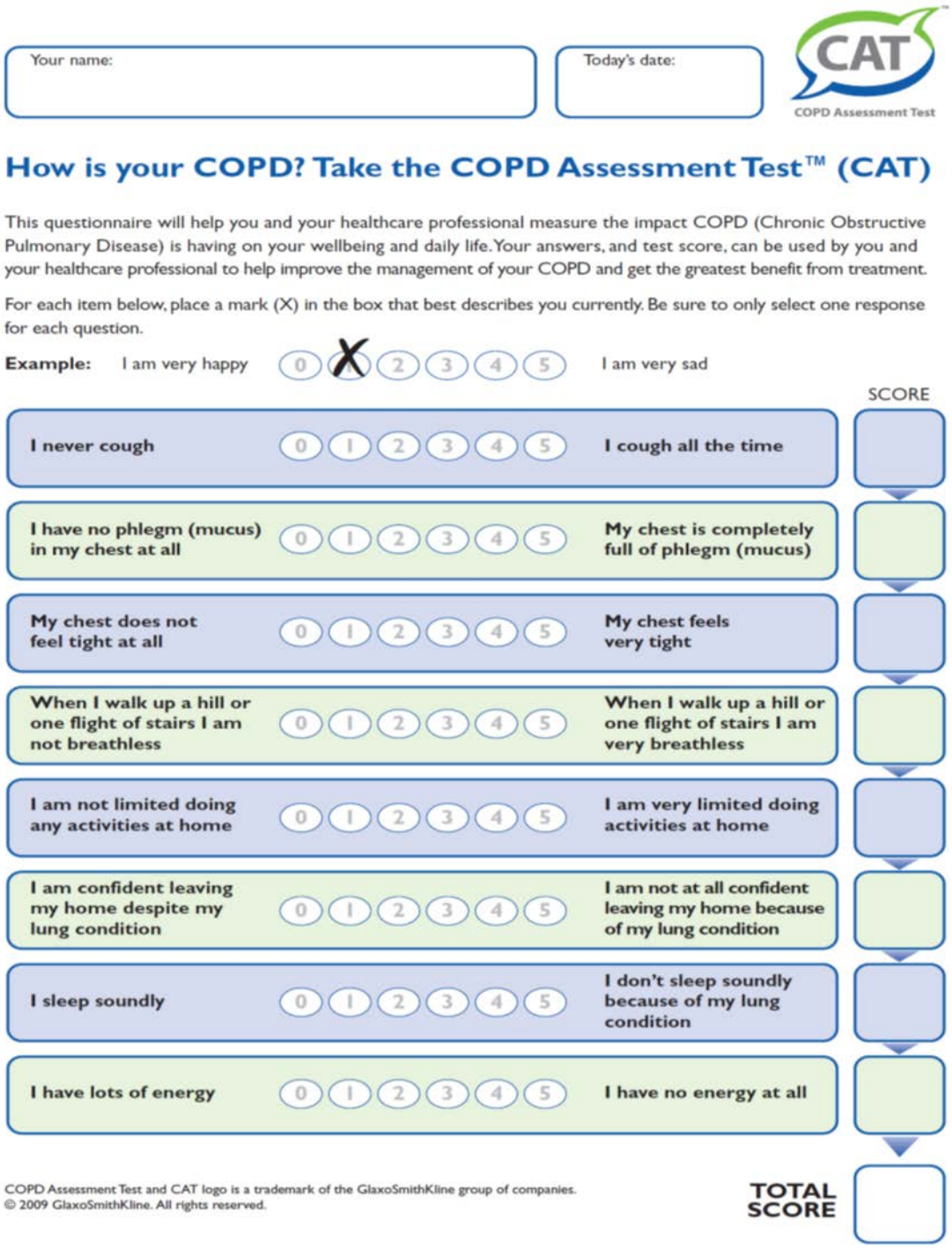
- The 2 largest values of FVC must be within 0.150 L of each other
- The 2 largest values of FEV_1 must be within 0.150 L of each other

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

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

Appendix 8 Chronic Obstructive Pulmonary Disease Assessment Test

(The sample provided here is for illustrative purposes only)



Your name:

Today's date:

CAT
COPD Assessment Test

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

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

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

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

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

TOTAL SCORE

Appendix 9 Baseline Dyspnea Index/Transition Dyspnea Index Questionnaire

(The sample provided here is for illustrative purposes only)

Baseline/Transition Dyspnea Index (BDI/TDI)

BASELINE DYSPNEA INDEX

Baseline Functional Impairment

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

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

Baseline Magnitude of Task

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

Baseline Magnitude of Effort

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

TRANSITION DYSPNEA INDEX

Change in Functional Impairment

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

Change in Magnitude of Task

_____-3	*Major Deterioration*	Has deteriorated two grades or greater from baseline status.
_____-2	*Moderate Deterioration*	Has deteriorated at least one grade but fewer than two grades from baseline status.
_____-1	*Minor Deterioration*	Has deteriorated less than one grade from baseline. Subject with distinct deterioration within grade, but has not changed grades.
_____0	*No Change*	No change from baseline.
_____+1	*Minor Improvement*	Has improved less than one grade from baseline. Subject with distinct improvement within grade, but has not changed grades.
_____+2	*Moderate Improvement*	Has improved at least one grade but fewer than two grades from baseline.
_____+3	*Major Improvement*	Has improved two grades or greater from baseline.
_____Z	*Further Impairment for Reasons Other than Shortness of Breath*	Subject has reduced exertion capacity, **but** not related to shortness of breath. For example, musculoskeletal problem or chest pain.

Change in Magnitude of Effort

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

Appendix 10 St. George Respiratory Questionnaire

(The sample provided here is for illustrative purposes only)

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

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

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

Before completing the rest of the questionnaire:

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

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

[redacted]

[redacted]

St. George's Respiratory Questionnaire
PART 1

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

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

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

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

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

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

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

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

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

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

USA / US English version 2

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St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your respiratory condition?

	Please check (✓) *one*:
The most important problem I have	☐
Causes me quite a lot of problems	☐
Causes me a few problems	☐
Causes no problems	☐

If you have ever held a job:

	Please check (✓) *one*:
My respiratory problems made me stop working altogether	☐
My respiratory problems interfere with my job or made me change my job	☐
My respiratory problems do not affect my job	☐

Section 2

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

	For each statement please check (✓) ***the box*** that applies to you ***these days***: True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

USA / US English version 3

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St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath these days.

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

Section 4

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

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

Section 5

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

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

USA / US English version 4

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St. George's Respiratory Questionnaire
PART 2

Section 6

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

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

Section 7

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

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

USA / US English version 5

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St. George's Respiratory Questionnaire

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

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

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

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

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

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

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

USA / US English version 6

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Appendix 11 European Quality of Life 5 Dimensions-5 Level Questionnaire (EQ-5D-5L)

(The sample provided here is for illustrative purposes only)

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

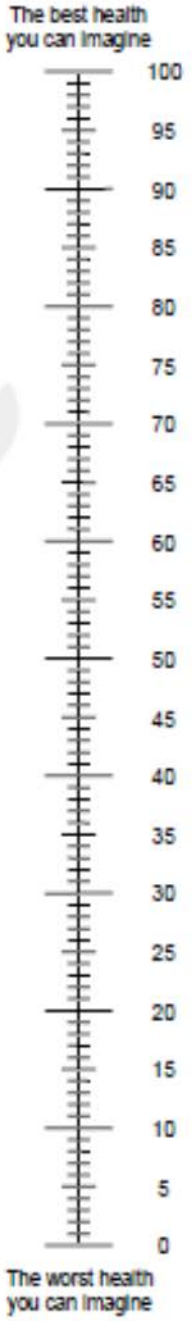
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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Appendix 12 EXACT

(The sample provided here is for illustrative purposes only)

EXACT version 1.1-English (Universal)

Please note that on 7 March 2016, the EXACT-Respiratory Symptoms Scale was renamed the Evaluating Respiratory Symptoms (E-RS) measure.

Description	Required Text	Translation
Title	EXACT Daily Diary	EXACT Daily Diary
DD	Daily Diary	Daily Diary
Q 1 of 14	Question 1 {1} of 14	Question 1 {1} of 14
Instructions	As you answer the following questions, please select the option that best describes your experience.	As you answer the following questions, please select the option that best describes your experience.
1		
	Did your chest feel congested today?	Did your chest feel congested today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
2		
	How often did you cough today?	How often did you cough today?
	Not at all	Not at all
	Rarely	Rarely
	Occasionally	Occasionally
	Frequently	Frequently
	Almost constantly	Almost constantly
3		
	How much mucus (phlegm) did you bring up when coughing today?	How much mucus (phlegm) did you bring up when coughing today?
	None at all	None at all
	A little	A little
	Some	Some
	A great deal	A great deal
	A very great deal	A very great deal
4		
	How difficult was it to bring up mucus (phlegm) today?	How difficult was it to bring up mucus (phlegm) today?

Description	Required Text	Translation
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Quite a bit	Quite a bit
	Extremely	Extremely
5		
	Did you have chest discomfort today?	Did you have chest discomfort today?
	Not at all	Not at all
	Slight	Slight
	Moderate	Moderate
	Severe	Severe
	Extreme	Extreme
6		
	Did your chest feel tight today?	Did your chest feel tight today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
7		
	Were you breathless today?	Were you breathless today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
8		
	Describe how breathless you were today:	Describe how breathless you were today:
	Unaware of breathlessness	Unaware of breathlessness
	Breathless during strenuous activity	Breathless during strenuous activity
	Breathless during light activity	Breathless during light activity
	Breathless when washing or dressing	Breathless when washing or dressing
	Present when resting	Present when resting
9		
	Were you short of breath today when performing your usual personal care activities like washing or dressing?	Were you short of breath today when performing your usual personal care activities like washing or dressing?
	Not at all	Not at all

Description	Required Text	Translation
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these
10		
	Were you short of breath today when performing your usual indoor activities like cleaning or household work?	Were you short of breath today when performing your usual indoor activities like cleaning or household work?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these
11		
	Were you short of breath today when performing your usual activities outside the home such as yard work or errands?	Were you short of breath today when performing your usual activities outside the home such as yard work or errands?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these
12		
	Were you tired or weak today?	Were you tired or weak today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
13		
	Last night, was your sleep disturbed?	Last night, was your sleep disturbed?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely

Description	Required Text	Translation
	Extremely	Extremely
14		
	How scared or worried were you about your lung problems today?	How scared or worried were you about your lung problems today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
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Training Material	Recommended Text	Translation (if available)
Standardized instruction given to patients with PDA training and with take-home instruction manual	Please complete your diary every evening, just before you go to bed.	Please complete your diary every evening, just before you go to bed.

Appendix 13 Rules for Evaluation of Abnormal Liver Laboratory Values

INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Pearl clinical representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug-Induced Liver Injury (DILI) caused by study drug.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

- Potential Hy's Law

The levels of AST or ALT ≥3x ULN and TBL ≥2x ULN at any point during the study irrespective of an increase in ALP. The elevations do not have to occur at the same time or within a specified time frame.

- Hy's Law

The levels of AST or ALT ≥3x ULN and TBL ≥2x ULN, where no other reason, other than the study drug, can be found to explain the combination of increases, eg., elevated ALP indicating cholestasis, viral hepatitis, or another drug. The elevations do not have to occur at the same time or within a specified time frame.

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3x ULN
- AST ≥3x ULN
- TBL ≥2x ULN

When a subject meets any of the identification criteria in combination, the central laboratory will immediately send an alert to the Investigator and Pearl representative.

The Investigator will also remain vigilant for any laboratory reports where the identification criteria are met, the Investigator will:

- Request a repeat of the test (new blood draw) by the central laboratory.

When the identification criteria are met from central laboratory results the Investigator will without delay:

- Determine whether the subject meets PHL criteria by reviewing all laboratory reports including previous visits.
- Notify the Pearl representative.
- Promptly enter the laboratory data into the laboratory CRF.

FOLLOW-UP

Potential Hy's Law Criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Inform the Pearl representative that the subject has not met PHL criteria.
- Perform follow up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

- Notify the Pearl representative who will then inform the central Study Team.

The Medical Monitor contacts the Investigator, to provide guidance, discuss, and agree on method of follow up and the continuous review of data. Subsequent to this contact, the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Pearl Medical Monitor.
- If at any time (in consultation with the Pearl Medical Monitor) the PHL case meets serious criteria, report the event as an SAE using standard reporting procedures.

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 2 weeks after the biochemistry abnormality was initially detected, the Pearl Medical Monitor contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused

by the study drug. The Pearl Medical Monitor and other subject matter experts (as appropriate) will collaborate in the review and assessment of these cases.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the standard reporting procedures.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the study drug:

- Report as an SAE (report term "Hy's Law case") according to Pearl standard processes.
- The "Medically Important" serious criterion should be used if no other serious criteria apply.
- As there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

If, there is an unavoidable delay of over 2 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation. Until an informed decision can be made, the following procedure should be followed:

- Report as an SAE (report term "Potential Hy's Law") applying serious criteria and causality assessment as per above.

Continue follow up and review according to the agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE Report Form according to the outcome of the review.

Appendix 14 Sponsor Signatures

Study Title: A Randomized, Double-Blind, Parallel-Group, 24-Week, Chronic-Dosing, Multi-Center Study to Assess the Efficacy and Safety of PT010, PT003, PT009 Compared With Symbicort® Turbuhaler® as an Active Control in Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease

Study Number: PT010006-02

Final Date: 25 Aug 2017

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: [redacted]

Appendix 15 Investigator's Signature

Study Title: A Randomized, Double-Blind, Parallel-Group, 24-Week, Chronic-Dosing, Multi-Center Study to Assess the Efficacy and Safety of PT010, PT003, PT009 Compared With Symbicort® Turbuhaler® as an Active Control in Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease

Study Number: PT010006-02

Final Date: 25 Aug 2017

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with the protocol and with any other study conduct procedures provided by Pearl Therapeutics, Inc. (hereafter referred to as Pearl).
- Not to implement any changes to the protocol without agreement from Pearl and prior review and written approval from the Institutional Review Board/Independent Ethics Committee, 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 and all applicable regulatory requirements.
- That I am thoroughly familiar with the appropriate use of the investigational product(s), and other information provided by Pearl including, but not limited to, the following: the protocol and the current Investigators Brochure (IB).
- To ensure that all persons assisting me with the study are qualified, adequately informed about the investigational product(s) and of their study-related duties and functions.
- To supply Pearl 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 electronic case report forms (eCRFs). The eCRFs will be provided to Pearl in a timely manner at the completion of the study, or as otherwise specified by Pearl.
- 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: _____

Site Name: _____