Clinical Trial Protocol: PT010007-01

Study Title:	A Randomized, Double-Blind, Parallel-Group, 28-Week, Chronic-Dosing, Multi-Center, Extension Study to Assess the Safety and Efficacy of PT010, PT003, and PT009 in Japanese Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) compared with Symbicort® Turbuhaler® as an Active Control
Study Number:	PT010007-01
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
Indication:	COPD
Investigators:	Multi-center
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]

	Version Number	Date
Original Protocol:	Version 1.0	05 July 2015
Amended Protocol:	Version 2.0	17 March 2017

SUMMARY OF CHANGES TO ORIGINAL PROTOCOL VERSION 1.0, DATED 05 JULY 2015

The amended study protocol, PT010007-01(Version 2.0), includes the following edits:

Location(s) and Description of Change	Rationale
Global Administrative changes to correct and/or clarify protocol language	Administrative changes include edits for: • Consistency • Grammar • Typographical errors
Changed Sponsor Contact on Title and Sponsor Signature Page	Revised to reflect named Clinical Program Head
Synopsis and Section 9.5.1.1 Statistical Methods-Efficacy Analysis Added baseline eosinophil count as continuous covariate.	Baseline eosinophil count is included as a continuous covariate as higher blood eosinophils may be predictive of the response to ICS.
Synopsis and Sections 7.3.6.3, 7.3.7, 7.3.15, 9.4.2, and 9.4.3	Clarified that there is a single Clinical Endpoint Committee with charters evaluating cardiovascular and cerebrovascular events, cause-specific mortality, and pneumonia.
Section 4.1 Overall Study Design and Plan, Figure-1	Corrected study schematic to reflect Visit 10a as the last visit of PT010006, added a note to clarify that Visit 10a and 10b occur on the same day, and indicated the 14-day follow-up applies for all study treatment arms.
Section 5.4.1 Allowed Medications to Treat a COPD Exacerbation Additional details to clarify treatment of COPD exacerbations.	Added details to clarify treatment of COPD exacerbations during the treatment period including guidance for treatment as deemed appropriate by the health care provider. This change also provides the guidance that subjects should be returned to their pre-exacerbation regimen as soon as practical.

Section 5.4.2 Prohibited COPD Medications, Table 5-1 Moved Roflumilast from footnote "b" to a Note and added "(or any PDE4 inhibitor)"	Revised to include the PDE4 medication class, use of other medications, and clarified use of theophylline if subjects received in Study PT010006.
Section 5.4.3 Other Prohibited Medications, Table 5-3, and footnote "a" Revision clarifies that if a subject is required to use any of the prohibited medications listed in Table 5-4, the subject should be discontinued from randomized treatment but continued in the study. Added exception for Carvedilol to treat subjects who may have Class I/II failure where use of this medication is appropriate. Clarified use of anticonvulsants for seizure disorders and allowed anticonvulsants for other indications. Antipsychotic agents and tricyclic antidepressants are allowed if, in the opinion of Investigator, there are no safety concerns and if the patient was on a stable dose during PT010006. Allowed systemic anticholinergic if used in Study PT010006 and dose remains unchanged.	This section is revised to align with criteria used in prior and ongoing studies in subjects with COPD in the Pearl COPD development program. This will maintain consistency across studies and avoid confusion for investigators participating in more than 1 Pearl COPD study.
Sections 4.1 and 5.5.2 Dietary Restrictions Added caffeine containing medications to list.	Added to have a more comprehensive list of caffeine sources.

Section5.5 Other Restrictions, ~~Illicit~~ Dangerous Drugs and Section 5.5.1 ~~Illicit~~ Dangerous Drugs Replaced the term 'Illicit' with 'dangerous' in these sections.	Clarification change based on local preference of terminology.
Section 5.6 Smoking Status: Deleted medical marijuana.	Correction
Section 5.7 Reasons for Treatment Discontinuation or Study Withdrawal Revised this section to define reasons for study treatment discontinuation that are required by the protocol versus Investigator discretion and emphasize that treatment discontinuation does not also mean study withdrawal.	Revised to discontinue treatment consistently across sites based on defined safety parameters, and to emphasize continued study participation after treatment discontinuation.
Section 7.1.1 Pulmonary Function Tests Deleted single spirometry assessment at Visit 14.	Revised to indicate 2 pre-dose spirometry assessments prior to return to appropriate COPD medication in order to align with other visits in PT010007.
Section 7.3.1 Performing Adverse Events Assessment Added language specifying email and fax for paper SAE form.	Contingency wording added in case of an unanticipated situation, such as electronic data capture system failure.
Sections 7.3.9.1 thru 7.3.9.5 Added "Head of the Medical Institution"	Addition of the Head of the Medical Institution as a recipient of SAE notifications and associated safety reporting.
Section 7.3.9.6 Health Authority Safety Reports Added Pharmaceuticals and Medical Devices Agency (PMDA)	Clarified safety reporting by adding PMDA.
Section 7.3.11 Pregnancy Added Email addresses and fax number for reporting using the Paper Pregnancy Report	Clarification by providing email addresses and fax number in protocol.

Form.	
Section 7.2.4.2 Clinical Chemistry, Table 7-1: Corrected timing of serum and urine hCG tests	Correction
New Section 7.3.12 Paternal Exposure	Added for consistent evaluation across the PT010 studies.
New Section 7.3.13 and Appendix 7 -Hy's Law	Added Hy's Law for continued assessment of liver safety from Study PT010006.
Section 8, Table 8-1, footnote "e"- In-clinic dosing time is recorded as time of the second puff/inhalation. The in-clinic dosing time should be timed to be within 12±2 hours of the prior evening dosing time. ~~if assigned to blinded treatment or 24±2 hours of the prior morning dosing time if assigned to Symbicort.~~ Record/document the dose indicator readings of the used device and the replacement device; this applies to all the study medications including Symbicort TBH.	Correction/Consistency
Section 8.7 Vital Status Confirmation at Week 52: Deleted "After the fifth attempt, the study site will contact the national death registries (if available) to confirm date and cause of death."	Correction.
Sections 9.3, 9.4, and 9.41: Deleted PT010007 Safety Population	Removed to simplify the number of study populations for analysis and to remove any redundancy with the Japanese Safety Population.
Section 10.2 Ethical Conduct of the Study and Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval: Added Japan specific requirements	Further clarified and added references to additional ordinances, related laws and regulations.
Section 10.9 Retention of Data: Added the Head of the Medical Institution	Clarified data retention responsibilities and timings.

responsibilities for data retention.	
Section 10.11 Investigator's Final Report Replaced "Investigator" with "Head of Medical Institution"	Clarified/corrected responsible party.

SYNOPSIS

Sponsor:

Pearl Therapeutics, Inc. ("Pearl")

[redacted]

Names of Finished Products:

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

Names of Active Ingredients:

Budesonide, Glycopyrronium, and Formoterol Fumarate

Glycopyrronium and Formoterol Fumarate

Budesonide and Formoterol Fumarate

Study Title:

A Randomized, Double-Blind, Parallel-Group, 28-Week, Chronic-Dosing, Multi-Center Extension Study to Assess the Safety and Efficacy of PT010, PT003, and PT009 in Japanese Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) compared with Symbicort® Turbuhaler® as an Active Control

Study Number: PT010007-01

Study Phase: III

Primary Objective:

- The primary objective of this extension study is to evaluate the long-term safety and tolerability of BGF MDI, GFF MDI, BFF MDI, and Symbicort Turbuhaler (TBH) in Japanese subjects with moderate to very severe COPD

Other Objectives:

- To assess the effect of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on lung function
- To assess the effect of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on COPD exacerbations
- To assess the effect of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on symptoms using the change in rescue medication use as an indirect measure of symptom control

Study Design:

This is a randomized, double-blind, parallel-group, 28-week, chronic-dosing, multi-center, active-controlled, safety extension of Study PT010006 to assess the safety of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH twice-daily (BID) as an active control over a 52-week period in Japanese subjects with moderate to very severe COPD who completed participation in Study PT010006. Efficacy assessments will also be measured.

All Japanese sites that participated in Study PT010006 will be eligible to contribute subjects to this study. It is planned that approximately 324 Japanese subjects with moderate to very severe COPD will continue into this study to provide approximately 300 subjects to complete the study. Based on the randomization ratio from the original lead in Study PT010006, this study will evaluate approximately 100 completed Japanese subjects in the BGF MDI and GFF MDI arms, and approximately 50 completed Japanese subjects in the BFF MDI and Symbicort TBH arms.

Study PT010007 will be initiated as a double-blind study as patients begin to enroll after completion of Study PT010006. Once patient participation has completed in Study PT010006 and that study is unblinded for reporting purposes, investigational sites and study patients will remain blinded to treatment assignment. Subjects will remain on the same therapy that they were receiving in Study PT010006 so that subjects completing Study PT010007 will have been exposed to treatment for 1 year. The entire study period, including Study PT010006, is scheduled to take approximately 58 weeks for most subjects.

Study Population:

Approximately 324 subjects with moderate to very severe COPD will be enrolled to provide approximately 300 subjects to complete the study.

Test Product, Dose, and Mode of Administration:

Investigational materials will be provided by 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 Product			
Budesonide and formoterol fumarate inhalation powder (Symbicort Turbuhaler) [†] 400/12 µg	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[a] inhalation aerosol 90 µg ex-actuator	US source: 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

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; MDI = metered-dose inhaler; DPI = dry powder inhaler; BID = twice daily; HFA= hydrofluouroalkane; µg = microgram.

[†] Active control

[a] Rescue medication. Albuterol sulfate is also known as salbutamol sulfate in some countries.

Duration of Treatment:

In this long-term extension study, each subject will receive study treatment for 28 weeks. The entire study participation, including participation in Study PT010006, from Screening to Follow-up, is scheduled to take approximately 58 weeks for each individual subject.

The data from this 28-week study will be combined with the 24 weeks of data obtained from the lead-in Study PT010006 to provide safety and efficacy data over 52 weeks of treatment. The baseline for all subjects will remain the original baseline (Visit 4 Randomization) of Study PT010006.

Safety Endpoints:

Overall safety and tolerability will be evaluated over 52 weeks using:

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

Efficacy Endpoints (over 52 weeks unless otherwise stated):

- Change from baseline in morning pre-dose trough FEV_1 over 52 weeks (Weeks 4 to 52) and at each post-randomization visit
- Change from baseline in average daily rescue Ventolin HFA (albuterol sulfate) use.
- Percentage of days with no rescue Ventolin HFA use
- Rate of moderate or severe COPD exacerbations
- Rate of COPD exacerbations of any severity
- Change from baseline in morning pre-dose trough for forced vital capacity (FVC), peak expiratory flow rate (PEFR), and forced expiratory flow 25-75% (FEF_{25-75}) over 52 weeks (Weeks 4 to 52) and at each post randomization visit
- Change from baseline in: the EXACT total score, the 11-item EXACT Respiratory Symptoms (E-RS) Total Score (RS-Total Score), as well as 3 subscale scores symptom (RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms) over 52 weeks and over each 4-week interval of the 52-week Treatment Period

Statistical Methods:

Safety Analyses (Primary):

The incidence (number and percentage) of subjects experiencing each adverse event will be tabulated for each treatment group using the coded MedDRA preferred term, and the MedDRA System Organ Class. Tabulations will be created by severity, by relationship to study drug, and AEs leading to withdrawal. Vital signs, clinical laboratory findings, and ECG results will all be tabulated by treatment group. No inferential analyses will be performed.

Efficacy Analyses:

The change from baseline in pre-dose trough FEV_1 over 52 weeks will be analyzed using a linear model with repeated measures. The model will include baseline trough FEV_1, baseline eosinophil count, and percent reversibility to Ventolin HFA as continuous covariates and visit, treatment, treatment by visit, and ICS use at Screening as categorical covariates. An unstructured covariance matrix will be used to model additional autocorrelation within subject. If this model fails to converge, a first order autoregressive [AR (1)] structure will be used instead; for this model subject will be considered a random effect. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be produced for each treatment difference.

Sample Size:

The sample size of approximately 324 subjects (108 per arm in the BGF MDI and GFF MDI groups and 54 per arm in the BFF MDI and Symbicort TBH groups) includes all Japanese subjects who were enrolled in Study PT010006. No statistical power calculations were performed to arrive at this number. The sample size was selected to provide approximately 100 completing subjects in the BGF MDI and GFF MDI arms.

Data Monitoring and Clinical Endpoint Committees:

Data Monitoring Committee:

An external Data Monitoring Committee (DMC) that was initiated in Study PT010006 will continue to provide systematic and unbiased assessments of safety. 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 independent, external clinical endpoint committee (CEC) that was initiated in Study PT010006 will continue to adjudicate for this study. 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

Date of Original Approved Protocol: 05 July 2015

Date of Protocol Amendment 1.0 (Version 2.0): 17 March 2017

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	Adverse Event of Special Interest
ALT	alanine aminotransferase (SGPT)
ANOVA	analysis of variance
AP	alkaline phosphatase
AR (1)	first order autoregressive
AST	aspartate aminotransferase (SGOT)
ATS	American Thoracic Society
BD	budesonide
BDI	baseline dyspnea index
BFF	budesonide and formoterol fumarate
BGF	budesonide, glycopyrronium, and formoterol fumarate
BID	bis in die, twice daily
BMP	basic metabolic panel
BP	blood pressure
BPM	beats per minute
BUN	blood urea nitrogen
CEC	Clinical endpoint committee
CCV	cardio- and cerebro-vascular
CFR	Code of Federal Regulations
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CRF	case report form
CV	coefficient of variation
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee

DPI	dry powder inhalation
ECG	electrocardiogram
ex actuator	dose delivered from the actuator (ie., mouthpiece) of the metered dose inhaler
EXACT	Exacerbations of Chronic Obstructive Pulmonary Disease Tool
FDA	Food and Drug Administration
FEF	forced expiratory flow
FEV_1	forced expiratory volume in 1 second
FF	formoterol fumarate
FVC	Forced vital capacity
GCP	Good Clinical Practice
GFF	glycopyrronium and formoterol fumarate
GGT	gamma glutamyl transferase
GOLD	Global Initiative for Chronic Obstructive Lung Disease
hCG	human chorionic gonadotropin
HFA	hydrofluoroalkane
HR	Heart Rate
HL	Hy's Law
ICF	Informed Consent Form
ICS	Inhaled corticosteroid
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	Interactive Web Response System
JRS	Japan Respiratory Society
LABA	long acting β2 agonist
LAMA	long acting antimuscarinic agents
mITT	modified intent-to-treat

MDI	metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
mL	milliliter
PEFR	peak expiratory flow rate
PFT	Pulmonary function test
PHL	Potential Hy's Law
PIN	Personal identification number
QID	four times daily
SABA	short acting β2 agonist
SAE	serious adverse event
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
TBH	Turbuhaler
TBL	Total bilirubin
µg	micrograms
ULN	upper limit of normal
US	United States

TRADEMARK INFORMATION

Trademarks Not Owned By Pearl Therapeutics, Inc.	
KoKo Spirometer	Ventolin
Oxis	Turbuhaler
Spiriva	
Symbicort	

1 INTRODUCTION AND STUDY RATIONALE

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients. Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality worldwide and results in significant economic and social burden that is both substantial and increasing. Pharmacologic therapy in COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance [Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2014); Japanese Respiratory Society (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, ie, Symbicort® is approved for use in patients with asthma and 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.

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 [Rennard, 2009; Tashkin, 2008].

1.1 Study Rationale

This is the 28-week extension of the Study PT010006 with the purpose to assess the long-term safety and tolerability of BGF MDI, GFF MDI, BFF MDI, and Symbicort Turbuhaler (TBH) in Japanese subjects with moderate to very severe COPD.

This study is intended to provide the long-term 1-year safety data to support registration of these investigational products in Japan.

2 STUDY OBJECTIVES

2.1 Primary Objective

- The primary objective of this extension study is to evaluate the long-term safety and tolerability of BGF MDI, GFF MDI, BFF MDI, and Symbicort Turbuhaler (TBH) in Japanese subjects with moderate to very severe COPD

2.2 Other Objectives

- To assess the effect of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on lung function
- To assess the effect of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on COPD exacerbations
- To assess the effect of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH on symptoms using the change in rescue medication use as an indirect measure of symptom control

3 STUDY ENDPOINTS

The data from this 28-week study will be combined with the 24 weeks of data obtained from the lead-in Study PT010006 to provide safety and efficacy data over 52 weeks of treatment. Baseline for all subjects will remain the original baseline (Visit 4 Randomization) from Study PT010006.

3.1 Safety Endpoints

Overall safety and tolerability will be evaluated over 52 weeks using:

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

3.2 Efficacy Endpoints (over 52 weeks unless otherwise stated):

- Change from baseline in morning pre-dose trough FEV_1 over 52 weeks (Weeks 4 to 52) and at each post-randomization visit
- Change from baseline in average daily rescue Ventolin HFA (albuterol sulfate) use

- Percentage of days with no rescue Ventolin HFA use
- Rate of moderate or severe COPD exacerbations
- Rate of COPD exacerbations of any severity
- Change from baseline in morning pre-dose trough for forced vital capacity (FVC), peak expiratory flow rate (PEFR), and forced expiratory flow 25-75% (FEF_{25-75}) over 52 weeks (Weeks 4 to 52) and at each post randomization visit
- Change from baseline in: the EXACT total score, the 11-item EXACT Respiratory Symptoms (E-RS) Total Score (RS-Total Score), as well as 3 subscale scores symptom (RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms) over 52 weeks and over each 4-week interval of the 52-week Treatment Period

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind, parallel-group, 28-week, chronic-dosing, multi-center, active-controlled, safety extension of Study PT010006 to assess the safety of BGF MDI, GFF MDI, BFF MDI, and Symbicort TBH (BID) as an active control over a 52-week period in Japanese subjects with moderate to very severe COPD who completed participation in Study PT010006.

All Japanese sites that participated in Study PT010006 will be eligible to contribute subjects to this study. It is planned that approximately 324 Japanese subjects with moderate to very severe COPD will continue into this study to provide approximately 300 subjects to complete the study. This study will evaluate approximately 100 completed Japanese subjects in the BGF MDI and GFF MDI arms, and approximately 50 completed Japanese subjects in the BFF MDI and Symbicort TBH arms.

Study PT010007 will be initiated as a double-blind study as patients begin to enroll after completion of Study PT010006. Once patient participation has completed in Study PT010006 and that study is unblinded for reporting purposes, investigational sites and study patients will remain blinded to treatment assignment.

There are 10 scheduled visits in the lead-in Study PT010006. The tenth visit comprises the last visit of the lead-in Study PT010006 and the first visit of the PT010007 extension study. In order to differentiate, assessments conducted at the completion of the lead-in study (Study PT010006) will be captured in Visit 10a and the initial assessment conducted in the extension study (Study PT010007) will be captured in Visit 10b. Visit 10b will begin immediately following completion of Visit 10a procedures.

At Visit 10b, all subjects who are eligible for participation in and agree to participate in Study PT010007 will sign an informed consent form prior to the conduct of any study assessments specific to Study PT010007. Subjects will be reminded to not use certain

prohibited COPD medications and to maintain their maintenance COPD therapy as adjusted for participation in Study PT010006.

Subjects who meet all entry criteria will undergo Visit 10b procedures will be maintained on the same treatment assignment from Study PT010006. Subjects will then be discharged from the clinic and will continue to administer study medication for 4 weeks at home until Visit 11.

Following enrollment (Visit 10b) into this safety extension study, subjects will be examined at Visit 11 (Week 28), Visit 12 (Week 36), Visit 13 (Week 44), and Visit 14 (Week 52). In total each completed subject will attend 5 scheduled visits in this study. For assessments at each visit refer to the schedule of events in Table 8-1.

Subjects will be required to take their study medication twice a day and will inhale 2 puffs in the morning between 06:00 and 10:00 AM (Breakfast time) and in the evening between 06:00 and 10:00 PM (Dinner time).

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

All visits will be scheduled relative to Visit 4 (Treatment Day 1, Randomization) of Study PT010006. Thus Visits 11, 12, 13, and 14, will be scheduled 28, 36, 44, and 52 weeks ± 7 days of Visit 4 of Study PT010006 respectively. Sites should make every effort to maintain subjects within the scheduled visit window (particular attention should be made to schedule the final visit as close to 52 weeks as possible). If a visit falls outside the expected visit window the subsequent visit should still be scheduled as planned relative to Visit 4.

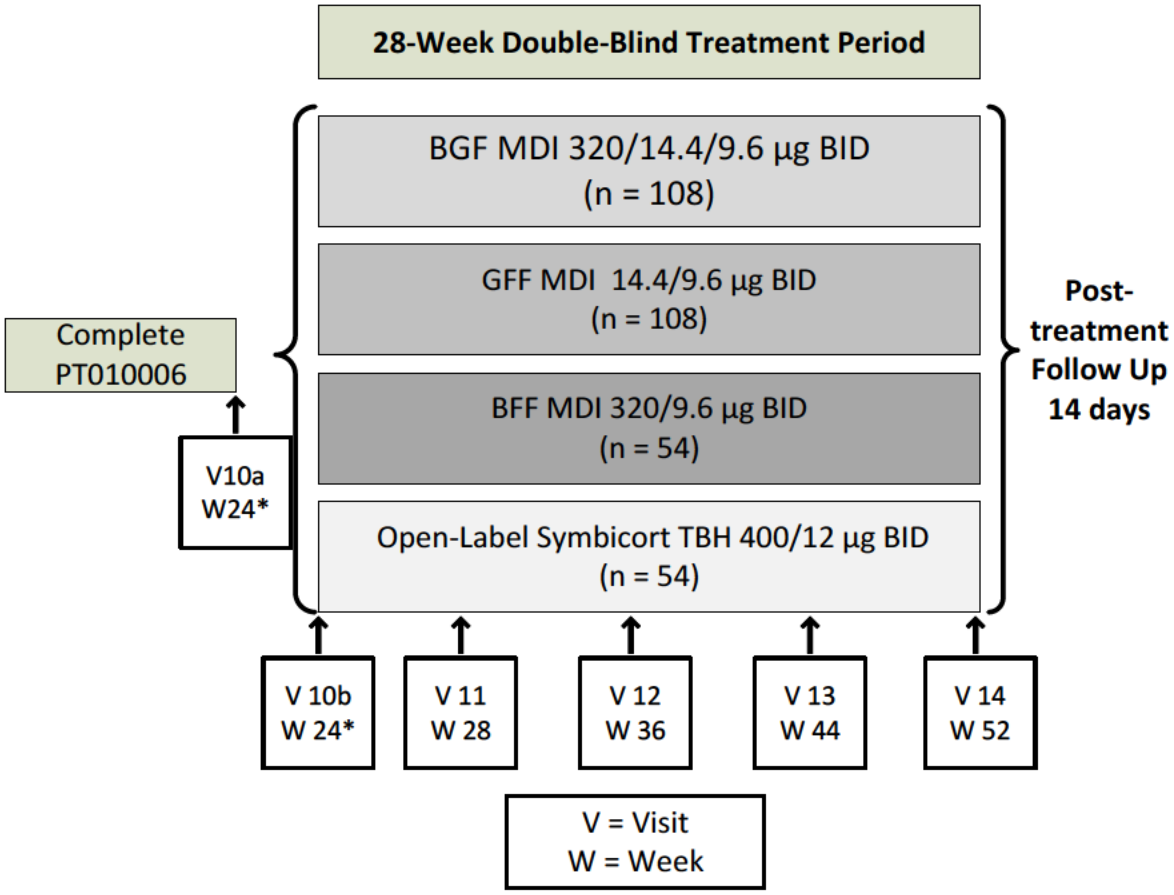
General Considerations for Treatment Visits 10b through Visit 14:

- At the start of each study visit, prior to any study procedures being performed, site personnel must confirm the subject withheld all COPD medications, including study medication, rescue Ventolin HFA, and maintenance medications (ICS, theophylline or PDE4s) for at least 6 hours, by confirming the last time of dosing for all COPD medication(s). **Note:** Subjects who inadvertently took COPD medication(s) within 6 hours of the start of study procedures must be rescheduled as soon as is practical but within the specified visit window. In addition, before the in-clinic dose is administered, the site must confirm the subject met all other protocol specified requirements (e.g. completion of Visit 10a)
- Subjects must not ingest xanthine and/or xanthine analogue (caffeine)-containing foods, beverages, or 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
- 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 of the lead-in study (Study PT010006) for all treatment visits (± 2 hours) but not to exceed 10:00 AM and will be required to remain at the clinic until completion of all protocol-defined assessments
- Sites should make every effort to ensure that the in-clinic dosing time is before 10:00 AM and within 12±2 hours of the prior at home evening dosing time
- The in-clinic dosing time will be recorded as the time of administration of the second puff.
- To ensure standardization of dosing times, it is recommended that sites encourage subjects to maintain a dosing schedule consistent with their in-clinic dosing time and that sites call the subject on the day before a scheduled visit to remind the subject of the following:
  - 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 (including ICS and phosphodiesterase inhibitors) for at least 6 hours prior to pulmonary function tests (PFTs);
  - Refrain from ingesting xanthine and/or xanthine analogue (caffeine)-containing foods, beverages, or 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;
  - Refrain from smoking for at least 4 hours prior to the study visit and throughout the duration of each study visit;
- Site personnel will instruct subjects not to take any COPD medications, without site personnel permission, during a visit until all study procedures have been completed, and the subject is discharged. Site personnel should take every precaution to prevent subject use of COPD medications during test day. Site personnel may request the subject to surrender all COPD medications prior to the start of the visit before performing any study procedures and return the COPD medications to the subject at the end of the visit when all study procedures are completed. Subjects will be asked to abstain wherever possible from using rescue Ventolin HFA during study visits. If a subject is experiencing severe symptoms and requires Ventolin HFA for relief of COPD symptoms at any time during a test day, site personnel must note the time and justification of use in the subject's chart and all subsequent spirometry assessments should be stopped. However, safety assessments should be continued at the discretion of the Investigator.

The Study Design is displayed in Figure 1 below.

Figure 1 Study Design



* V10a and V10b will be conducted at the same visit. Visit 10b will begin immediately following completion of Visit 10a procedures.

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

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

1. Give their signed written informed consent to participate.
2. Completion of the treatment phase of the lead-in Study PT010006.
3. Compliance with Study PT010006 study procedures and study drug dosing.
4. No medical contraindication as judged by the principle investigator.

5.2 Exclusion Criteria

1. Requiring and currently being administered contraindicated medications refer to Sections 5.4.2and 5.4.3.

   Note: Participation in observational studies is not exclusionary.
2. Discontinuation of treatment in Study PT010006.

5.3 Subject Identification

All subjects who participate in this study will maintain the unique screening identification number and unique subject randomization number assigned to them for participation in Study PT010006.

5.4 Prior, Concomitant, and Prohibited Medications

Any additions, deletions, or changes in the dose of medications while in the study should be entered on the CRF. Any current ongoing medications, including OTC drugs and herbal supplements, will be allowed provided they are not prohibited by the protocol (refer to Sections 5.4.2 and 5.4.3) and are approved by the investigator. Subjects should also be instructed to contact the investigator if they develop any illnesses.

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

5.4.1 Allowed Concomitant 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.

In the instance a subject is hospitalized for a severe COPD exacerbation and study drug is interrupted to allow COPD medications to be prescribed, the subject may be able to restart study drug upon stopping the COPD medications. If a subject is not able to discontinue prescribed COPD medications during the exacerbation treatment (Table 5-1) within 14 days, then the subject must be permanently discontinued from the study drug and encouraged to complete the remaining study visits.

5.4.2 Prohibited COPD Medications

The following medications used for the treatment of COPD are not permitted during this study. These medications must have been discontinued during the Screening Period of Study PT010006 and are also not permitted during this extension study, refer to Table 5-1.

Table 5-1 Prohibited COPD Medications

Class of Medication
LAMAs
Short acting muscarinic antagonists (SAMA)
LABAs (inhaled)
Fixed combinations of LABA/LAMA
Fixed combinations of LABA/ICS
Fixed combinations of SABAs and SAMAs
SABAs[a]
Oral β-agonists
Theophylline (total daily dose >400 mg/day)[b]

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

a Other than sponsor-provided open-label Ventolin HFA

b Theophylline is allowed if the total daily dose is ≤400 mg\ and the subject was receiving theophylline in Study PT010006.

Notes:

- During the Treatment Period (Visit 10b to Visit 14), subjects may be treated with systemic corticosteroids, if required as described in Section 5.4.1.
- Subjects who are steroid dependent and maintained on an equivalent of ≤5 mg oral prednisone per day or ≤10 mg oral prednisone every other day are permitted to enroll in the study provided they have been on a stable dose of therapy during participation in Study PT010006
- Roflumilast (or any PDE4 inhibitor) is allowed provided the subject has been on stable dose of therapy during participation in Study PT010006.

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

Table 5-2 Other Prohibited Respiratory/Nasal Medications:

Class of Medication
Leukotriene antagonists (e.g., zafirlukast, montelukast, and zilueton)
Cromoglycate or other mast cell inhibitors (e.g., Intal and Tilade)
Nedocromil
Ketotifen *

*Ketotifen eye drops are allowed

5.4.3 Other Prohibited Medications

Table 5-3 lists certain non-COPD medications that can be used under the stated conditions during this study.

Table 5-3 Non-COPD Medications Allowed Under Certain Conditions

Medications	Condition
Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and noradrenergic and specific serotonergic antidepressants (NaSSAs)	Subject was receiving a stable dose in Study PT010006
Intranasal corticosteroids, intranasal antihistamines, intranasal anticholinergics, or any combination thereof	Subject was receiving a stable dose Study PT010006

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 5-4 are prohibited from participating in this study as specified below. 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 and resume the appropriate COPD maintenance therapy and be encouraged to complete the remaining study visits.

Table 5-4 Prohibited Medications

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

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 seizure disorders are allowed if the subject has been receiving a stable dose and the subject was free of seizures during Study PT010006

[c] Anticonvulsants for other indications are allowed at any time throughout the study

[d] 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

[e] 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)

[f] Systemic anticholinergics are allowed providing the patient was treated with this class of medications during Study PT010006 and the dose remains unchanged

5.5 Other Restrictions, Dangerous Drugs or Drugs of Abuse

5.5.1 Dangerous Drugs

Dangerous drugs or drugs of abuse will not be allowed during the study from Visit 10b to Visit 14 or to whenever the subject discontinues the study. If any dangerous 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.

5.5.2 Dietary Restrictions

Subjects must not ingest xanthine and/or xanthine analogue (caffeine)-containing foods, beverages, or medications for at least 6 hours prior to and for the duration of each study visit. Examples of such products include coffee, tea, chocolate, and cola. Decaffeinated beverages are acceptable.

5.6 Smoking Status

Changes in a subject's smoking status (e.g., stopping or re-starting smoking) may have an impact on the efficacy outcome measures. At all visits the subject will be asked about any recent change in their smoking status (i.e. whether a subject's status has changed from smoker to non-smoker or vice versa). Smoking status changes during the 28-week Treatment Period will be captured in the eCRF, but the subject will be permitted to continue in the study. Subjects will be required to refrain from smoking (including electronic cigarettes) for at least 4 hours prior to each study visit and throughout the duration of each study visit. Study participants may utilize various nicotine replacement treatments such as chewing gum and patches (PRN), in accordance with recommendations from the Investigator during the entire study visit.

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

5.7 Reasons for Treatment Discontinuation or Study Withdrawal

5.7.1 Reasons for Treatment Discontinuation

Subjects may be withdrawn from the study at any time at their own request, upon request of the Investigator, or by Pearl at any time or for any reason. 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 discontinue for any reason, they, their family or healthcare providers, will be contacted 52 weeks post-randomization to determine vital status, and if appropriate, cause of death (Section 8.7). 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 must be discontinued from randomized treatment but can continue 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 on randomized treatment in 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 the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula or a clinically relevant change from baseline as determined by the Investigator

Subjects requiring any of the prohibited medications listed in Section 5.4 (other than study-provided medication or COPD medications used during the treatment of a severe COPD exacerbation as described in Section 5.4.1) should be withdrawn from randomized study drug but encouraged to continue in the study and complete all study visits.

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).

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 (Section 7.3.12).

5.7.2 Reasons for Study Withdrawal

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 (Section 7.3.11).

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

6.1 Subject Information

Clinical supplies will be packaged to support enrollment of the study. Study personnel will have access to an Interactive Web Response System (IWRS) to allocate subjects, to assign drug to subjects and to manage the distribution of clinical supplies. Clinical supplies will be packaged according to a component schedule generated by the Sponsor. Each person accessing the IWRS system must be assigned an individual unique 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 6-1.

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

Ventolin HFA will be a US-sourced product. 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 6-1 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
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 Product			
Budesonide and formoterol fumarate inhalation powder (Symbicort Turbuhaler) † 400/12 µg	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[a] inhalation aerosol 90 µg ex-actuator	US source: 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

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; MDI = metered-dose inhaler; DPI = dry powder inhaler; BID = twice-daily; HFA= hydrofluouroalkane; µg = microgram

† Active control

[a] Rescue medication. Albuterol sulfate is also known as salbutamol sulfate in some countries.

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

Open-label Symbicort TBH DPIs 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. Ventolin HFA will be supplied as open-label MDI.

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 Ventolin HFA will be provided as an individually-labeled MDI. The 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:

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 and Ventolin HFA) will be packaged in individual boxes as outlined in Table 6-2. Box configuration is subject to change as a result of packaging constraints.

Table 6-2 Description of Boxes

Drug Supplies	Individual Box Contents
Blinded	1 MDI
Symbicort Turbuhaler	1 DPI
Ventolin (albuterol sulfate) HFA	1 MDI

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

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

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

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.

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, and 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 3 for instructions on administration and cleaning of BGF MDI, GFF MDI, and BFF MDI.

6.7.2 Symbicort® Turbuhaler®

Refer to Appendix 4 for instructions on the administration and cleaning of Symbicort® Turbuhaler®.

6.7.3 Ventolin HFA®

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 applicable local guidelines (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. Please refer to Section 6.6.

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 as needed to evaluate the nature of the complaint and determine what further action may be required.

7 STUDY PROCEDURES

A schedule of events is provided in Table 8-1.

7.1 Efficacy Assessments

7.1.1 Pulmonary Function Tests

Forced expiratory spirometry maneuvers for derivation of FEV_1, FVC, and PEFR will be assessed using a spirometer that meets or exceeds minimum performance recommendations of the ATS (See Appendix 1).

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

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

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

Spirometry assessments will be obtained at the conclusion of Study PT010006 (Visit 10a) and will not be obtained during Visit 10b of this study.

Spirometry assessments will be conducted 60 minutes and 30 minutes *prior* to study drug administration at Visit 11 through Visit 13. Spirometry assessments will be conducted at approximately 60 minutes and 30 minutes prior to receiving the appropriate COPD maintenance therapy at Visit 14.

7.1.2 Subject Electronic Diary (eDiary) Data Collection

Subjects will continue to use their eDiary provided during participation in Study PT010006 to continue to record time of study medication administration, morning and evening symptoms, use of rescue albuterol (Ventolin HFA), and dose indicator reading (if assigned to BGF MDI, GFF MDI or BFF MDI only).

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

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

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

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

7.1.2.1 Rescue Medication Usage

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

7.1.2.2 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 Recording of Dose Indicator Reading

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

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

Prior to dosing at Visits 11 to 13 and at the final Visit 14, site personnel will observe the dose indicator reading on the study drug returned by the subject and record the dose indicator reading in the source.

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

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

7.1.2.4 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 the 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 AEs unless considered a serious AE (SAE).

7.1.3.4 Other Information

Pearl Therapeutics will be using an 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 Questionnaire

The exacerbations of chronic pulmonary disease tool (EXACT) questionnaire will be captured via the subject eDiary (see Appendix 6).

7.2 Safety Assessments

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

7.2.1 Medical/Surgical History and Physical Examination

Medical history and history of COPD exacerbation will be taken at Screening in Study PT010006. A complete physical examination will be performed at the conclusion of Study PT010006 (Visit 10a) and will not be obtained during Visit 10b of this study. A complete physical examination will be conducted at the Final Visit (Visit 14) or at the Treatment Discontinuation/Withdrawal Visit. A complete physical examination will include the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. Weight, assessed in ordinary indoor clothing with shoes removed, will be recorded at Visit 14.

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.

Vital signs will be obtained at the conclusion of the lead-in study PT010006 (Visit 10a) and will not be obtained during Visit 10b of this study.

At Visits 11 to 13:

- Pre-dose vital signs will be obtained within 60 minutes *prior* to study drug dosing
- Post-dose vital signs will be obtained at 30 minutes post study drug dosing

A single set of vital signs will also be obtained at a Visit 14 (Week 52) or at the Treatment Discontinuation/Withdrawal Visit, if applicable.

Note: Temperature will be obtained pre-dose at all visits and will not be repeated post-dose at subsequent time points unless clinically indicated.

7.2.3 12-Lead Electrocardiogram

ECGs will be obtained at the conclusion of Study PT010006 (Visit 10a) and will not be obtained during Visit 10b of this study.

At Visit 12 (Week 36) only, an ECG will be obtained within 60 minutes prior to study drug dosing.

An ECG will also be obtained at Visit 14 (Week 52) or at the Treatment Discontinuation/Withdrawal Visit, if applicable.

To standardize ECG collection, all sites will be provided with identical ECG equipment (Global Instrumentation M12R recorder, Global Instrumentation, Syracuse, NY, USA) 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 (iCardiac Technologies, Rochester, NY, USA). 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 greater than 500 msec, and have increased by 60 msec or more over test day baseline value, the investigator will make a determination on the suitability of continuing the subject in the study. If QTcF interval prolongation exceeding these limits is verified during treatment, the subject's medical history should be examined closely for risk factors that may have contributed to the event, including evidence of prior genotyping for hereditary long QT syndromes, if appropriate.

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

All such subjects, including subjects with cardiac arrhythmias, should be monitored closely. If appropriate, ECG monitoring should be performed until the QT and QTcF interval and waveform morphology have returned to normal. If the prolongation or abnormal rhythm persists, the Pearl Therapeutics Medical Monitor must be contacted immediately.

7.2.4 Clinical Laboratory Tests

Clinical safety laboratory tests will be analyzed by a central laboratory according to standardized, validated assays. The laboratory will supply detailed instructions and all containers for blood and urine investigations. Blood sample volumes will meet the laboratory's specification. Clinical laboratory tests will be obtained prior to dosing at the final visit of Study PT010006 (Visit 10a), and will not be obtained during Visit 10b of this study. During the course of this study, clinical laboratory tests will be obtained prior to dosing at Visit 12 (Week 36) only. Clinical laboratory tests will also be obtained at Visit 14 (Week 52) or at the Treatment Discontinuation/Withdrawal Visit, if applicable.

7.2.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured prior to dosing at the final visit of Study PT010006 (Visit 10a), and will not be obtained during Visit 10b of this study. During the course of this study, hematology assessments will be obtained prior to dosing at Visit 12 (Week 36). Hematology assessments will also be obtained at Visit 14 (Week 52) or at the Treatment Discontinuation/Withdrawal Visit, if applicable.

7.2.4.2 Clinical Chemistry

A comprehensive chemistry panel will be measured prior to dosing at the final visit of Study PT010006 (Visit 10a), and will not be obtained during Visit 10b of this study. During the course of this study, clinical chemistry assessments will be obtained prior to dosing at Visit 12 (Week 36) only. Clinical chemistry assessments will be obtained at Visit 14 (Week 52) or at the Treatment Discontinuation/Withdrawal Visit, if applicable.

Refer to Table 7-1 for a list of study-associated laboratory tests. The central laboratory will supply procedures for the preparation and collection of these samples.

Table 7-1. Clinical Laboratory Tests

Hematology	
Hemoglobin	Mean corpuscular hemoglobin
Hematocrit	Mean corpuscular hemoglobin concentration
White blood cell count with differential	Mean corpuscular volume
Red blood cell count	Eosinophils
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
	Bicarbonate
	Creatinine[a]
	Glucose[a]
	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 child-bearing potential only): serum [human chorionic gonadotropin (hCG)] at Visit 14 or Treatment Discontinuation/Withdrawal visit only and urine hCG at Visits 11, 12, and 13 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

Urinalysis will be measured at the final visit of Study PT010006 (Visit 10a), and will not be obtained during Visit 10b of this study. During the course of this study, urinalysis will be obtained prior to dosing at Visit 12 (Week 36). Urinalysis will be obtained at Visit 14 (Week 52) or at the Treatment Discontinuation/Withdrawal Visit, if applicable.

7.2.4.4 Pregnancy Test

A serum pregnancy test will be performed at the Central Laboratory in pre-menopausal women who are not surgically sterile at the final visit of Study PT010006 (Visit 10a), and will not be obtained during Visit 10b of this study. A serum pregnancy test will also be obtained at Visit 14 (Week 52) or Treatment Discontinuation/Withdrawal Visit. A urine pregnancy test will be performed at all Visits 11 to 13. If any of these tests are positive, the subject must be discontinued from the study. The pregnancy test should be performed prior to ECG, blood collection for laboratory assessments, or spirometry.

7.3 Adverse Events

7.3.1 Performing Adverse Events Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's 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 7.3.9) are classified as "serious" and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as an SAE to Pearl or its designee. If a situation arises where reporting of a Serious Adverse Event is not possible due to an unanticipated situation such as a failure of the EDC system, SAEs must be reported to Pearl Therapeutics (E-mail or Fax) via paper Serious Adverse Event Form.

[redacted]

In the case of SAEs, after discussing the details of the AE, the Investigator and the Sponsor or representative may discontinue the subject prematurely.

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

7.3.3 Severity

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

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

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

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

7.3.4 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.

7.3.5 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 AE unless considered an SAE.

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

7.3.6 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.

7.3.6.1 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.

7.3.6.2 Local Steroid Effects

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

7.3.6.3 Pneumonia

In order to adequately assess and characterize the risk of pneumonia in patients in a non-biased manner, a Clinical Endpoint Committee (CEC) will review all AEs 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.

7.3.6.4 Paradoxical Bronchospasm

Monitoring for paradoxical bronchospasm will occur through spontaneous reporting.

7.3.7 Major Adverse Cardiovascular Events (MACE)

Due to the prevalence of cardiovascular diseases in patients with COPD, MACE will be evaluated according to pre-defined criteria as described in the Clinical Endpoint Adjudication Charters. The CEC will review potential clinical events 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 7.3.15 Clinical Endpoint Committee.

7.3.8 Clinical Laboratory Adverse Events

Many laboratory abnormalities observed during the course of a study will be included under a reported AE describing a clinical syndrome (e.g., elevated 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.

7.3.9 Serious Adverse Events

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

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

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate judgment, they may jeopardize the subject or 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.

7.3.9.1 Reporting Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for AE identification, documentation, grading, assignment of causality, and prompt notification of SAEs to Pearl Pharmacovigilance or designee. All SAEs must be reported to Pearl 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 7.3.9.4.

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

The Principle Investigator will report SAEs to Pearl and to the Head of the Medical Institution during the performance of this protocol.

7.3.9.2 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 and to the Head of the Medical Institution. 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 and to the Head of the Medical Institution.

7.3.9.3 Post-Study Follow-Up of 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. The Principle Investigator will report SAEs to Pearl and to the Head of the Medical Institution during the performance of this protocol.

7.3.9.4 Notification of Post-Study Serious Adverse Events

Investigators are not obligated to actively follow subjects after the completion of the study. However, if the 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. The Principle Investigator will report SAEs to Pearl and to the Head of the Medical Institution during the performance of this protocol.

7.3.9.5 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. Notifications of Serious Adverse Events to the IRB/IEC including any follow-up reports should also be provided to the Head of the Medical Institution.

7.3.9.6 Health Authority Safety Reports

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

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

7.3.10 Overdose

An overdose is defined as a dose greater than the high dose level evaluated in this study as described in Section 6.2 (Product Descriptions) 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 documents 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.

7.3.11 Pregnancy

To ensure subject safety, each pregnancy in a female subject from Visit 1 (Screening) until study completion must be reported to Pearl within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be recorded on a Paper Pregnancy 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.

If pregnancy is confirmed for a female subject, it shall be reported to Pearl Therapeutics within 24 hours via E-mail or Fax using the paper pregnancy form.

7.3.12 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.

7.3.13 Hy's Law

Cases where a subject shows an AST or ALT ≥ 3x Upper Limit of Normal (ULN) with Total Bilirubin (TBL) ≥ 2x ULN may need to be reported as SAEs. Please refer to Appendix 7 for further instructions in cases of combined increase of aminotransferase and TBL.

7.3.14 Use of Steroids during the Trial

At each visit, subjects will be asked whether they have been administered oral, intramuscular, or intravenous corticosteroids since last visit. Use of oral, intramuscular, or intravenous corticosteroids for the management of COPD exacerbations or other condition is not a reason for early 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.

7.3.15 Clinical Endpoint Committee

An external CEC that was initiated in Study PT010006 will continue to adjudicate for this study. The CEC 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

7.3.15.1 Cardiovascular and Cerebrovascular (CCV) Clinical Endpoint Adjudication Charter

A CCV Clinical Endpoint Adjudication Charter will be referenced for the review and assessment of non-fatal serious CCV events and classification of MACE. The CEC will review potential events to determine if the event meets MACE criteria.

7.3.15.2 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.

7.3.15.3 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.

7.3.16 Data Monitoring Committee

An external Data Monitoring Committee (DMC) that was initiated in Study PT010006 will continue to provide systematic and unbiased assessments of safety for Study PT010007. 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.

7.4 Termination of the Study

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

Pearl reserves the right to discontinue the study at any time for clinical or administrative reasons. Such a termination must be implemented by the Investigator, if instructed to do so by Pearl, in a time frame that is compatible with the subjects' wellbeing.

8 STUDY ACTIVITIES

A time and events schedule is provided in Table 8-1.

Table 8-1 Schedule of Events

Procedures	Treatment Period					Follow-Up
	Visit 10b	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**14 Days Post-Dose**
Study Day/Week [a]	**Week 24 ±7 Days**	**Week 28 ±7 Days[a]**	**Week 36 ±7 Days[a]**	**Week 44 ±7 Days[a]**	**Week 52 ±7 Days[a]**	**Week 54 ±7 Days[a]**
Obtain Informed Consent	X					
Review Incl/Excl Criteria	X					
Verify Continued Eligibility		X	X	X	X	
Smoking Status		X	X	X	X	
Physical Examination					X	
Prior/Concomitant Medications[b]		X	X	X	X	X
COPD Exacerbations and Adverse Events		X	X	X	X	X
Adjust COPD Medications[c]					X	
Vital Signs[d]		X	X	X	X	
Urine Pregnancy Test[d]		X	X	X		
Serum Pregnancy Test[d]					X	
12-Lead ECG[d]			X		X	
Clinical Laboratory Testing[d]			X		X	
Spirometry[d]		X	X	X	X	
Study Drug Dispensing/Collection	X	X	X	X	X	
Review of Electronic Diary Data[d]		X	X	X	X	
Study Drug Administration[e]		X	X	X		
Record Dose Indicator Reading[e]	X	X	X	X	X	
Telephone Contact[f]		X[f]	X[f]	X[f]	X[f]	X[g]

a. **Scheduling visits**: All visits will be scheduled relative to Visit 4 (Treatment Day 1, Randomization) of the lead-in study (PT010006).

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

c. At the end of Visit 14, return subject to pre-study or other appropriate inhaled maintenance COPD medications.

d. Refer to Section 7 for specific assessments and specific time points to be performed at each treatment visit.

e. In-clinic dosing time is recorded as time of the second puff/inhalation. The in-clinic dosing time should be timed to be within 12±2 hours of the prior evening dosing time. Record/document the dose indicator readings of the used device and the replacement device; this applies to all the study medications including Symbicort TBH.

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

g. Refer to Section 8.6for details of the follow-up telephone call.

Note: Refer to Section 8.5for procedures that may be required at a premature discontinuation visit. Treatment Discontinuation/Withdrawal Visits will be captured as unscheduled visits.

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

8.1 Visit 10b (Week 24 Safety Extension Entry Visit)

There are 10 scheduled visits in Study PT010006; the tenth visit is the last visit of the Study PT010006 and the first visit of the extension study (PT010007). In order to differentiate, assessments conducted at the completion of the Study PT010006 will be captured in Visit 10a and procedures conducted in the extension study will be captured in Visit 10b. Visit 10b will be completed **following completion of all Visit 10a study procedures.** A reminder phone contact should be made prior to Visit 11.

Note: All subjects in Japan who completed and were compliant with all study procedures in Study PT010006 will be invited to participate in Study PT010007. Visit 10b will be completed only in subjects who consent to participate in the safety extension study.

- Obtain informed consent
- Review safety extension inclusion/exclusion criteria and confirm subject eligibility to enroll into the safety extension study
- **Confirm all visit 10a procedures have been completed before proceeding to register subjects in IWRS**
- Register subject in IWRS to confirm participation in the safety extension study
- Return electronic diary to subjects and provide retraining if appropriate
- When assigned blinded study drug site personnel will complete priming in the clinic before dispensing to the subject for at home use
- Refer to Section 6.7for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits
- Record/document the dose indicator reading. The dose indicator count recorded by the site staff will be dose indicator count observed after priming but prior to subject dosing. Refer to Section 7.1.2for more details
- Subject will administer first dose of safety extension study drug at home in the evening. **Note:** During the extension study subjects will continue on the same treatment that they were assigned in Study PT010006
- Subjects will be instructed to bring their eDiary and all study medication (including used study drug, replacement MDI kit if assigned to blinded study drug and sponsor-provided rescue Ventolin HFA) to the next scheduled clinic visit
- Schedule next visit and ensure subject has adequate supply of study drug including a replacement MDI kit if assigned to blinded study drug and sponsor-provided rescue Ventolin HFA

8.2 Visit 11 (Week 28) and Visit 13 (Week 44)

- Confirm subject eligibility to continue
- Collect study drug including sponsor-provided Ventolin HFA
- 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. If the time of dosing was not in accordance with the protocol, then the visit must be rescheduled
- Review subject diary for data collection compliance
- Review smoking status
- Record COPD exacerbations and adverse events (if any)
- Review all prior/concomitant medications and ensure adherence to COPD regimen
- Obtain vital signs within 60 minutes prior to dosing
- Perform urine pregnancy test
- Obtain pre-dose spirometry at -60 and -30 minutes prior to dosing
- Return electronic diary to subjects and provide retraining if appropriate
- Prior to dosing, site personnel will use IWRS to assign subjects a new kit of study drug for in-clinic dosing and to continue dosing at home until the next scheduled visit
- Refer to Section 6.7 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits
- Record/document the dose indicator readings of the used device and the replacement device. This applies to all the study drugs, including Symbicort TBH.
- For new MDIs, the recorded count will be the count following the priming of the device but before the subject doses. Refer to Section 7.1.2for more details
- **Administer in-clinic study drug dosing from the new kit assigned at the visit**
- Obtain vital signs 30 minutes post study drug dosing
- Subjects will be instructed to track study drug dosing in their electronic diary between study clinic visits
- Subject assigned to blinded study drug will be instructed to dose while at home from the site-primed MDI **only**, unless all of the following **replacement conditions** are met:
  - Dose indicator is in the red zone (See Appendix 8 for dose indicator reading instructions),
  - If the dose indicator registers ≤10 puffs remaining, and their next scheduled study clinic visit is not the following day.

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

8.3 Visit 12 (Week 36)

- Confirm subject eligibility to continue
- Collect study drug including sponsor-provided Ventolin HFA
- 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. If the time of dosing was not in accordance with the protocol, then the visit must be rescheduled
- Review subject diary for data collection compliance
- Review smoking status
- Record COPD exacerbations and adverse events (if any)
- Review all prior/concomitant medications and ensure adherence to COPD regimen
- Obtain vital signs within 60 minutes prior to dosing
- Perform urine pregnancy test
- Obtain 12-lead ECG within 60 minutes prior to study drug dosing
- Obtain clinical laboratory samples prior to study drug dosing
- Obtain pre-dose spirometry at -60 and -30 minutes prior to dosing
- Return electronic diary to subjects and provide retraining if appropriate
- Prior to dosing, site personnel will use IWRS to assign subjects a new kit of study drug for in-clinic dosing and to continue dosing at home until the next scheduled visit
- Refer to Section 6.7 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits
- Record/document the dose indicator readings of the used device and the replacement device. This applies to all the study drugs, including Symbicort TBH.

- For new MDIs, the recorded count will be the count following the priming of the device but before the subject doses. Refer to Section 7.1.2for more details
- **Administer in-clinic study drug dosing from the new kit assigned at the visit**
- Obtain vital signs 30 minutes post study drug dosing
- Subjects will be instructed to track study drug dosing in their electronic diary between study clinic visits
- Subject assigned to blinded study drug will be instructed to dose while at home from the site-primed MDI **only**, unless all of the following **replacement conditions** are met:
  - Dose indicator is in the red zone (See Appendix 8 for dose indicator reading instructions),
  - If the dose indicator registers ≤10 puffs remaining, and their next scheduled study clinic visit is not the following day.
  - If these replacement conditions are met, subjects will be instructed to open one of their replacement kits, prime the MDI and start using for at home dosing until the next scheduled study clinic visit.
  - Subjects will be instructed to bring their eDiary and all study medication (including used study drug, replacement MDI kit if assigned to blinded study drug and sponsor-provided rescue Ventolin HFA) to the next scheduled clinic visit.
- Schedule next visit and ensure subject has adequate supply of study drug including two replacement MDI kits if assigned to blinded study drug and sponsor-provided rescue Ventolin HFA
- Perform reminder phone contact prior to the next visit

8.4 Visit 14 (Week 52) Final Visit

- Confirm subject eligibility to continue
- Collect study drug including sponsor-provided Ventolin HFA
- 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. If the time of dosing was not in accordance with the protocol, then the visit must be rescheduled
- Review subject diary for data collection compliance
- Review smoking status
- Perform physical examination, including weight
- Record COPD exacerbations and adverse events (if any)
- Review all prior/concomitant medications and ensure adherence to COPD regimen

- Obtain vital signs measurements
- Perform serum pregnancy test
- Obtain 12-lead ECG measurements
- Obtain clinical laboratory samples
- Obtain pre-dose spirometry at -60 and -30 minutes prior to dosing with appropriate COPD maintenance therapy
- Return subject to pre-study or appropriate maintenance COPD medications
- Collect subject eDiary
- Record/document the dose indicator readings of the used device and the replacement device. This applies to all the study drugs, including Symbicort TBH.
- 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 14

8.5 Unscheduled Visit/Premature Discontinuation Visit

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

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

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

8.6 Follow-Up Telephone Call

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

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

8.7 Vital Status Confirmation at Week 52

All subjects who discontinue study treatment post-Visit 10b but prior to Visit 14 will have their vital status confirmed at 52 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 52 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 52 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 52 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 5 weeks after 52 weeks post-randomization

8.8 Completion of the Study

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

- Subject discretion (document reason)
- Investigator considers it to be in the best interest of the subject
- Adverse events(s)
- Administrative reasons (e.g., early termination of the study)
- Subject lost-to-follow-up
- Lack of efficacy
- Major protocol violation

- Death
- Completion of the study
- Protocol specified criteria such as heart rate, systolic or diastolic blood pressure, or use of prohibited medications (see Section 5.7)

9 PLANNED STATISTICAL METHODS

9.1 Introduction

This study will be conducted as a double-blind, parallel-group study evaluating the following treatments in approximately 324 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 (200/6 µg)

The primary objective of this study is to evaluate the long-term safety and tolerability of BGF MDI, GFF MDI, BFF MDI, and Symbicort Turbuhaler (TBH) in Japanese subjects with moderate to very severe COPD.

This study will include a 28-week treatment period that will immediately follow an initial 24-week treatment period from Study PT010006. Analyses will include data from subjects enrolled in Japan in Study PT010006 whenever applicable in order to minimize the impact of bias caused by dropout and in order to allow inferences to be made over 52 weeks. Baseline for all subjects will remain the original baseline from Study PT010006. For clinic measured values, the baseline is the assessment obtained prior to initial dosing at Visit 4. Specifically for the primary efficacy measure, baseline is the average of the -60 min and -30 min assessments. For diary data, the baseline is the average of the values obtained during the seven days prior to Visit 4 including the morning of Visit 4 prior to initial dosing.

9.2 Protocol Variables

The data from this 28-week study will be combined with the 24 weeks of data obtained from Study PT010006 to provide safety and efficacy data over 52 weeks of treatment.

9.2.1 Safety Endpoints

The safety endpoints (over 52-weeks) for this study include:

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

9.2.2 Efficacy Endpoints (over Week 52 unless otherwise stated)

- Change from baseline in morning pre-dose trough FEV_1 over 52 weeks (Weeks 4 to 52) and at each post-randomization visit
- Change from baseline in average daily rescue Ventolin HFA (albuterol sulfate) use
- Percentage of days with no rescue Ventolin HFA use
- Rate of moderate or severe COPD exacerbations
- Rate of COPD exacerbations of any severity
- Change from baseline in morning pre-dose trough for FVC, PEFR, and FEF_{25-75} over 52 weeks (Weeks 4 to 52) and at each post randomization visit
- Change from baseline in: the EXACT total score, the 11-item EXACT Respiratory Symptoms (E-RS) Total Score (RS-Total Score), as well as 3 subscale scores symptom (RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms) over 52 weeks and over each 4-week interval of the 52-week Treatment Period

9.3 Study Populations

- The **Japanese Modified Intent-To-Treat** (mITT) **Population** is defined as the subgroup of Japanese mITT subjects from Study PT010006, regardless of participation in PT010007. Subjects will be analyzed according to the active treatment they were assigned to at randomization in Study PT010006. (Note that a subject who used a study treatment, but took less than one full dose of treatment will qualify for this population). Data from both Study PT010006 and Study PT010007 will be included.
- The **Japanese Safety Population** is defined as all Japanese subjects who received any amount of study medication in Study PT010006, regardless of participation in PT010007. Subjects will be analyzed according to the actual treatment they received.

Analyses will be performed as follows:

Demographics will be summarized for the Japanese mITT population and the Japanese Safety Populations. Extent of exposure and safety will be summarized for the Japanese Safety Population. Efficacy Analyses will be performed for the Japanese mITT Population.

9.4 Safety Analyses

Safety data will be summarized cumulatively over 52 weeks using data observed during Study PT010006 and this 28-week extension Study PT010007. Analyses involving change from baseline will use baseline values from Study PT010006.

9.4.1 Adverse Events

All AEs will be summarized for the Japanese Safety Population. 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 incidence (number and percentage) of subjects experiencing 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.

9.4.2 Cardio- and Cerebrovascular Events Determined by Adjudication 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 adjudication committee working practices) for MACE.

MACE events will be summarized by treatment group.

9.4.3 Pneumonia Events Determined by Adjudication Committee

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

9.4.4 Clinical Laboratory Measurements

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

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

grade during the treatment; also, the subject's maximum post-baseline grade during treatment will be tabulated for all baseline grades combined.

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

9.4.5 Vital Signs

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

9.4.6 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 is defined as ($QT/ (RR^{1/3})$). Heart rate (bpm) is estimated as 60,000/RR. These assessments will be tabulated for each treatment and assessment time. PCS values for ECG parameters will be defined in the SAP, and the percentage and number of subjects with PCS ECG values will be tabulated. No hypothesis tests will be performed.

9.4.7 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.

9.5 Efficacy Analyses

9.5.1 Efficacy Analysis

For the 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). P-values will be reported as 2-sided.

9.5.1.1 Change from Baseline in Morning Pre-dose Trough FEV_1

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, and 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. Baseline is defined as the average of the non-missing 60 minute and 30 minute values obtained prior to dosing at Visit 4. An unstructured covariance model will be used to model variability across time within each subject. If this model fails to converge, an AR (1) structure will be used instead; for this model, subject will be included as a random effect. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be produced for each treatment difference. The analysis will assess the treatment effects over the entire 52 weeks of treatment, i.e. subject data from the first 24 weeks of Study PT010006 will be included in the analyses.

Additional supportive analyses of morning pre-dose trough FEV_1 will include treatment differences at individual time points estimated by the RM model.

9.5.1.2 Rescue Ventolin HFA Use

The number of puffs of rescue Ventolin HFA taken in the previous 12 hours will be recorded in the subject diary in the morning and evening. For every period of time for which the mean number of puffs of rescue will be calculated, missing values will be ignored in both the numerator and denominator. As such, the denominator will be adjusted based on the number of days (including half days) with non-missing values.

The mean change from baseline in rescue use will be summarized by treatment group over 52 weeks and over each post-randomization 4-week interval (Interval 1 to Interval 13).

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

As a supportive analysis, percentage of days with ‘no rescue Ventolin HFA use’ over 52 weeks will be summarized using descriptive statistics. A ‘day with no rescue use’ is defined using rescue Ventolin HFA usage data from days where rescue Ventolin HFA usage data is non-missing as any day where the subject reported no puffs of rescue Ventolin HFA.

9.5.1.4 Chronic Obstructive Pulmonary Disease Exacerbations

The rate of moderate or severe COPD exacerbations will be summarized by treatment group. 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. 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. The rate of COPD exacerbations of any severity will be presented in a similar manner.

<u>Duration of COPD Exacerbation</u>

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.

9.5.1.5 Other Spirometry Analyses

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 9.5.1. Treatment differences in the change from baseline in pre-dose trough FVC, PEFR, and FEF_{25-75} will be evaluated in a similar manner to the pre-dose trough FEV_1.

9.5.1.6 Exacerbations of Chronic Pulmonary Disease Tool (EXACT)

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 E-RS is an 11-item subset which will be used to measure the effect of treatment on the severity of respiratory symptoms. Mean change from baseline in: the daily EXACT Total Score, the daily total symptom score (RS-Total Score), as well as 3 subscale scores, RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms, will be calculated over each 4-week interval of the 52-week Treatment Period. The last 7 days of the Screening Period from lead-in Study PT010006 will be used to calculate the baseline. The mean change from baseline in RS-Total Score, RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms will be summarized by treatment group over 52 weeks and over each post-randomization 4-week interval (Interval 1 to Interval 13).

9.5.2 Type I Error Control

Since the primary objective of this extension study is the evaluation of safety, no additional controls of type I error are planned.

9.6 Randomization

All randomization will be conducted in Study PT010006. No further randomization will be done in Study PT010007.

9.7 Experimental Design

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

9.8 Sample Size Consideration

The sample size of 324 subjects [redacted] includes all Japanese subjects who were enrolled in Study PT010006. The sample size was not calculated to achieve statistical power but was selected to provide approximately 100 completing subjects in the BGF MDI and GFF MDI arms.

9.9 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 efficacy results.

9.10 Analysis Plan

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

9.11 Handling of Missing Data

Missing data will not be imputed, only observed data will be used.

9.12 Statistical Software

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

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

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

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

This clinical study complies with:

- the standards described in Article 14, Paragraph 3, and Article 80-2 of the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices (commonly called the Drugs and Medical Devices Law),
- the ordinances and related laws and regulations regarding good clinical practices (J-GCP), and
- the Good Clinical Practice (GCP) prescribed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH),
- and it will be conducted in accordance with the ethical principles of the EU Directive (2001/20/EC), U.S. Code of Federal Regulations Title 21, Part 50 (21CFR50), and the J-GCP.

The clinical study will be conducted in accordance with GCP. These standards respect the following guidelines:

- Guideline for GCP E6 (R1): Consolidated Guideline [ICH 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 and the Sponsor 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, 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, or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/CRF 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/CRF 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 privacy laws (i.e., Health Insurance Portability and Accountability Act; Unlawful Disclosure of Confidential Information), 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 Therapeutics.

10.8 Study Monitoring

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

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

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

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

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

After the final review of the study files, the files should be secured for the appropriate time period as specified in Section 10.9. The investigator will also permit inspection of the study files by Pearl Therapeutics' 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.

The Head of the Medical Institution implementing the clinical study shall appropriately retain documents and records related to the study that should be retained, including records and source documents, for three years following the date the marketing and manufacturing approval for the pharmaceutical related to the test drug is received or the date that the study is terminated or ends, whichever is latest. Moreover, based on the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices, if the pharmaceutical related to the test drug receives approval, the study sponsor shall retain these records appropriately for five years from the date that the recipient of the approval received the approval (in the case of a review which exceeds five years from the date the approval was received, until the time the review ends), and shall retain the records for a period decided upon with the sponsor.

10.10 Financial Disclosure

The Principal Investigator or sub-Investigators named on the Form FDA 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 Head of the Medical Institution 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 ISMPP. 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.

11 REFERENCE LIST

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12 APPENDICES

Appendix 1 Spirometry Performance Recommendations

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

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

FEV_1 AND FVC MANEUVERS

Equipment Requirements

The spirometer must be capable of accumulating volume for >15 s (longer times are recommended) and measuring volumes of >8 L (body temperature (i.e., 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 $L\text{-}s^{-1}$. The total resistance to airflow at 14.0 $L\text{-}s^{-1}$ must be <1.5 $cmH_2O\ L^{-1}s^{-1}$ (0.15 $kPa\ L^{-1}s^{-1}$). The total resistance must be measured with any tubing, valves, pre-filter, etc. included that may be inserted between the subject and the spirometer. Some devices may exhibit changes in resistance due to water vapor condensation, and accuracy requirements must be met under BTPS conditions for up to 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 trials, the sequencing of the blows should be apparent to the user. For the start of test display, the volume–time display should include >0.25 s, and preferably 1 s, before exhalation starts (zero volume). This time period before there is any change in volume is needed to calculate the back extrapolated volume (EV) and to evaluate effort during the initial portion of the maneuver. Time zero, as defined by EV, must be presented as the zero

point on the graphical output. The last 2 s of the maneuver should be displayed to indicate a satisfactory end of test.

When a volume–time curve is plotted as hardcopy, the volume scale must be >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 (e.g., industrial surveys), calibration checks and quality-control procedures must be repeated before further testing begins.

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

Table A1-2 Summary of Equipment Quality Control

Test	Minimal Interval	Action
Volume	Daily	Calibration check with a 3 L syringe
Leak	Daily	2 cm H_2O (0.3 kPa) constant pressure for 1 minute
Volume Linearity	Quarterly	1 L increments with a calibrating syringe measured over the entire volume range
Flow Linearity	Weekly	Test at least three different flow ranges
Time	Quarterly	Mechanical recorder check with stop watch
Software	New versions	Log installation date and perform test using "known" subject

Calibration is the procedure for establishing the relationship between sensor-determined values of flow or volume and the actual flow or volume. A calibration check is different from calibration and is the procedure used to validate that the device is within calibration limits, e.g., +3% of true. If a device fails its calibration check, then 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 (e.g., monthly) leak tested at more than one volume up to their maximum; this can be done by attempting to empty them with the outlet corked. A dropped or damaged syringe should be considered out of calibration until it is checked.

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

Quality Control for Volume-Measuring Devices

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

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

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

Volume-type spirometer systems must be evaluated for leaks every day. The importance of undertaking this daily test cannot be overstressed. Leaks can be detected by applying a constant positive pressure of >3.0 cmH_2O (0.3 kPa) with the spirometer outlet occluded (preferably at or including the mouthpiece). Any observed volume loss of 0.30 mL after 1 minute indicates a leak and needs to be corrected.

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

Quality Control for Flow-Measuring Devices

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

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

VC AND IC MANEUVERS

Equipment

For measurements of VC and IC, the spirometer or flow meter must comply with the requirements for FVC (as described previously) and be capable of accumulating volume for >30 s. Expiratory maneuvers or, ideally, both inspiratory and expiratory maneuvers should be included in the display of VC maneuver. Regardless of whether the inspiratory or expiratory

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

TECHNICAL CONSIDERATIONS

Minimal recommendations for spirometry systems

Accurate results require accurate equipment. Spirometer equipment recommendations apply to all spirometers and are minimal requirements. In some circumstances, it may be appropriate to exceed these requirements (i.e., in some research/surveillance applications). Instrumentation recommendations should be followed to provide accurate spirometric data and information that is comparable from laboratory to laboratory and from one time period to another. The accuracy of a spirometry system depends on characteristics of the entire system, from the volume or flow transducer and the use of an in-line filter, to the recorder, display or processor. Changes in any aspect of the equipment or errors at any step in the process can affect the accuracy of the results. For example, if the BTPS correction factor is wrong, an accurately measured FVC will be incorrectly reported. Spirometers are not required to measure all of the indices in Table A1-3, 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 2 Spirometry Assessment Criteria

Acceptable Versus Usable Tests

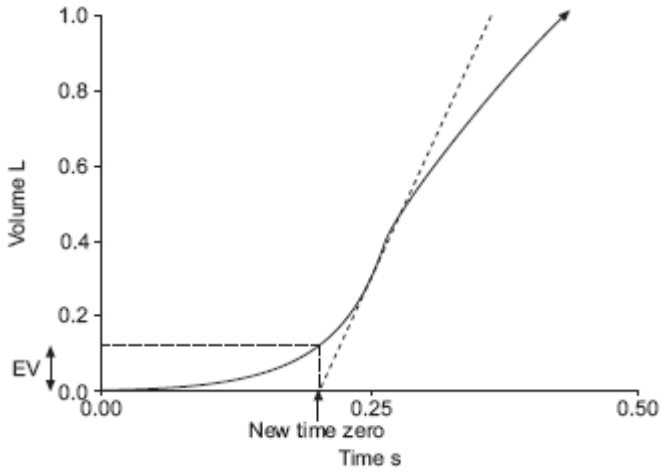
***Acceptable* Tests must meet the following 7 Criteria:**

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

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

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

Figure A2-1 Example of a Usable Spirogram



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

Between-Maneuver Reproducibility Criteria

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

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

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

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

Appendix 3 Subject Instructions for Use of 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**.

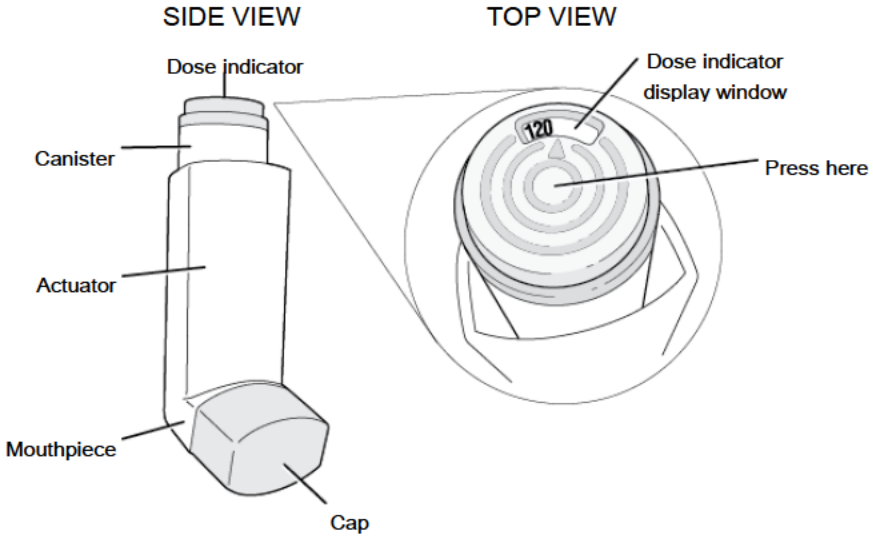


Figure 1

- 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.

Figure 2a
120 puffs

Figure 2b
110 puffs

Figure 2c
100 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**

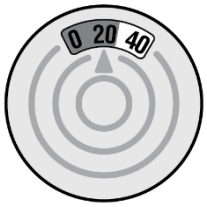


Figure 2d

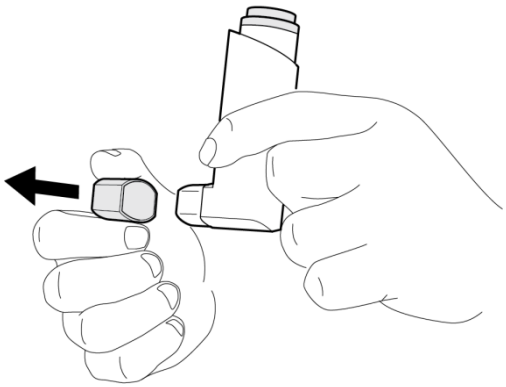
20 puffs

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.

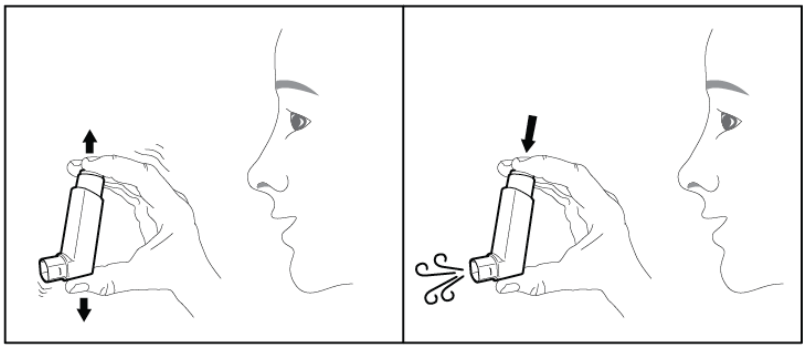


Figure 4a **Figure 4b**

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**.

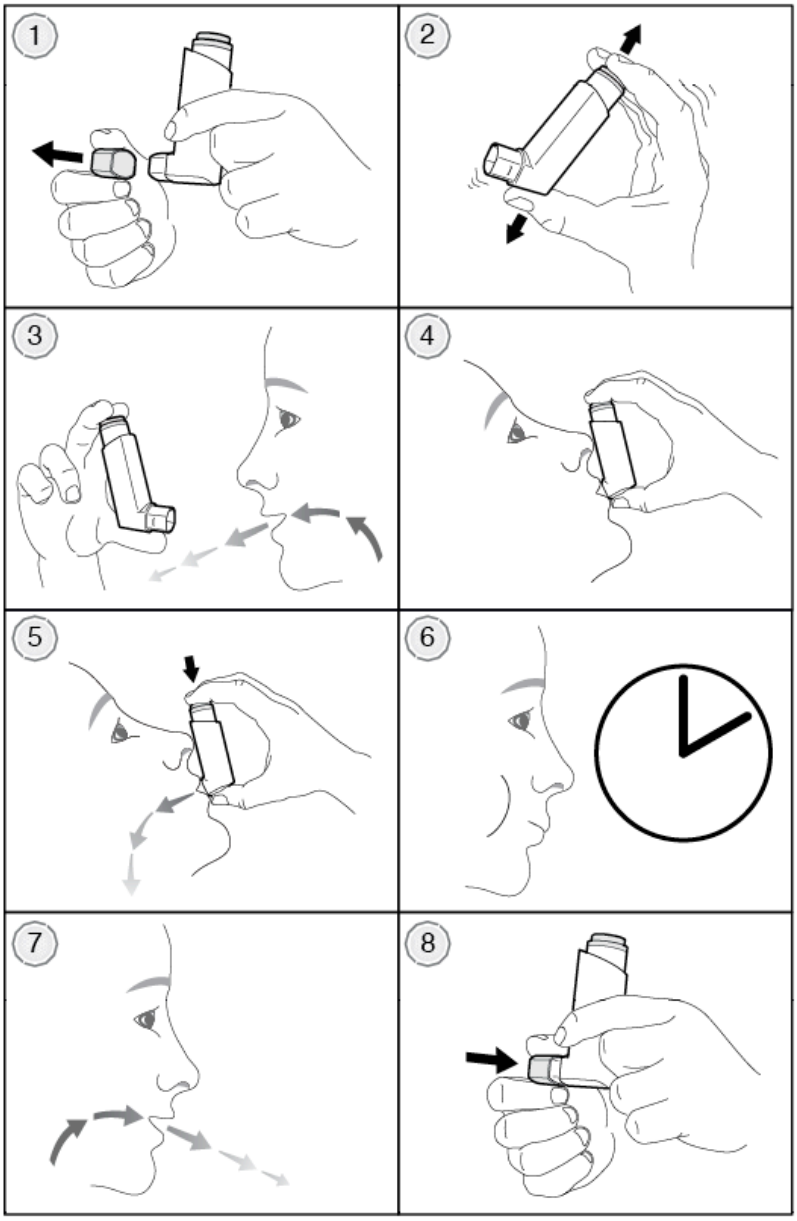


Figure 5

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.**

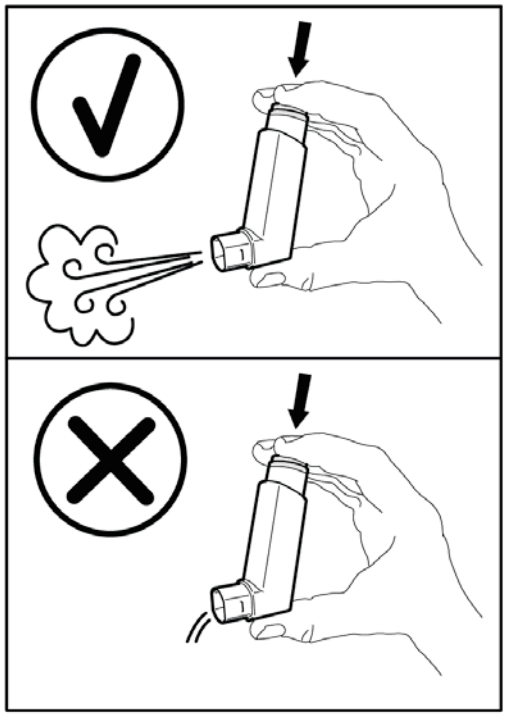
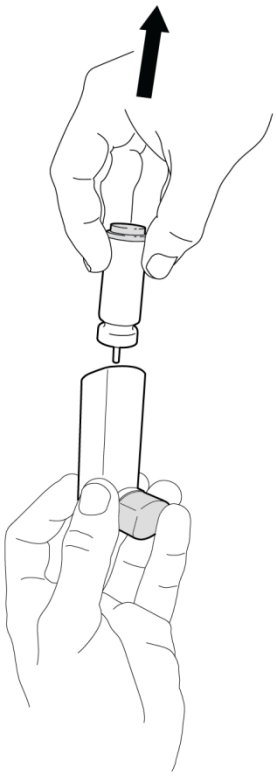


Figure 6

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**).

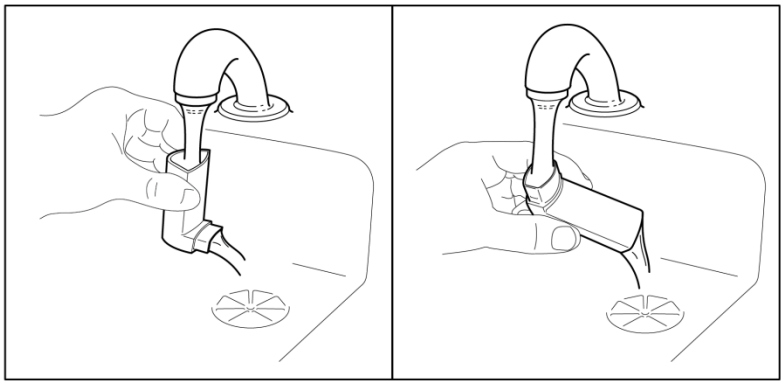


Figure 8

- **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.

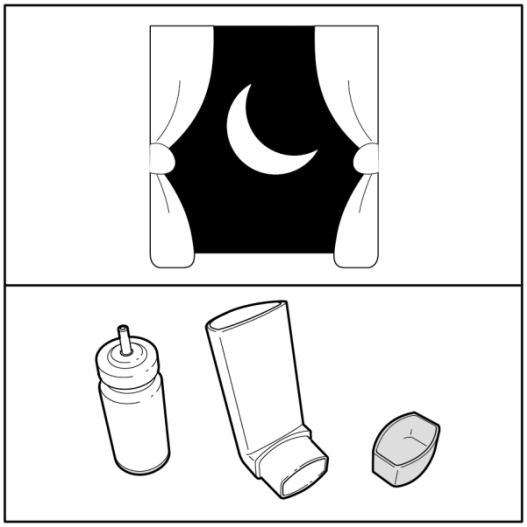


Figure 9

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.

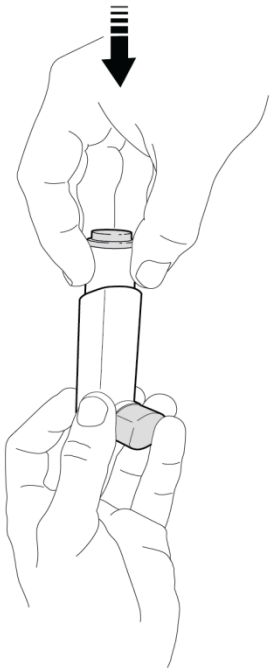


Figure 10

- 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 4 Instructions for Use of Symbicort Turbuhaler® Inhalation Powder Device

Preparing your new Symbicort Turbuhaler:

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 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.**

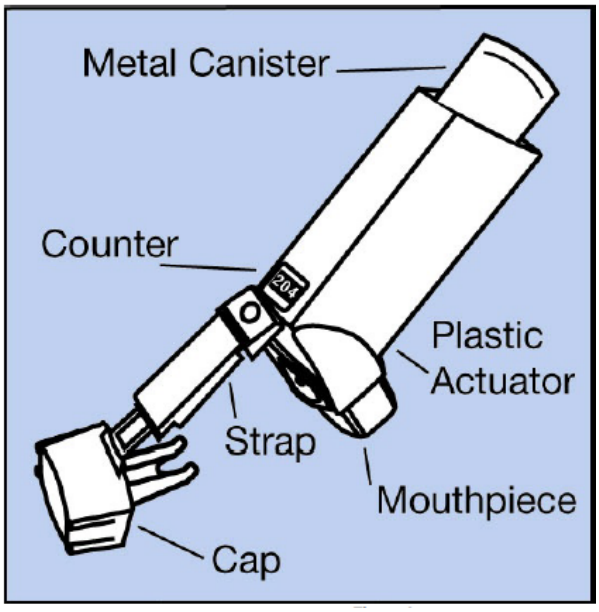


Figure A

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**.

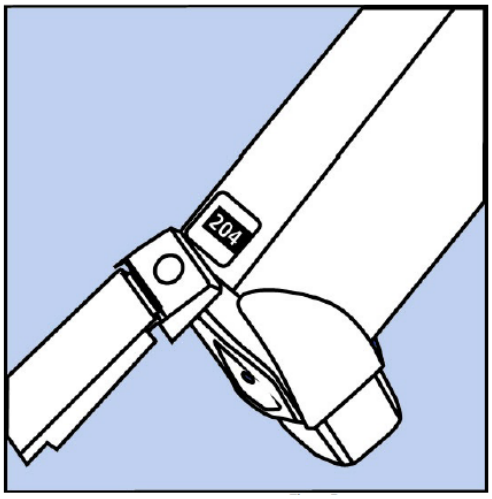


Figure B

- 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**.

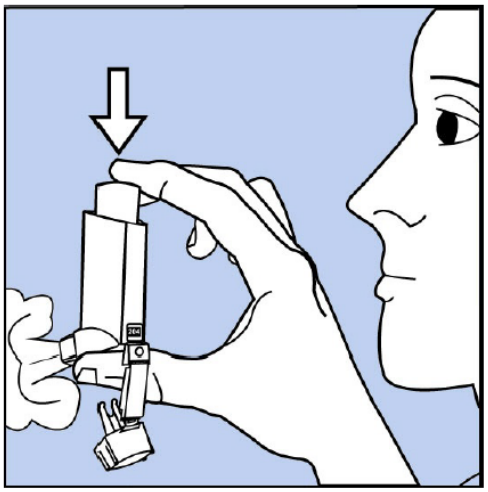


Figure C

- 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**.

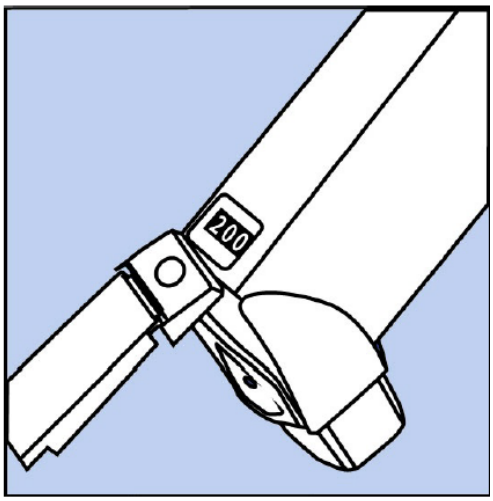


Figure D

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**.

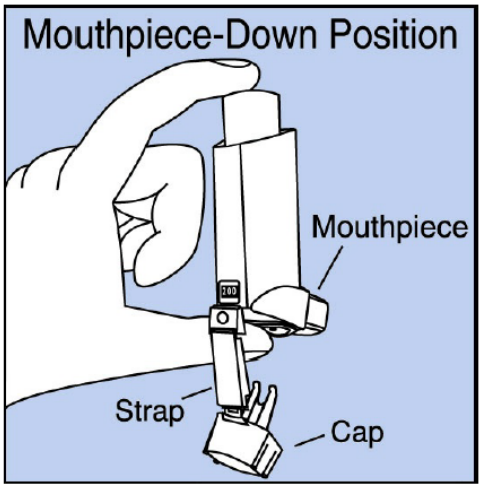


Figure E

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**.

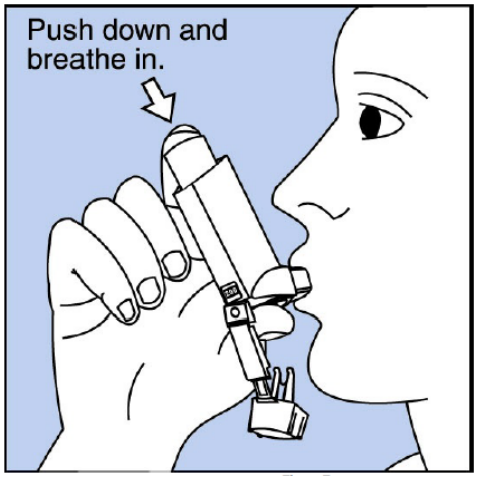


Figure F

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 as 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**.

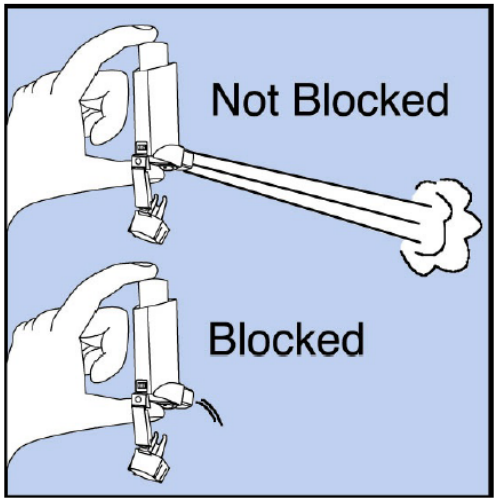


Figure G

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**.

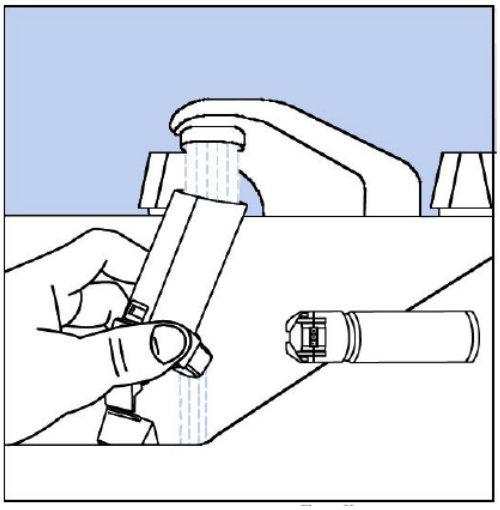


Figure H

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

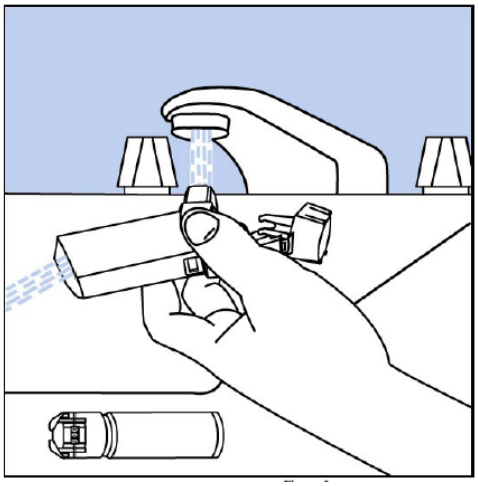


Figure I

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**.

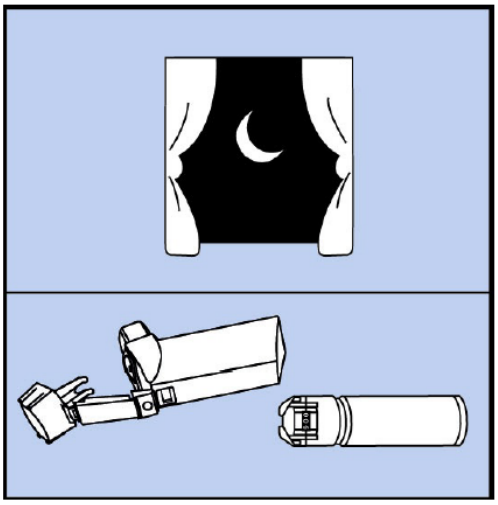


Figure J

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 Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT) - Patient-Reported Outcomes

(The sample provided here is for illustrative purposes only)

EXACT version 1.1 English (Universal)

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

Description	Required Text	Translation
	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?
	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

Description	Required Text	Translation
	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
	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		

Description	Required Text	Translation
	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		
	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
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

Description	Required Text	Translation
	Extremely	Extremely
Copyright	EXACT© 2013, Evidera, Inc. All rights reserved.	EXACT© 2013, Evidera, Inc. All rights reserved.

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 7 Hy's Law

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 with TBL ≥2x ULN at any point during the study irrespective of an increase in alkaline phosphatase (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 with 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:

- 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 8 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 9 Sponsor Signatory

Study Title: A Randomized, Double-blind, Parallel Group, 28-Week Chronic Dosing, Multi-Center Extension Study to Assess the Safety and Efficacy of PT010, PT003, and PT009 in Japanese Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) compared with Symbicort® Turbuhaler® as an Active Control

Study Number: PT010007-01

Final Date: 17 March 2017

This clinical study protocol was subject to critical review and has been approved by the sponsor.

Signed: [redacted]

Appendix 10 Investigator's Agreement and Signature Page

Study Title: A Randomized, Double-blind, Parallel Group, 28-Week Chronic Dosing, Multi-Center Extension Study to Assess the Safety and Efficacy of PT010, PT003, and PT009 in Japanese Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) compared with Symbicort® Turbuhaler® as an Active Control

Study Number: PT010007-01

Final Date: 17 March 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
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the IRB/IEC, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements)
- That I am aware of, and will comply with good clinical practices (GCP) and all applicable regulatory requirements
- That I am thoroughly familiar with the appropriate use of the investigational product(s), and other information provided by the Sponsor including, but not limited to, the following: the protocol and the current Investigator's Brochure (IB)
- To ensure that all persons assisting me with the study are qualified, adequately informed about the investigational product(s) and of their study-related duties and functions
- To supply Pearl Therapeutic with any necessary information regarding ownership interest and financial ties; to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and agree that Pearl Therapeutics may disclose any information it has about such ownership interests and financial ties to regulatory authorities
- I agree to report all information or data in accordance with the protocol and any other study conduct procedures provided by Pearl Therapeutics
- That since the information in this protocol and IB is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision or conduct of the study is prohibited
- To accurately transfer all required data from each subject's source document to the case report forms (CRFs). The CRFs will be provided to the sponsor in a timely manner at the completion of the study, or as otherwise specified by the sponsor
- To allow authorized representatives of Pearl Therapeutics or regulatory authority representatives to conduct on-site visits to review, audit and copy study documents. I will personally meet with these representatives to answer any study-related questions
-

Signature: _____ Date: _____

Name: _____

Site Name: _____