AstraZeneca

Revised Clinical Study Protocol

Study Code	PT009002
NCT #	NCT02766608
EudraCT	2016-000154-34

A Randomized, Double-Blind, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT009 Compared to PT005, PT008, and Open-label Symbicort® Turbuhaler®, as an Active Control, on Lung Function over a 24-Week Treatment Period in Subjects With Moderate to Very Severe COPD

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

Amendment No.	Date of Amendment
Version 1	08 March 2016
Version 2, Amendment 1	01 July 2016
Version 3, Amendment 2	24 October 2017

Clinical Trial Protocol: PT009002-02

Study Title:	A Randomized, Double-Blind, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT009 Compared to PT005, PT008, and Open-label Symbicort® Turbuhaler®, as an Active Control, on Lung Function over a 24-Week Treatment Period in Subjects With Moderate to Very Severe COPD
Study Number:	PT009002
Study Phase:	III
Product Name:	Budesonide and Formoterol Fumarate Inhalation Aerosol (PT009, BFF MDI) Formoterol Fumarate Inhalation Aerosol (PT005, FF MDI) Budesonide Inhalation Aerosol (PT008, BD MDI) Symbicort® Turbuhaler® (TBH) Inhalation Powder
US IND Number:	122166
EudraCT Number:	2016-000154-34
Indication:	Chronic Obstructive Pulmonary Disease (COPD)
Investigators:	Multicenter
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]

	Version Number	Date
Original Protocol	Version 1.0	[redacted]
Amended Protocol	Version 2.0	[redacted]
Amended Protocol	Version 3.0	[redacted]

SUMMARY OF CHANGES TO AMENDED PROTOCOL PT009002-01 VERSION 2.0, DATED [redacted]

The current amended study protocol, PT009002-02 (Version 3.0), includes the following edits:

Section(s)/Description of Change	Rationale
Changes to the protocol objectives: Synopsis/Section 2.2 • Amendment adds COPD exacerbations to the list of secondary objectives.	• The evaluation of COPD exacerbations was elevated to secondary objective status to align across the PT009 and PT010 COPD development programs.
Changes regarding "time to 1st moderate or severe COPD exacerbation" endpoint: Synopsis/Sections 3.2 and 9.3.2.1 • New text elevates "time to 1st moderate or severe COPD exacerbation" to be a secondary efficacy endpoint. Sections 3.3 and 9.3.3.4 • Amendment removes time to 1st moderate or severe COPD exacerbation as an "other" efficacy endpoint.	• Exacerbations are an important clinical endpoint and are evaluated as a secondary endpoint to align across the PT009 and PT010 COPD development programs. There is sufficient sample size to observe a possible numerical benefit in the form of a trend, even though the study is not optimized to demonstrate statistical significance.
Changes regarding "time to 1st clinically important deterioration" and sustained deterioration endpoints: Sections 3.2 and 9.3.2.2 • New text elevates "time to 1st clinically important deterioration" as a secondary endpoint in the EU regulatory approach. Sections 3.3 and 9.3.3.4 • New text adds "Time to CID" and "Time to sustained CID" to the list of other efficacy endpoints.	• The composite endpoint of clinically important deterioration (CID) is now commonly reported in COPD studies and may be a more accurate measure of decline in disease status than individual CID component measurements. • Time to CID is an "other" efficacy endpoint in the US regulatory approach. Time to sustained CID is an "other" efficacy endpoint in all regulatory approaches. Both composite endpoints may be more accurate measures of decline in disease status than individual CID component measurements.
Changes regarding EXACT and RS-Total Score endpoints: Sections 3.2 • Amendment removes EXACT Total Score as a secondary endpoint in the EU regulatory	• The RS-Total Score is a more relevant clinical endpoint than the EXACT Total Score in this

approach. Sections 3.2 and 9.3.2.8 • New text elevates Evaluating Respiratory Symptoms in COPD (E-RS: COPD) total score (RS-Total Score) as a secondary endpoint in the EU regulatory approach.	lung function study.
Synopsis/Sections 3, 3.1, 3.2, 9.3.1.1, 9.3.1.2, 9.3.2.3, 9.3.2.4, 9.3.2.5, 9.3.2.6, 9.3.2.7. 9.3.2.8, 9.3.2.9, 9.3.4, and 9.9 • Amendment removes references to the Japan Regulatory Approach.	Japan is not participating in the study.
Sections 3.1, 3.2, 9.3.1.1, 9.3.1.2, 9.3.2.3, 9.3.2.7, 9.3.2.8, and 9.3.4.2 • Amendment clarifies that non-inferiority comparisons to Symbicort TBH will only be performed for BFF MDI 320/9.6µg.	BFF MDI 320/9.6 µg is the treatment with an ICS dose that is nominally comparable to the ICS dose in Symbicort TBH.
Synopsis/Section 3.6 • New text identifies FEV_1 AUC_{0-12} as the primary endpoint in the PFT sub-study. • All other spirometry parameters are now identified as "other endpoints".	FEV_1 AUC_{0-12} is the most important spirometry parameter collected in the PFT sub-study. This change differentiates it from the other spirometry parameters.
Synopsis/Section 3.6 • Amendment removes AUC_{0-6}, AUC_{6-12}, and time to peak observed value as parameters of interest from the PFT sub-study.	Differentiating between treatment groups in these parameters is of lesser clinical importance. The planned analyses will retain the analyses of AUC_{0-12} and peak value between treatment groups.
Sections 3.3 and 9.3.3.4 • New text clarifies that "Time to discontinuation" is "Time to treatment discontinuation".	This change was made to clarify the endpoint in question.
Sections 3.3, 7.1.3.5, and 9.3.3.5 • Amendment renames "EXACT 11-item Respiratory Symptoms Total Score" to be "Evaluating Respiratory Symptoms in COPD (E-RS: COPD) Total Score".	This change was made to reflect the current name of instrument.
Section 3.5 • New text clarifies that "the number of days missed from work" pertains to the number of days	The list of HCRU endpoints was updated to align

missed due to COPD. • New text for some HCRU endpoints indicates that a category for "any health-care provider" will be created in addition to existing categories. • New text indicates that time spent (or not spent) in either the ICU or CCU will be summarized for some HCRU endpoints.	across the PT009 and PT010 development programs.
Section 7.3.7.3 and 7.3.8 • Changed the terms "Pneumonia Adjudication Committee" and "CCV and Mortality Adjudication Committees" to be "Clinical Endpoint Committee".	New text clarifies the current name of the committee.

Sections 9.3.1.1 and 9.3.1.2
 	
• New text clarifies the following:
  • The efficacy estimand will be the primary analysis for superiority
  • The per protocol estimand will be the primary analysis for non-inferiority
  • The attributable estimand will be a secondary analysis
  • The treatment policy estimand will be a supportive analysis
	New text clarifies the relationship between the estimands and the analysis populations.

Sections 9.3.2.2 and 9.3.3.4 • New text makes reference to and provides the technical definitions of the terms "clinically important deterioration" and "sustained clinically important deterioration," respectively.	Both CID and sustained CID are composite endpoints that require definition.
Section 9.3.2.10 • New text changes the analysis of time to onset of action on Day 1 to be a formal comparison to BD MDI.	Since BD MDI is not expected to produce bonchodilator effects immediately on Day 1, it will be used as an active control in this analysis.
Section 9.3.3.4 • New text clarifies that the analysis of time to death is conditional on observing 30 or more deaths in the study.	A minimum number of events is needed to fit the model and to provide a reasonable estimate of the hazard ratio. If "Death" is not analyzed for efficacy, it will be evaluated descriptively for safety.
Section 9.3.3.8 • New text clarifies the general summarization strategy for the EQ-5D-5L data.	New text clarifies the current summarization strategy for this instrument.

Section 9.3.4 • New text for section 9.3.4 revamps the Type I Error control strategy to account for new secondary endpoints and the analysis of the primary endpoints under the attributable estimand. It also removes the non-inferiority comparisons of BFF MDI 160/9.6 µg vs Symbicort TBH.	New secondary endpoints and the need to include the analysis of the primary endpoint as a first secondary endpoint for the attributable estimand required a new Type I error control strategy.
Section 9.4.1.4 • New text defines baseline ECG as the average of the pre-dose measurements taken prior to treatment at the randomization visit.	Baseline ECG was defined as the most recent pre-treatment ECG at the randomization visit. This new definition accounts for both pre-treatment ECG measurements at the randomization visit.
Section 9.5 • New text allows for the possibility of performing additional analyses of the HCRU data beyond descriptive summaries.	Additional analyses of the HCRU data may be performed beyond descriptive summaries.
Section 9.12 • Section 9.12 was renamed to be "Analysis Populations and Estimands" • Two subsections were created under Section 9.12. Sections 9.12.1 and 9.12.2 were created to define "analysis populations" and "estimands," respectively. Section 9.12.1 contains the text from Section 9.12 under the previous amendment. • Language was added to the beginning of Section 9.3 to reference Section 9.12.	This section was reconfigured to describe both estimands and analysis populations in the same section.
Section 9.12.1 • New text clarifies that the mITT population will be the primary efficacy analysis population with the exception of non-inferiority analyses, where the PP population will be the primary population for analysis. • New text defines a Rescue Ventolin User (RVU) population. • New text for the per protocol and safety populations was inserted.	• The primary analysis population for non-inferiority analyses is typically the per-protocol population. • Due to the expectation that some subjects will not be taking rescue medication at baseline and hence not be capable of improving with treatment, the RVU population is defined and will be used in the evaluation of rescue medication usage. • New text for the per protocol and safety populations is inserted to make the definition consistent across the clinical development program, which resulted in no material change in

• The amendment replaces the wording that communicates what analyses will be performed in what populations. The new text is more detailed and includes the RVU population.	the definition. • New text makes it easier to understand what analyses will be performed in what populations.
Section 9.12.2 • This new section defines the estimands to be used in the study.	This new section was inserted to communicate what estimands will be used in the analysis of the clinical trial data.
Section 9.13 This new section describes the subgroup analyses to be performed.	This new section clarifies the pre-specified subgroup analyses in the study.
Other administrative changes to correct and/or clarify protocol language were also addressed. These changes included edits for consistency, grammar, and typographical errors, which are not summarized in this table.	

SYNOPSIS

Sponsor Pearl Therapeutics, Inc. (Pearl) [redacted]
Name of Finished Product Budesonide and Formoterol Fumarate Inhalation Aerosol (PT009, BFF MDI) Formoterol Fumarate Inhalation Aerosol (PT005, FF MDI) Budesonide Inhalation Aerosol (PT008, BD MDI) Symbicort® Turbuhaler® (TBH) Inhalation Powder
Name of Active Ingredient(s) Budesonide and Formoterol Fumarate Formoterol Fumarate Budesonide
Study Title A Randomized, Double-Blind, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT009 Compared to PT005, PT008, and Open-label Symbicort® Turbuhaler®, as an Active Control, on Lung Function over a 24-Week Treatment Period in Subjects with Moderate to Very Severe COPD
Study Number: PT009002-02
Study Phase: III
Primary Objectives • To assess the effects of BFF MDI relative to FF MDI and BD MDI on lung function
Secondary Objectives • To assess the effects of BFF MDI relative to FF MDI and Symbicort TBH on COPD exacerbations • To assess the effects of BFF MDI relative to FF MDI, BD MDI, and Symbicort® TBH on symptoms of COPD • To assess the effects of BFF MDI relative to FF MDI, BD MDI, and Symbicort® TBH on quality of life • To determine the time to onset of action on Day 1
Safety Objective • To assess the safety of BFF MDI, FF MDI, BD MDI, and Symbicort® TBH
Pulmonary Function Test (PFT) Sub-Study Objective • To characterize FEV_1 over 12 hours at Week 12
Study Population Approximately 2,420 subjects with moderate to very severe COPD will be enrolled to provide roughly 1,900 completed subjects. This study will be conducted in approximately

200 sites with each site enrolling 10 to 14 subjects.

To be eligible for the study, subjects must:

- be receiving one or more inhaled maintenance bronchodilators at Visit 1
- not be receiving ICS, LABA, and LAMA (as inhaled triple maintenance therapy) within 30 days of Visit 1
- be symptomatic (CAT score ≥ 10) at Visit 1
- exhibit post-bronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ of the predicted normal value calculated using appropriate reference equations at Visit 2
  - if post-bronchodilator percent predicted FEV_1 is < 30% then FEV_1 must be ≥ 750 ml

A history of exacerbations in the prior year will be obtained to characterize the population, but the entry criteria do not require an exacerbation in the prior year. FEV_1 reversibility to Ventolin will be used for characterization and stratification purposes only and not for determining study eligibility.

Study Design

This is a Phase III randomized, double-blind, parallel group, multi-center, 24-week lung function study with BFF MDI (320/9.6 µg and 160/9.6 µg) compared to FF MDI 9.6 µg, BD MDI 320 µg, and open-label Symbicort® TBH (400/12 µg) administered BID.

Subjects will undergo a 1- to 4-week Screening Period.

At Visit 1, subjects receiving an ICS/LABA will discontinue the ICS/LABA, but continue the ICS component for the remainder of the Screening Period. Similarly, subjects treated with an ICS as part of their inhaled maintenance therapy will continue their ICS for the remainder of the Screening Period. ICS medications will be discontinued at Randomization.

All subjects will be placed on Sponsor-provided Ventolin® HFA (albuterol sulfate inhalation aerosol) for rescue use throughout Screening and Randomized Treatment Periods.

In order to allow for adequate washout of previous COPD maintenance medications, subjects will undergo a Washout Period of one week or longer, depending on their specific medication(s), but no greater than 26 days prior to returning to clinic for Visit 2.

Subjects who successfully complete the Screening Period will be randomized in a 3:3:3:1:1 scheme to one of the following five treatment groups:

- BFF MDI 320/9.6 µg BID (N=660)
- BFF MDI 160/9.6 µg BID (N=660)
- FF MDI 9.6 µg BID (N=660)
- BD MDI 320 µg BID (N=220)
- Symbicort® TBH 400/12 µg BID (open-label; N=220)

Randomization will be stratified by reversibility to Ventolin (measured at Visit 2), post-bronchodilator FEV_1 (< 50% or 50% to < 80% predicted, measured at Visit 2), blood eosinophil count (< 150 or ≥ 150 cells per mm^3), and country. Enrollment will be targeted to achieve a 2:1 ratio for the blood eosinophil strata with twice as many randomized subjects in the ≥ 150 cells per mm^3 category. Following randomization, subjects will enter the Treatment Period and undergo 6 additional treatment visits over 24 weeks.

Subjects who discontinue study treatment prior to the end of study (Week 24, Visit 9) will be

encouraged to remain in the study to complete all remaining study visits. Subjects participating in the Pulmonary Function Test (PFT) Sub-Study who choose to discontinue from treatment will only complete regularly scheduled assessments and not complete any remaining Sub-Study assessments.

Pulmonary Function Test (PFT) Sub-Study

A total of 510 subjects (153 from each of the BFF MDI arms and the FF MDI arm and 51 from the BD MDI arm) will be enrolled in the PFT Sub-Study where 12-hour lung function data will be collected at Week 12 (Visit 6) only.

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
Blinded Study Medications			
BFF MDI 320/9.6 µg	160/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
BFF MDI 160/9.6 µg	80/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
FF MDI 9.6 µg	4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
BD MDI 320 µg	160 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
Open-Label Products			
Albuterol Sulfate inhalation aerosol 90 µg[a]	Ventolin® HFA[b] Each inhalation contains 108 µg albuterol sulfate corresponding to 90 µg albuterol base	MDI/ 60 or 200 inhalations	4 inhalations for reversibility testing at Visit 2 Taken as needed throughout Screening and Treatment Periods
Budesonide and formoterol fumarate inhalation powder 400/12 µg	Symbicort® TBH[c] 200/6 µg per actuation Each inhalation contains 200 µg budesonide and 6 µg formoterol fumarate dihydrate corresponding to a delivered dose of 160 µg budesonide and 4.5 µg formoterol fumarate dihydrate	DPI/ 120 inhalations	Taken as 2 inhalations BID

BFF MDI = Budesonide and Formoterol Fumarate Inhalation Aerosol; BID = Twice Daily; FF MDI = Formoterol Fumarate Inhalation Aerosol; HFA = Hydrofluoroalkane; MDI = Metered Dose Inhaler; TBH = Turbuhaler

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

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

[c] Active Control. Symbicort Turbuhaler is also known as Symbicort Turbohaler in some countries.

Duration of Treatment

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

Duration of Study

The entire study period is expected to range between 27 to 30 weeks for each subject. The study is anticipated to last approximately 18 months.

Efficacy Endpoints (US Approach)

Additional efficacy endpoints, including those for the EU approach, are described in Section 3.

Primary Efficacy Endpoints

- Change from baseline in morning pre-dose trough FEV_1 at Week 24 (BFF MDI vs FF MDI)
- Change from baseline in FEV_1 AUC_{0-4} at Week 24 (BFF MDI vs BD MDI)

Secondary Efficacy Endpoints

- Time to first moderate or severe COPD exacerbation (BFF MDI vs FF MDI)
- Percentage of subjects achieving an MCID of 4 units or more in Saint George's Respiratory Questionnaire (SGRQ) total score at Week 24 (BFF MDI vs FF MDI; BFF MDI vs BD MDI)
- Change from baseline in morning pre-dose trough FEV_1 at Week 24 (BFF MDI vs BD MDI)
- Peak change from baseline in FEV_1 at Week 24 (BFF MDI vs BD MDI)
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks (BFF MDI vs BD MDI)
- Time to onset of action on Day 1 (BFF MDI vs BD MDI)

Safety Endpoints

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

PFT Sub-study Endpoints (at Week 12 only)

Primary Endpoint

- FEV_1 AUC_{0-12}

Other Endpoints

- Peak FEV_1
- FVC, PEFR, and FEF_{25-75} will be evaluated using AUC_{0-12} and at peak

Statistical Methods

Primary Efficacy Analysis

The primary analysis will be conducted on the mITT Population. The change from baseline in morning pre-dose trough FEV_1 will be analyzed using linear repeated measures ANCOVA model. The model will include treatment, visit, treatment-by-visit interaction, screening eosinophil category, and ICS use at Screening as categorical covariates and baseline FEV_1 and percent reversibility to Ventolin as continuous covariates. All primary analysis comparisons will be for superiority. Analyses of FEV_1 AUC_{0-4} will use a similar model to trough FEV_1.

Sample Size

For trough FEV_1, a standard deviation (SD) of 200 mL for the change from baseline at Week 24 has been assumed. A SD of 220 mL for FEV_1 AUC_{0-4} at Week 24 is assumed.

US Approach

It is estimated that a sample size of 2,420 subjects (660 per arm in the BFF MDI [320/9.6 µg and 160/9.6 µg] and FF MDI groups; and 220 per arm in the BD MDI and Symbicort TBH groups) will provide approximately 90% power to detect a difference of 40 mL between BFF MDI and FF MDI in change from baseline, and in morning pre-dose trough FEV_1 at Week 24 with Type I error controlled at a two-sided alpha level of 0.05, and approximately 99% power to detect a difference between BFF MDI and BD MDI of 100 mL in change from baseline in FEV_1 AUC_{0-4} at Week 24 with Type I error controlled at a two-sided alpha level of 0.05. The above calculations assume a 20% dropout rate.

Sample size rationale for the EU approach can be found in Section 9.

Data Monitoring Committee

An external Data Monitoring Committee (DMC) will be set up to provide systematic and unbiased assessment of safety data. Members of the DMC will review data at predetermined intervals. Based on the safety implications of the data, the DMC may recommend modification or termination of the study.

Clinical Endpoint Committee

A blinded, independent, external clinical endpoint committee (CEC) will be established 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:

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

Date of Original Approved Protocol: [redacted]

Date of Protocol Amendment 01 (Version 2.0): [redacted]

Date of Protocol Amendment 02 (Version 3.0): [redacted]

TABLE OF CONTENTS

LIST OF IN TEXT TABLES

LIST OF IN TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

λ_z	Terminal Elimination Rate Constant
AE	Adverse Event
AR(1)	Autoregressive Order 1
ATS	American Thoracic Society
AUC	Area Under the Curve
AUC_{0-2}	Area Under the Curve From 0 to 2 Hours
AUC_{0-6}	Area Under the Curve From 0 to 6 Hours
AUC_{0-12}	Area Under the Curve From 0 to 12 Hours
AUC_{6-12}	Area Under the Curve From 6 to 12 Hours
AUC_{0-t}	Area Under the Curve from 0 to Time of the Last Measurable Concentration
BD	Budesonide
BDI	Baseline Dyspnea Index
BFF	Budesonide and Formoterol Fumarate
BID	*Bis In Die*, Twice Daily
BP	Blood Pressure
BPM	Beats Per Minute
BTPS	Body Temperature and Pressure Saturated
CBC	Complete Blood Count
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CI	Confidence Interval
CID	Clinically Important Deterioration
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation (according to National Kidney Disease Education Program)
CL/F	Clearance
C_{max}	Maximum Plasma Concentration
CMP	Comprehensive Metabolic Panel
CONSORT	CONsolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease

CRF	Case Report Form
CT	Computerized Tomography
DBP	Diastolic Blood Pressure
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
e.g.	*Exempli Gratia*, For Example
ERS	European Respiratory Society
EV	Back Extrapolation Volume
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second
FF	Formoterol Fumarate
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
hCG	Human Chorionic Gonadotropin
HR	Heart Rate
HFA	Hydrofluoroalkane
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroid
ID	Identification
i.e.	*Id Est,* That Is
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISMPP	International Society for Medical Publications Professionals
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
L	Liter
LABA	Long-Acting β_2-Agonist

LAMA	Long-Acting Muscarinic Antagonist
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
mL	Milliliter
msec (ms)	Millisecond
NHANES III	Third National Health and Nutrition Examination Survey
OTC	Over-the-Counter
PEFR	Peak Expiratory Flow Rate
PIN	Personal Identification Number
PFT	Pulmonary Function Test
QTcF	QT Corrected Using Fridericia's Formula (QT/[RR $^{1/3}$])
RVU	Rescue Ventolin User
SABA	Short-Acting Beta 2 Agonist
SAC	Self-administered Computerized
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
$t_{½}$	Half-Life
TDI	Transition Dyspnea Index
t_{max}	Time of Maximum Plasma Concentration
US	United States
VC	Vital Capacity
Vd/F	Apparent Volume of Distribution

TRADEMARK INFORMATION

[redacted]

Symbicort®

Ventolin®

1 INTRODUCTION

Pearl Therapeutics, Inc. (Pearl) is developing a combination product, Budesonide and Formoterol Fumarate Inhalation Aerosol (PT009; hereafter referred to as budesonide and formoterol fumarate metered dose inhaler [BFF MDI]), as a long-term, twice daily (BID) treatment for subjects with chronic obstructive pulmonary disease (COPD). Pearl is also developing Formoterol Fumarate Inhalation Aerosol (PT005; hereafter referred to as formoterol fumarate metered dose inhaler [FF MDI]) as a BID maintenance treatment in subjects with COPD. In addition, Pearl is developing Budesonide Inhalation Aerosol (PT008; hereafter referred to as budesonide metered dose inhaler [BD MDI]).

1.1 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 lung and associated airways to noxious particles or gases. COPD is a leading cause of morbidity and mortality worldwide and results in a significant economic and social burden that is both substantial and increasing. [Global Initiative for Chronic Obstructive Lung Disease [GOLD 2016].

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are β_2-agonists and anticholinergics 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.

When combined with a long-acting β2-agonist (LABA), an inhaled corticosteroid (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. Regular treatment with ICS improves symptoms, lung function, and quality of life and reduces the frequency of COPD exacerbations in subjects with a forced expiratory volume in one second (FEV_1) value of <60% of predicted. Withdrawal from treatment of ICS may lead to exacerbations in some patients [GOLD 2016].

1.2 Pearl Therapeutics' BFF MDI

Pearl has developed a particle engineering technology that utilizes porous particles for pulmonary drug delivery via MDIs. This technology is based on spray-dried porous particles comprised of distearoylphophatidylcholine and calcium chloride that are co-suspended with crystalline active drug substances and formulated into suspension-based hydrofluoroalkane (HFA) MDIs. *In vitro* and *in vivo* testing suggest that the Pearl formulations will provide highly efficient, reproducible administration of therapeutics from MDIs in a wide dosing range [Hirst, 2002; Dellamary, 2000]. Pearl is developing a broad range of MDI-based inhalation products using its porous particle technology platform.

2 STUDY OBJECTIVES

2.1 Primary Objectives

- To assess the effects of BFF MDI relative to FF MDI and BD MDI on lung function

2.2 Secondary Objectives

- To assess the effects of BFF MDI relative to FF MDI and Symbicort TBH on COPD exacerbations
- To assess the effects of BFF MDI relative to FF MDI, BD MDI, and Symbicort® TBH on symptoms of COPD
- To assess the effects of BFF MDI relative to FF MDI, BD MID, and Symbicort® TBH on quality of life
- To determine the time to onset of action on Day 1

2.3 Safety Objective

- To assess the safety of BFF MDI, FF MDI, BD MDI, and Symbicort® TBH

2.4 Healthcare Resource Utilization (HCRU) Objective

- To assess overall and COPD-specific HCRU of BFF MDI relative to FF MDI, BD MDI, and Symbicort® TBH

2.5 Pulmonary Lung Function (PFT) Sub-Study Objectives

- To characterize FEV_1 over 12 hours at Week 12

3 STUDY ENDPOINTS

The primary endpoints, treatment comparisons of interest, and analysis timeframes may differ by country or region due to local regulatory agency requirements. The Sponsor has defined 2 registration approaches in this study, the US and EU approaches. The US approach is for countries or regions where the primary endpoints are generally evaluated at a point in time. The EU approach is for registration purposes in countries or regions where the primary endpoints are generally evaluated over a period of time. The multiplicity controls for the primary analyses will be delineated by approach.

3.1 Primary Efficacy Endpoints

US APPROACH

- Change from baseline in morning pre-dose trough FEV_1 at Week 24 (BFF MDI vs FF MDI)
- Change from baseline in FEV_1 AUC_{0-4} at Week 24 (BFF MDI vs BD MDI)

EU APPROACH

- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks (BFF MDI vs FF MDI; BFF MDI 320/9.6 µg vs Symbicort TBH, non-inferiority)
- Change from baseline in FEV_1 AUC_{0-4} over 24 weeks (BFF MDI vs BD MDI; BFF MDI 320/9.6 µg vs Symbicort TBH, non-inferiority)

3.2 Secondary Efficacy Endpoints

US APPROACH

- Time to first moderate or severe COPD exacerbation (BFF MDI vs FF MDI)
- Percentage of subjects achieving an MCID of 4 units or more in Saint George's Respiratory Questionnaire (SGRQ) total score at Week 24 (BFF MDI vs FF MDI; BFF MDI vs BD MDI)
- Change from baseline in morning pre-dose trough FEV_1 at Week 24 (BFF MDI vs BD MDI)
- Peak change from baseline in FEV_1 at Week 24 (BFF MDI vs BD MDI)
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks (BFF MDI vs BD MDI)
- Time to onset of action on Day 1 (BFF MDI vs BD MDI)

EU APPROACH

- Time to first moderate or severe COPD exacerbation (BFF MDI vs FF MDI)
- Time to clinically important deterioration (CID) (BFF MDI vs FF MDI)
- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks (BFF MDI vs BD MDI)
- TDI focal score over 24 weeks (BFF MDI vs FF MDI; BFF MDI vs BD MDI; BFF MDI 320/9.6 µg vs Symbicort TBH, non-inferiority)
- Percentage of subjects achieving an MCID of 4 units or more in Saint George's Respiratory Questionnaire (SGRQ) total score over 24 weeks (BFF MDI vs FF MDI; BFF vs BD MDI; BFF MDI 320/9.6 µg vs Symbicort TBH, non-inferiority)
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks (BFF MDI vs BD MDI)
- Peak change from baseline in FEV_1 over 24 weeks (BFF MDI vs BD MDI)
- Change from baseline in Evaluating Respiratory Symptoms in COPD (E-RS: COPD) total score (RS-Total Score) over 24 weeks (BFF MDI vs FF MDI; BFF MDI vs BD MDI; BFF MDI 320/9.6 µg vs Symbicort TBH, non-inferiority)
- Time to onset of action on Day 1 (BFF MDI vs BD MDI)

3.3 Other Efficacy Endpoints

Unless already categorized as a secondary endpoint in one of the regulatory approaches above, all of the following endpoints will be categorized as "Other efficacy endpoints", with the treatment comparisons of interest being BFF MDI vs FF MDI, BFF MDI vs BD MDI, and BFF MDI vs Symbicort TBH (non-inferiority).

DAY 1 ENDPOINTS

- Change from baseline at each post-dose time point and in AUC_{0-4} for FEV_1, forced vital capacity (FVC), peak expiratory flow rate (PEFR), and forced expiratory flow from 25% to 75% (FEF_{25-75})
- Proportion of subjects achieving an improvement from baseline in FEV_1 using different thresholds (e.g., ≥ 10%, ≥ 12%, ≥ 15%, ≥100 mL, ≥ 200 mL; and ≥12% and ≥200 mL)

ENDPOINTS OVER 24 WEEKS (UNLESS OTHERWISE STATED)

- Rate of moderate or severe COPD exacerbations
- Time to CID
- Time to sustained CID
- Rate of COPD exacerbations of any severity

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

3.4 Safety Endpoints

The safety endpoints for this study include AEs and SAEs, vital signs (BP and HR), clinical laboratory values (hematology and clinical chemistry), and ECGs.

3.5 Health Care Resource Utilization Endpoints

- The number of days missed from work due to COPD
- The number of days that primary caregivers of subjects missed from work as a result of the subject's COPD
- The percentage of subjects with telephone calls to health-care providers

  - Calls to any health-care provider (physician or other)
  - Calls to physician
  - Calls to other healthcare provider
- The mean number of telephone calls to health-care providers
  - Calls to any health-care provider (physician or other)
  - Calls to physician
  - Calls to other healthcare provider
- The percentage of subjects with visits to health-care providers
  - Visits to any health-care provider (general practitioner [GP], specialist, or other)
  - Visits to GP
  - Visits to specialist
  - Visits to other health-care provider
- The mean number of visits to health-care providers
  - Visits to any health-care provider (GP, specialist, or other)
  - Visits to GP
  - Visits to specialist
  - Visits to other health-care provider
- The percentage of subjects with Emergency Room (ER) visits
- The mean number of visits to ERs
- The percentage of subjects hospitalized
- The mean number of subject hospitalizations
- The mean number of days in the hospital
- The mean number of hospitalizations in which subjects spent some time in the Intensive Care Unit (ICU) or the Coronary Care Unit (CCU)
- The percentage of subjects hospitalized with some time spent in the ICU or CCU
- The mean number of days in the hospital with some time spent in the ICU or CCU
- The mean number of hospitalizations in which subjects spent no time in the ICU or CCU
- The percentage of subjects hospitalized with no time spent in the ICU or CCU
- The mean number of days in the hospital with no time spent in the ICU or CCU
- The mean number of days in ICU
- The percentage of subjects in the ICU
- The mean number of days in CCU
- The percentage of subjects in the CCU
- The percentage of subjects who required ambulance transport
- The mean number of times ambulance transport was required

3.6 Pulmonary Function Test Sub-Study Endpoints

The assessments will provide PFT profiles over 12-hours post-dose at Week 12.

Primary Endpoint:

- FEV_1 AUC_{0-12}

Other Endpoints:

- Peak FEV_1
- FVC, PEFR, and FEF_{25-75} will be evaluated using AUC_{0-12} and at peak

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase III, randomized, double-blind, parallel group, multi-center, 24-week lung function study comparing BFF MDI (320/9.6 µg and 160/9.6 µg) to FF 9.6 µg MDI, BD MDI 320 µg and Symbicort® TBH, administered BID, in subjects with moderate to very severe COPD.

To be eligible for the study, subjects must:

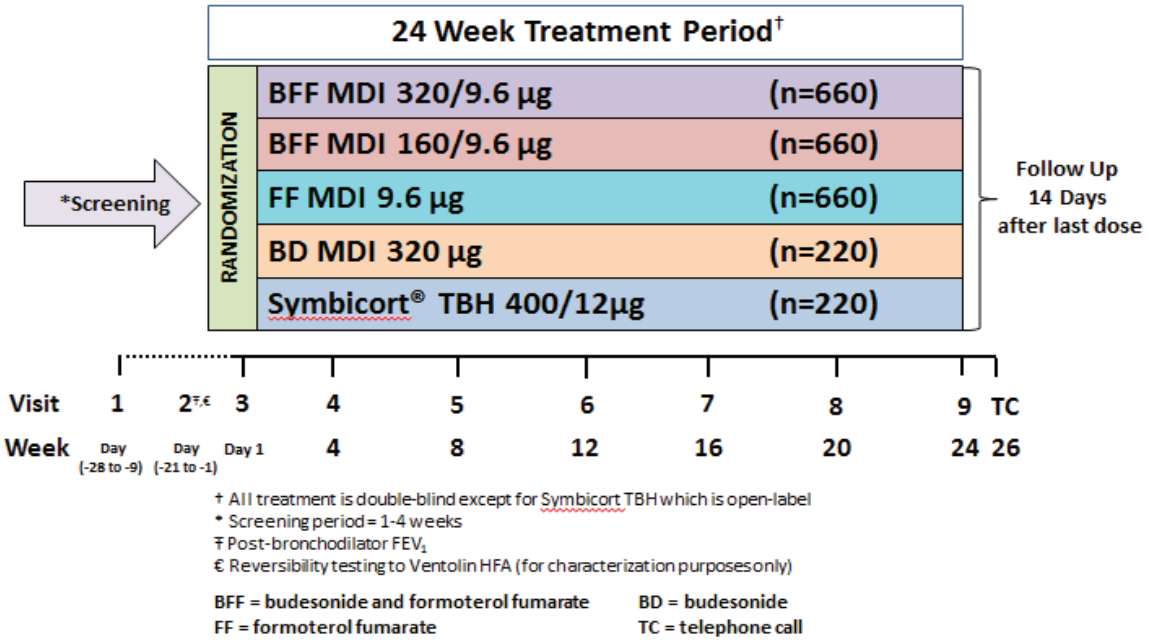
- be receiving one or more inhaled maintenance bronchodilators at Visit 1
- not be receiving ICS, LABA, and LAMA (as inhaled triple maintenance therapy) within 30 days of Visit 1
- be symptomatic, as measured by the COPD Assessment Test (CAT score ≥ 10) at Visit 1
- exhibit post-bronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ of the predicted normal value calculated using appropriate reference equations at Visit 2
  - if post-bronchodilator percent predicted FEV_1 is < 30% then FEV_1 must be ≥ 750 ml

Subjects will undergo a 1- to 4-week Screening Period.

Subjects meeting inclusion criteria and no exclusion criteria will be randomized into the study. Randomization will be stratified by reversibility to Ventolin, post-bronchodilator FEV_1, blood eosinophil count, and country. Enrollment will be targeted to achieve a 2:1 ratio for blood eosinophil strata with twice as many randomized subjects in the ≥ 150 cells per mm^3 category. Following randomization, subjects will enter the Treatment Period and undergo six additional treatment visits over 24 weeks. **Note:** The End of the Study is defined as the date on which data are collected for the last subject's Follow-up Telephone Call.

The overall study design is illustrated in Figure 4-1.

Figure 4-1 Study Design



This study will be conducted at approximately 200 sites, contributing approximately 10 to 14 subjects per site. It is planned that approximately 2,420 subjects will be randomized so that approximately 1,900 subjects complete the study.

4.2 Rationale of Study and Study Design

4.2.1 Study Rationale

BFF MDI is being fully developed in order to demonstrate adequate evidence of efficacy and safety for marketing approval.

GOLD guidelines acknowledge combination therapy with an ICS and LABA is more effective than the individual components in improving lung function and health status in patients with moderate to very severe COPD [GOLD 2016]. BFF MDI is a fixed-dose, dual combination MDI product formulated with budesonide and formoterol fumarate for use in subjects with moderate to very severe COPD. This Phase III study is intended to demonstrate the long-term efficacy and safety of BFF MDI compared with FF MDI and BD MDI on lung function, as well as subject-reported symptom outcomes and health status.

4.2.2 Population

This study will evaluate a patient population with moderate to very severe COPD, who has airflow limitation and remains symptomatic (demonstrated by a CAT $\geq$ 10) despite treatment with at least one inhaled maintenance bronchodilator. A beneficial effect of adding ICS to a bronchodilator is expected based on lung function measurements in this patient population. ICS are recommended for patients with severe and very severe airflow limitation [GOLD 2016]. Decreasing symptoms is a goal of COPD treatment and adding ICS in a symptomatic

population is expected to decrease symptoms [GOLD 2016]. In addition, regular treatment with ICS improves symptoms, lung function and quality of life in COPD patients with a $FEV_1 < 60\%$ predicted, which is a population included in this study [GOLD 2016].

4.2.3 Choice of Study Doses

Data from Phase I and II studies indicate that budesonide at two doses (320 and 160 µg BID) and formoterol fumarate at a dose of 9.6 µg BID are the correct doses to investigate in a Phase III program in COPD.

4.2.4 Choice of Comparators/Control Groups

Comparing BFF MDI with FF MDI will demonstrate the expected contribution of the budesonide component of BFF MDI in stabilizing pre-dose lung function. The comparison of BFF MDI with BD MDI will demonstrate the expected bronchodilatory contribution of the formoterol component of BFF MDI. Inclusion of two doses of BFF MDI may demonstrate a dose ordering effect of budesonide on lung function.

4.2.5 Study Duration

The specified study duration of 24 weeks will provide sufficient time to observe lung function changes in the chosen patient population.

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

Each subject must meet the following criteria, in relationship to Visit 1, unless otherwise noted, to be enrolled in this study:

1. Give their signed written informed consent to participate
2. Are at least 40 years of age and no older than 80 years
3. COPD Diagnosis: subjects with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) [Celli, 2004] or by locally applicable guidelines, e.g., JRS Guidelines [JRS, 2013] characterized by:
   - Progressive airflow limitation associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking
4. COPD Severity: subjects with established COPD clinical history and who are symptomatic (CAT $\geq$ 10) and severity defined and calculated using NHANES III reference equations [Or reference norms applicable to other regions, e.g., for Japan, use JRS reference equations; (JRS, 2013)] as below:
   - At Visit 1, FEV_1/FVC ratio must be < 0.70 and FEV_1 must be < 80% predicted normal value
   - At Visit 2, post-bronchodilator FEV_1/FVC ratio of < 0.70 and post-bronchodilator FEV_1 must be $\geq$ 30% but < 80% predicted normal value.
     - if post-bronchodilator percent predicted FEV_1 is < 30% then FEV_1 must be $\geq$ 750 ml
   - At Visit 3, the average of the -60 min and -30 min pre-dose FEV_1 assessments must be < 80% predicted normal value
5. Required COPD Maintenance Therapy
   - All subjects must be receiving one or more inhaled bronchodilators as maintenance therapy for the management of their COPD for at least six weeks
     Notes: the following are included
     - Scheduled SABA and/or scheduled SAMA
     - Nebulized COPD maintenance medications, as long as their use is discontinued at Visit 1 and they are not used for the remainder of the study
6. Tobacco Use: current or former smokers with a history of at least 10 pack-years of cigarette smoking.[Number of pack-years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years represent 10 pack-years)]
7. Willing and, in the opinion of the investigator, able to adjust current COPD therapy, as required by protocol
8. Demonstrate acceptable MDI administration technique
9. A female is eligible to participate in the study if:

- Non-childbearing potential [i.e., physiologically incapable of becoming pregnant, including any female who is two years post-menopausal, or surgically sterile (defined as having a bi-lateral oophorectomy, hysterectomy or tubal ligation)]
- **Note**: for purposes of this protocol, menopause is defined as women ≥ 50 years old who are amenorrheic for 12 consecutive months or more following cessation of all exogenous hormonal treatment
- Practicing abstinence
- If sexually active, a woman of childbearing potential agrees to prevent pregnancy by using one of the following methods of birth control from the date the ICF is signed until two weeks after the final dose of investigational product is taken:
  - Hormonal contraception (e.g., oral contraceptive, contraceptive implant, or injectable hormonal contraceptive)
  - Double-barrier birth control (e.g., condom plus intrauterine device or diaphragm plus spermicide)
  - Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy
- If a woman is of childbearing potential, she must have a negative serum pregnancy test

10. Screening Period lab tests must be acceptable to the Investigator
11. Screening Period ECG must be acceptable to the Investigator
12. Chest x-ray or computed tomography (CT) scan of the chest/lungs must be acceptable to the Investigator. A chest x-ray must be conducted if the most recent chest x-ray or CT scan is more than 6 months old, except in countries with restrictive radiology assessment practice where only subjects who have had a chest x-ray or CT scan in the last 6 months are allowed to be enrolled. Alternatively, in these countries, an MRI may be used instead of a CT scan or chest x-ray as per local practice assessment.
13. Compliance: willing to remain at study center as required per protocol to complete all study visit assessments.

5.2 Exclusion Criteria

Subjects who meet any of the following criteria, in relationship to Visit 1 unless otherwise stated, will be excluded from the study:

1. Receiving an ICS, LABA, and LAMA (as inhaled triple maintenance therapy) in the past 30 days
2. Respiratory
   a. Current diagnosis of asthma, in the opinion of the Investigator
   b. COPD due to α_1-Antitrypsin Deficiency
   c. Sleep apnea that, in the opinion of the Investigator, is uncontrolled
   d. Other Respiratory Disorders: known active tuberculosis, lung cancer, cystic fibrosis, significant bronchiectasis (high resolution CT evidence of bronchiectasis that causes repeated acute exacerbations), sarcoidosis, idiopathic interstitial pulmonary fibrosis, primary pulmonary hypertension, or pulmonary thromboembolic disease
   Note: allergic rhinitis is not exclusionary

e. Pulmonary resection or Lung Volume Reduction Surgery during the past 6 months [i.e., lobectomy, bronchoscopic lung volume reduction (endobronchial blockers, airway bypass, endobronchial valves, thermal vapor ablation, biological sealants, and airway implants)]
f. Hospitalized due to or has poorly controlled COPD within six weeks prior to Visit 1
g. Lower respiratory tract infections that required antibiotics within six weeks prior to Visit 1
h. Treatment with systemic corticosteroids and/or antibiotics (for criteria 2f or 2g above), within four weeks prior to Visit 1
i. Pneumonia not clinically resolved within 14 days
j. Upper respiratory tract infection not resolved at least 7 days
k. Clinically significant chest x-ray (frontal and lateral) with suspicion of pneumonia or other condition/abnormality that will require additional investigation/treatment, or put the subject at risk because of participation in the study
l. Immune deficiency and/or severe neurological disorders affecting control of the upper airway or other risk factors that place the subject at substantial risk of pneumonia, in the opinion of the Investigator
m. Long-term-oxygen therapy (≥ 15 hours a day).
Note: as needed oxygen use is not exclusionary
n. Any non-invasive positive pressure ventilation device
Note: Subjects using continuous positive airway pressure or bi-level positive airway pressure for Sleep Apnea Syndrome are allowed in the study if not used for ventilatory support
o. Change in smoking status (i.e., start or stop smoking) or initiation of a smoking cessation program within 6 weeks and prior to Randomization.
p. Acute phase of a pulmonary rehabilitation program within 4 weeks or scheduled acute phase of a pulmonary rehabilitation program during the study. These subjects will be allowed to rescreen after completion of the acute phase of pulmonary rehabilitation.
Note: subjects who are in the maintenance phase of a pulmonary rehabilitation program are not to be excluded
q. Initiated or altered the dose regimen of intranasal corticosteroids, intranasal antihistamines, or a combination thereof, within seven days and prior to Randomization
r. Unable to withhold short-acting bronchodilators for 6-hours prior to spirometry testing at each study visit
s. Use of spacer device to compensate for poor hand-to-breath coordination with MDI
t. Spirometry Performance: subjects who
    - Acceptability: cannot perform acceptable spirometry (i.e., meet ATS/ERS acceptability criteria)
    - Repeatability: cannot perform technically acceptable spirometry with ≥ 3 acceptable flow-volume curves with ≥ 2 meeting ATS repeatability criteria for FEV_1 during ≥ 1 of the pre-bronchodilator assessments at Visit 2 (-60 minute or -30 minute) and at the post-bronchodilator assessment at Visit 2

- FEV_1 Baseline Stability: cannot meet protocol-specified baseline stability criteria. FEV_1 baseline stability is defined as the average of the -60 minute and -30 minute pre-dose FEV_1 assessments at Visit 3 being within ± 20% or 200 mL of the mean of the pre-bronchodilator FEV_1 assessments obtained at Visit 2

3. Cardiovascular
   a. Unstable ischemic heart disease, left ventricular failure, or documented myocardial infarction within 6 months
   b. Acute coronary syndrome or undergone percutaneous coronary intervention (PTCA) or coronary artery bypass graft (CABG) within 3 months
   c. Congestive heart failure (CHF) NYHA Class III and IV
   d. Clinically significant abnormal ECG findings as defined below or deemed by the Investigator, but not limited to:
      - Conduction abnormalities (i.e., left bundle branch block, Wolff-Parkinson-White syndrome or evidence of Mobitz Type II second degree or third degree atrioventricular block [unless pacemaker or defibrillator has been inserted])
      - Arrhythmias (i.e., atrial fibrillation [AF] atrial flutter, ventricular tachycardia). **Note:** clinically stable AF appropriately treated with anticoagulation and rate controlled therapies (i.e., selective β-blocker, calcium channel blocker, digoxin, ablation therapy) for at least six months is allowed. At pre-randomization visits, resting ventricular rate must be < 100 beats per minute [bpm]. During the Screening Period, AF must be confirmed by central reading.
      - Corrected QT interval for heart rate, using Fridericia's formula (QTcF), ≥ 500 milliseconds (msec) with QRS < 120 msec; and ≥ 530 msec with QRS ≥ 120 msec
      - Ventricular rate < 45 bpm
      - Clinical significant ST-T wave abnormalities, as deemed by Investigator. **Note:** non-specific ST-T wave abnormalities not deemed clinically significant are allowed
      - Uncontrolled hypertension despite pharmacological treatment, as deemed by Investigator
4. Neurological
   a. Seizure disorder
      Note: subjects with seizures treated with anticonvulsant medication for ≥ 12 months with no seizure events are eligible
   b. Selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) with unstable dosing for ≥ four weeks or altered at any point during the Screening Period, or exceeds maximum labeled dose
   c. Cerebrovascular accident (CVA) within six months
5. Renal
   a. Underlying significant renal disease that may place subject at risk, as deemed by Investigator
6. Endocrine
   a. Uncontrolled hypo- or hyperthyroidism, hypokalemia, or hyperadrenergic state

b. Uncontrolled Type I or II diabetes

7. Liver
   a. Liver function tests defined as AST, ALT, or total bilirubin ≥1.5 times upper limit of normal at Visit 1 and on repeat testing prior to Visit 2
      Note: Chronic stable Hepatitis B and C is acceptable
8. Eye
   a. Narrow angle glaucoma not adequately treated, as deemed by the Investigator. All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective beta-blockers (such as betaxolol, carteolol, levobunolol, metipranolol, and timolol), and prostaglandin analogues
9. Cancer
   a. Not in complete remission for at least 5 years
      Note: squamous and basal cell carcinomas of the skin or localized prostate cancer are eligible, if in the opinion of the Investigator, the condition has been adequately worked up, is clinically controlled and the subject's participation in the study would not represent a safety concern
10. Women who are pregnant or lactating, planning to become pregnant during the study, or of childbearing potential and not using acceptable contraception method
11. Hypersensitivity to β_2-agonists or corticosteroids or any component of the MDI or DPI
12. Significantly abuse alcohol or drugs, in the opinion of the investigator
13. Unable to abstain from protocol-defined prohibited medications during the Screening Period and Randomized Treatment period (refer to Section 5.4)
14. Using any herbal products by inhalation or nebulization within two weeks and does not agree to stop for the duration of the study
15. Received a live attenuated vaccination within seven days
16. Unable to comply with study procedures including non-compliance with diary completion (i.e., < 70% subject completion of diary assessments in the last 7 days preceding Visit 3)
17. Study Investigators, Sub-investigators, and Coordinators, and their employees or immediate family members
18. Hospitalized for psychiatric disorder or attempted suicide within one year
19. History of psychiatric disease, intellectual deficiency, poor motivation, or other conditions limiting informed consent validity
20. Treatment with investigational study drug (or device) in another clinical study within the last 30 days or five half-lives, whichever is longer
    Note: observational studies (i.e., studies not requiring change to medication or an additional intervention) are allowed
21. Previously randomized in PT009 or PT010 study conducted or sponsored by Pearl

5.3 Subject Identification

All subjects who undergo screening procedures will be assigned a unique screening identification number at Visit 1. Only subjects continuing to meet inclusion/exclusion

criteria at Visit 3 will be assigned a unique subject randomization number. Randomization will be centralized with an Interactive Web Response System (IWRS).

5.4 Prior, Concomitant, and Prohibited Medications

5.4.1 Prior Medications

All prescription and over-the-counter (OTC) medications, as well as any herbal or vitamin supplements, taken by the subject within 30 days of Visit 1 should be recorded on the Prior/Concomitant Medications electronic Case Report Form (eCRF); indication, total daily dose, and dates of drug administration should be captured to the best of the subject's and site's ability.

5.4.1.1 Concomitant Medications and Vaccinations

Any current ongoing medications, including OTC drugs and herbal supplements, will be allowed provided they are not prohibited by the protocol (see Section 5.4.2). All concomitant medications taken during the study will be recorded on the Concomitant Medications eCRF page with indication, total daily dose, and dates of drug administration. Any additions, deletions, or changes in the dose of these medications while in the study should be entered in the eCRF. Subjects should also be instructed to contact the Investigator if they develop any illnesses, especially those requiring medicinal intervention.

5.4.1.2 Allowed Medications to Treat a COPD Exacerbation

Medications to treat a COPD 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 be treated initially with a 5-day course of steroids [Leuppi, 2013; GOLD 2016] and should not exceed 14 days. During a COPD exacerbation, it is important for subjects to be treated as deemed appropriate by the treating health care provider. However, all supplemental medication used to treat the COPD exacerbation should be discontinued as soon as it is considered safe by the Investigator and subjects should return to their pre-exacerbation medication regimen as soon as practical.

5.4.1.3 Pneumococcal and Annual Influenza Vaccination

All subjects should be vaccinated with pneumococcal and annual influenza vaccine per local guidelines. For subjects previously vaccinated with pneumococcal vaccine, the Investigator should assess whether a booster vaccination is required. If a subject has egg intolerance or refuses to be vaccinated, the vaccination may be omitted. Pneumococcal and/or annual influenza vaccine can be given at Visit 1 or at any other visit throughout the study at the discretion of the Investigator; however, administration should occur after obtaining all requisite spirometry assessments for that specific test day. There should be at least 7 days between vaccination and subsequent spirometry assessments.

5.4.2 Prohibited Medications

COPD MEDICATIONS

Subjects meeting entry criteria at Visit 1, who are being treated with any of the medications listed in Table 5-1, need to discontinue these medications and observe the minimum washout requirement before returning for Visit 2. These medications are prohibited throughout the course of study. Subjects requiring the use of any listed medications in Table 5-1 should be discontinued from randomized treatment but encouraged to continue in the study and complete all remaining study visits.

Table 5-1 Prohibited COPD Medications and Required Washout Periods Prior to Visit 2

Class of Medication	Minimum Washout Period Prior to Visit 2
SAMA	6 hours
LAMA	7 days: aclidinium, glycopyrronium, umeclidinium 14 days: tiotropium
LABA (inhaled)	7 days: salmeterol, formoterol, vilanterol 14 days: indacaterol, olodaterol
Fixed-dose combinations of LABA/LAMA	7 days: umeclidinium/vilanterol 14 days: glycopyrronium/indacaterol, tiotropium/olodaterol
Fixed-dose combinations of LABA/ICS	7 days
Fixed-dose combinations of SABAs and SAMAs	6 hours
SABA[a]	6 hours
Oral β-agonists	2 days
Theophylline (total daily dose >400 mg/day)[b]	7 days

COPD=chronic obstructive pulmonary disease; ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist; LAMA=long-acting muscarinic antagonist; SABA=short-acting β_2-agonist; SAMA=short-acting muscarinic antagonist
[a] Discontinue and use only sponsor-provided rescue Ventolin HFA throughout the study
[b] Theophylline (≤400 mg/day) is permitted provided the subject has been on a stable dose of therapy for at least four weeks prior to Visit 3

Subjects will adjust their maintenance therapy for COPD at Visit 1 for the duration of the Screening and Treatment Periods as follows:

- Subjects who are receiving an ICS/LABA will discontinue the ICS/LABA, but continue the ICS component for the remainder of the Screening Period. The ICS medications will be discontinued at Randomization.
- Subjects treated with an ICS as part of their inhaled maintenance therapy will continue their ICS for the remainder of the Screening Period. The ICS medications will be discontinued at Randomization.
- Discontinue all other COPD maintenance "as needed" medications as indicated in Table 5-1
- Initiate Sponsor-provided Ventolin to be administered as needed, up to 8 inhalations per day, for control of symptoms

- Subjects receiving phosphodiesterase inhibitors at stable doses for at least 4 weeks prior to Visit 1, may continue on these medications throughout the Screening and Treatment periods

It is preferred that Ventolin HFA be US-sourced products. In cases where it is not possible for the US-sourced product to be used, a locally available product will be provided by the Sponsor.

CORTICOSTEROIDS

Subjects who discontinue use of the medications in Table 5-2 may be considered for study enrollment provide they have met the minimum Washout Period prior to Visit 1. These medications, however, are permitted during the Treatment Period (only), if the subject requires them for any medical condition.

Table 5-2 Prohibited Corticosteroids and Required Washout Periods Prior to Visit 1

Route of Administration	Minimum Washout Period Prior to Visit 1
Depot (intra-articular and intraocular)[a]	12 weeks
Oral, IV, IM[a]	4 weeks

IV=intravenous; IM=intramuscular
[a] After randomization, subjects may be treated, for any reason, with systemic corticosteroids, when required

Note: Subjects who are steroid dependent and maintained on an equivalent of up to 5 mg of prednisone per day or up to 10 mg every other day for at least 3 months prior to Visit 1 are eligible for enrollment. The oral steroid dose needs to remain consistent, not exceeding this threshold, for the two weeks prior to Visit 3 in order to be randomized.

OTHER RESPIRATORY AND/OR NASAL MEDICATIONS

Subjects meeting entry criteria at Visit 1 who are being treated with any of the medications listed in Table 5-3 need to discontinue these medications and observe the minimum wash-out requirement before returning for Visit 2.

Table 5-3 Other Prohibited Respiratory and/or Nasal Medications and Required Washout Periods Prior to Visit 2

Class of Medication	Minimum Washout Period Prior to Visit 2
Leukotriene antagonist (e.g., zafirlukast, montelukast, and zilueton)	7 days
Inhaled/oral cromoglycate[a]	7 days
Inhaled nedocromil	7 days
Ketotifen[b]	7 days

[a] Intranasal cromoglycate is allowed
[b] Ketotifen eye drops allowed

NON-COPD AND NON-RESPIRATORY MEDICATIONS

Subjects requiring medications presented in Table 5-4 are prohibited from participating in this study. Subjects who recently discontinued use of these medications may be considered for study enrollment provided they have met the minimum Washout Period prior to Visit 1. These medications are prohibited throughout the course of the study. If a subject requires the use of any of the listed medications, the subject should be discontinued from randomized treatment but encouraged to continue in the study and complete all remaining study visits.

Table 5-4 Non-COPD and Non- Respiratory Medications

Prohibited Medications	Minimum Washout Period Prior to Visit 1
Any drug with potential to significantly prolong the QT-interval[a]	14 days or 5 half-lives, whichever is longer
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Non-selective β-blocking agents (except carvedilol for CHF-NYHA Class I and II)	7 days
Cardiac anti-arrhythmics (Class Ia, III)	7 days, unless amiodarone, then 3 months
Anticonvulsants for seizure disorder	Allowed if stable dose for 12 months and free of seizures for 1 year
Anticonvulsants for other indications	Allowed if stable dose for 3 months and free of seizures for 1 year
Tricyclic antidepressants[a]	14 days
Monoamine oxidase inhibitors	14 days
Anti-tumor necrosis factor α antibodies (e.g., infliximab and any other members of this class of drugs)	30 days or 5 half-lives, whichever is longer
Monoclonal antibodies	30 days or 5 half-lives, whichever is longer
Antipsychotic drugs[b]	30 days
Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors (e.g., ritonavir)o and cimetidine	30 days
Systemic anticholinergics[c]	7 days
Chinese complementary and alternative bronchodilatory medicines (CAM) (i.e., herbal therapies such as *Astragalus membranaceus* [huáng qí]*, Panax ginseng* [*ginseng products*] and *Cordyceps sinensis. A. membranaceus* [*ghost moth caterpillar fungus*])[d]	10 days

Note: Benzodiazepines are not exclusionary

[a]Subjects who are on medications that have the potential to prolong the QTc interval may be enrolled provided the dose has remained stable for at least 3 months prior to Visit 1, the subject meets all of the ECG inclusion criteria and none of the ECG exclusion criteria and if, in the opinion of the Investigator, there are no safety concerns for the subject to participate in the study. Initiation of medications with the potential to significantly prolong the QT interval is prohibited throughout the study.
[b]Antipsychotic agents and tricyclic antidepressants used for previously diagnosed underlying medical conditions are allowed if, in the opinion of the Investigator, there are no concerns regarding patient safety, and if the patient has been on a stable dose for at least six weeks.
[c]Allowed only if used for treatment of overactive bladder which has been constant for at least one month prior to study enrollment.
[d]Requires case-by-case review by the Investigator to determine appropriate washout period, if needed.

5.4.3 Other Prohibited Medications

Table 5-5 lists certain non-COPD medications that may be used under the stated conditions during this study. Each concomitant drug must be individually assessed against all exclusion criteria.

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

Medications Allowed Under Certain Conditions	Condition
SSRIs or SNRIs	Treatment regimen has been stable for at least four weeks prior to Visit 1 and not altered during the Screening Period, and does not exceed the maximum recommended dose
Intranasal corticosteroids, intranasal antihistamines, intranasal cromoglycate or combination thereof	Administered at constant dose and dosing regimen for at least seven days prior to Visit 1 and during the Screening Period

SNRI=serotonin–norepinephrine reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors

5.5 Other Restrictions, Illicit Drugs or Drugs of Abuse

5.5.1 Illicit Drugs or Drugs of Abuse

Illicit drugs or drugs of abuse will not be allowed from Visit 1 to the end of the Follow-up TC or to whenever the subject withdraws from the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented and the subject will be discontinued at the discretion of the Investigator. Medical marijuana is not an exclusionary drug if used for medical purposes, and there is no change in the dose or frequency of consumption.

5.5.2 Dietary Restrictions

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

5.6 Smoking Status

Changes in a subject's smoking status (i.e., stopping or restarting smoking) may have an impact on efficacy outcome measures. Therefore, at Visits 1 through 9, subjects will be asked about any recent changes in their smoking status (i.e., subject has gone from a smoker to a nonsmoker or vice versa). Any change in smoking status between Visits 1 to 3 will result in a screen failure. Smoking status changes during Visits 3 to 9 will be captured in the eCRF, but the subject will be permitted to continue in the study.

All subjects will be required to refrain from smoking (including medical marijuana, Nicotrol inhaler, and electronic cigarettes) for at least 4 hours prior to each study visit and throughout the duration of each study visit. Study participants may utilize various nicotine replacement

treatments, such as chewing gum and patches as needed, in accordance with recommendations from the Investigator, during the entire study visit.

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

5.7 Reasons for Treatment Discontinuation or Study Withdrawal

Subjects who suffer an 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. (Please see Section 8.6 and Section 8.7 for additional procedures.)

Subjects may be withdrawn from the study at their own request, upon the request of the Investigator or Pearl at any time and for any reason. (Please see Section 8.6 and Section 8.7 for additional procedures.)

5.7.1 Reasons for Treatment Discontinuation

If a subject experiences any of the changes of concern listed below, a repeat assessment should be obtained, and if confirmed, the subject <u>should</u> be discontinued from randomized treatment, but encouraged to continue in the study and complete all remaining study visits:

- Calculated QTcF intervals > 500 msec which has increased by ≥ 60 msec from pre-dose baseline value at Visit 3

  <u>*EU-specific regions only*</u> - Calculated QTcF intervals ≥ 500 msec OR ≥ 60 msec from pre-dose baseline value at Visit 3
- Hepatic impairment, defined as abnormal liver function test of AST, ALT or total bilirubin ≥3 times upper limit of normal

If a subject experiences any of the changes of concern listed below, a repeat assessment should be obtained, and if confirmed, the Investigator needs to make a determination as to the suitability of continuing the subject on randomized treatment:

- Following dosing, a heart rate >120bpm and in which there is an increase of >40 bpm from the pre-dose value for a given study visit

  <u>*EU-specific regions only*</u> - Following dosing, a heart rate increase of > 25 bpm from the pre-dose value for a given study visit
- Following dosing, a systolic blood pressure (SBP) > 160mmHg and an increase of > 40 mmHg from the pre-dose value for a given study visit

  <u>*EU-specific regions only*</u> - Following dosing, a SBP increase of > 30 mmHg from the pre-dose value for a given study visit or a clinically relevant change from baseline as determined by the Investigator
- A decreased creatinine clearance to a value ≤ 30 mL/minute using the CKD-EPI formula or a clinically relevant change from pre-dose baseline as determined by the Investigator

  <u>*EU-specific regions only*</u> - A decrease of 33% in calculated creatinine clearance from pre-dose baseline using CKD-EPI

5.7.2 Reasons for Study Withdrawal

Subjects requiring any prohibited medications listed in Section 5.4.2 (other than study-provided medication and COPD exacerbation medication), should be withdrawn from study participation.

If a female subject becomes pregnant during the course of the study, study medication will be discontinued and the subject will be followed until delivery or final outcome.

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

6.1 Subject Information

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

6.2 Product Description

Investigational materials will be provided by Pearl as summarized in Table 6-1 below. Pearl will provide open-label Ventolin® HFA and manufacturer's instructions for drug administration are provided in Appendix 1.

Table 6-1 Product Descriptions

Product Name & Dose	Product Strength	Dosage Form/Fill Count	Administration
Blinded Study Medications			
BFF MDI 320/9.6 µg	160/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
BFF MDI 160/9.6 µg	80/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
FF MDI 9.6 µg	4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
BD MDI 320 µg	160 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
Open-Label Products			
Albuterol Sulfate inhalation aerosol 90 µg[a]	Ventolin® HFA[b] Each inhalation contains 108 µg albuterol sulfate corresponding to 90 µg albuterol base	MDI/ 60 or 200 inhalations	Four inhalations for reversibility testing at Visit 2 Taken as needed throughout Screening and Treatment Periods
Budesonide and formoterol fumarate inhalation powder 400/12 µg	Symbicort® TBH[c] 200/6 µg per actuation Each inhalation contains 200 µg budesonide and 6 µg formoterol fumarate dihydrate corresponding to a delivered dose of 160 µg budesonide and 4.5 µg formoterol fumarate dihydrate	DPI/ 120 inhalations	Taken as 2 inhalations BID

BFF MDI = Budesonide and Formoterol Fumarate Inhalation Aerosol; BID = Twice Daily; FF MDI = Formoterol Fumarate Inhalation Aerosol; HFA = Hydrofluoroalkane; MDI = Metered Dose Inhaler; TBH = Turbuhaler

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

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

[c] Active Control. Symbicort Turbuhaler is also known as Symbicort Turbohaler in some countries.

6.3 Primary Packaging and Labeling

Investigational materials will be packaged by the Sponsor.

Blinded Supplies: Each BFF MDI, BD MDI, and FF MDI will be contained in a box and labeled with a single label. Inside the box will be a labeled actuator and a labeled foil pouch containing the MDI canister of study medication.

Open-label Supplies: Open-label Ventolin will be provided as individually labeled MDIs with a single label on the actuator and a foil pouch containing the Ventolin canister. Open-label Symbicort TBH will be provided as individually labeled DPIs with a single label on the actuator and a foil pouch containing the Symbicort TBH canister.

Labels will be printed with black ink and may include the following text:

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

ID = identification; # = number

6.4 Secondary Packaging and Labeling

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

Table 6-2 Description of Boxes

Drug Supplies	Individual Box Contents
Blinded	1 MDI
Ventolin (albuterol sulfate) HFA[a]	1 MDI
Symbicort (budesonide and formoterol fumarate) TBH[b]	1 DPI

DPI = dry powder inhaler; HFA = hydrofluoroalkane; MDI = metered dose inhaler; TBH = Turbuhaler

[a] US-sourced products are the preferred product for use during the study. In regions where it is not possible for US-sourced products to be used, a locally available comparable product will be provided by the Sponsor.

[b] Symbicort Turbuhaler is also known as Symbicort Turbohaler in some countries.

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

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

6.5 Emergency Unblinding of Treatment Assignment

The Investigator or designee 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.

Emergency unblinding of study drug, for a given subject, must be done utilizing the IWRS as a study treatment disclosure envelope will not be provided with the clinical supplies. Whenever possible, the Investigator should first discuss options with the Pearl Medical Monitor or other appropriate Pearl 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 other subjects currently enrolled in the study.

If the Investigator contacts IWRS to unblind a subject, s/he must provide the requested subject identifying information and confirm the necessity to unblind treatment. The date and reason for the unblinding must be recorded in the appropriate eCRF.

6.6 Storage Requirements

Blinded supplies: BFF MDI, BD MDI, and FF MDI should be stored below 25°C (77°F) in a dry place. Excursions permitted up to 30°C (86°F).

Ventolin® HFA supplies: Store between 15°C and 25°C (59°F and 77°F). Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use. Do not use or store near heat or open flame. Exposure to temperatures above 120°F (49°C) may cause bursting. Never throw into a fire or incinerator.

Symbicort® TBH supplies: Should not be stored above 30°C (86° F). Keep the container tightly closed, in order to protect from moisture.

The temperature of the site's storage area, for study supplies, must be monitored by site staff for temperature ranges consistent with those specified in the protocol. Documentation of temperature monitoring should be maintained at the site and available for review.

6.7 Instructions for Dispensing and Preparation of Treatments for Administration

6.7.1 BFF MDI, BD MDI, and FF MDI

TREATMENT DISPENSING

Individual BFF MDI, BD MDI, and FF MDI inhalers 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 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.

TREATMENT PREPARATION FOR ADMINISTRATION

All MDIs must be primed before the first use. Priming involves releasing 4 sprays 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.

MDIs must be primed in a separate room from the subject treatment area. Once primed, subjects should be instructed on use and dosing (2 puffs in the morning and 2 puffs in the evening approximately 12 hours apart). The MDI should then be given to the subject for dose administration. Site personnel should observe the subject take their first dose and should record the time of second puff in the eCRF as the time of dose administration.

Refer to Appendix 2 for additional instructions on the administration and cleaning of the BFF MD, FF MDI and BD MDI.

6.7.2 Ventolin HFA® (Albuterol Sulfate)

Refer to Appendix 1 for instructions on the administration and cleaning of Ventolin. Open-label MDIs will also be packaged in a visit treatment box. The visit treatment box will have a label with a component ID number.

6.7.3 Symbicort TBH® (Budesonide and Formoterol Fumarate)

Refer to Appendix 3 for instructions on preparation and administration of Symbicort® TBH (Budesonide and Formoterol Fumarate).

Open-label DPIs will also be packaged in a visit treatment box. The visit treatment box will have a label with a component ID number.

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 that only the Investigator and designated study personnel have access. Clinical supplies should 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 drug should be handled in accordance with Good Pharmacy Practices (e.g., gloves should always be worn by study personnel if directly handling study drug that is returned). The Pearl Medical Monitor or designee 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 study personnel 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 Pearl Medical Monitor or designee.

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.

Used study drug must be stored separately from unused study drug.

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

7 STUDY PROCEDURES

A schedule of events for all study assessments is provided in Table 8-1. Detailed visit schedules for all pre-and post-dose timed assessments and for the PFT sub-study are described in Table 8-2 and Table 8-3, respectively.

7.1 Efficacy Assessments

7.1.1 Pulmonary Function Tests (PFTs)

All PFTs, including FEV_1, FVC, and PEFR, as defined in ATS/ERS guidelines, will be performed based on ATS criteria (refer to Appendix 4) [Miller, 2005]. Forced expiratory spirometry maneuvers for derivation of FEV_1, FVC, and PEFR will be assessed using a spirometer that meets or exceeds minimum performance recommendations of the ATS (refer to Appendix 5).

The volume accuracy of the spirometer is to be checked daily using a 3 L syringe across three flow ranges (i.e., low, medium, and high flows), with temperature and barometric pressure correction. The calibration syringe must meet ATS specifications and 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 5).

To standardize spirometry, all sites will be provided with identical spirometry systems [redacted] with customized, study-specific software. Every effort will be made to provide all sites with standardized spirometry equipment. The volume accuracy of the spirometer is to be checked daily with appropriate documentation in a calibration log prior to the conduct of PFT's on each test day.

In the event that it is not logistically possible to provide such equipment in a specific country, use of local PFT equipment will be permitted merely for patient eligibility and characterization purposes. Local equipment needs to be reviewed by the study monitor and must meet or exceed ATS minimum performance recommendations (refer to Appendix 5).

All study staff responsible for performing pulmonary function testing will receive standardized training at the Investigator Meeting. All technicians are required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable PFTs (ATS criteria), prior to performing PFTs on study subjects [Miller, 2005]. 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 [Miller, 2005]. All PFT testing will be stored electronically. After completion of testing, the study staff will electronically transmit the spirometric measurements for centralized quality assurance review [redacted]. Feedback on the quality of the measurements will be provided to the investigational site and to Pearl or designee for central data management.

For exact spirometry collection and specifications, please refer to Table 8-1 and Table 8-2.

- At Visit 1: a single spirometry assessment will be conducted
- At Visit 2: spirometry will be conducted 60 minutes and 30 minutes prior to bronchodilator administration and 30 minutes post-bronchodilator

- Pre-dose assessments: at all remaining visits spirometry will be conducted 60 and 30 minutes prior to study drug administration
- Post-dose assessments: at Visits 3, 4, 6, and 9 spirometry will be done at 5 minutes (Visit 3 ONLY), 15 minutes, 30 minutes, 1 hour, 2 hours and 4 hours after dosing

Subjects discontinuing treatment/withdraws consent: pre- and post-dose measurements will be obtained at the Premature Discontinuation Visit.

Subjects will be required to return to the clinic at approximately the same time as Visit 3 for all treatment visits (± 2 hours). All in-clinic dosing must occur prior to 10 AM; timing of visits must be planned accordingly. The subjects will be required to remain at the clinic until completion of all protocol-defined assessments.

Note: During the Screening Period, spirometry must meet both acceptability and repeatability criteria (Visit 2 only). (Refer to Exclusion Criteria, Section 5.2).

PFT SUB-STUDY

For exact PFT Sub-study collection & specifications please see Table 8-3.

For Subjects participating in the 12-hour PFT sub-study, at Visit 6, additional spirometry assessments will be conducted at 6 hours, 8 hours, 10 hours, 11.5 hours and 12 hours after dosing.

7.1.1.2 Characterization of Reversibility

Reversibility to Ventolin® HFA (SABA) will be evaluated, for subject characterization purposes, at Visit 2 as follows:

- Perform pre-bronchodilator PFTs at -60 minutes and -30 minutes prior to administration of Ventolin
- Administer 4 puffs of Ventolin
- Perform post-bronchodilator PFTs at 30 minutes after the administration of Ventolin

Reversibility will be a comparison of the average best FEV_1 effort obtained at -60 minute and -30 minute pre-bronchodilator to the best FEV_1 effort obtained at 30 minutes post-bronchodilator following administration of Ventolin. A subject is considered reversible to Ventolin if the improvement in FEV_1 at 30 minutes post-Ventolin is $\geq$ 12% and $\geq$ 200 mL.

7.1.1.3 FEV_1 Baseline Stability Criteria

All comparisons will be made to the baseline (mean of 60 and 30 minutes prior to dosing) values obtained at Visit 3 (Randomization). It is important to ensure that the baseline FEV_1 is stable and reflective of the subjects COPD severity prior to being randomized into the study. As such, the baseline FEV_1 at Visit 3 must be within ±20% or 200 mL of the mean of the pre-dose FEV_1 obtained at the preceding visit (average of 2 pre-dose FEV_1 values obtained at Visit 2). At Visit 3, if the pre-dose FEV_1 average is outside of the ±20% or 200 mL range, but the -30 min assessment is within ±22% or 220 mL, then another assessment may be conducted 30 minutes later. If the last 2 assessments meet the FEV_1baseline stability requirements (i.e., within ±20% or 200 mL), the initial 60 minute pre-dose assessment will not be used and the last 2 assessments will be used to establish the

eligibility criteria. If the test day FEV_1 is not within ±20% or 200 mL, the subject will not be randomized and will be considered a screen failure.

7.1.1.4 Subject's Electronic Diary Data Collection

Prior to issuing the electronic Diary (eDiary) to the subject, site personnel are responsible for programming the eDiary and training the subject on its use. Subjects will receive their eDiary at Visit 1. The eDiary is to be completed twice a day throughout the study. The following information will be captured in the eDiary: time of study medication administration, daily symptoms [using the Exacerbations of Chronic pulmonary disease Tool (EXACT) scale], and use of any rescue medication (i.e., Ventolin).

ELECTRONIC DIARY COMPLIANCE REQUIREMENT

Between Visits 1 to 3, subjects will be required to demonstrate acceptable eDiary collections and compliance in order to be eligible for randomization. Subject participation may be terminated at any time during the study for the following reasons:

- Subjects who are unable to meet the compliance requirement (≥ 70% subject completion of eDiary assessments) in the 7 days prior to Visit 3 will be considered a screen failure.
- Chronic failure, in the judgment of the Investigator, to comply with eDiary compliance, despite documentation at the site of repeated efforts to reinforce compliance. As defined for this study, compliance requires ≥ 70% subject completion of eDiary assessments for the duration of the study. Pearl may also instruct a site to discontinue a subject based on consistent noncompliance.

7.1.1.5 Rescue Medication Use

Use of rescue medication (i.e., Sponsor-provided Ventolin or locally available equivalent product) during the conduct of the study is to be recorded, by the subject in the eDiary, on the day of use. Each time rescue medication is taken, the number of puffs (i.e., actuations) should be captured in the eDiary for the corresponding study day.

Subjects requiring more than 8 puffs per day on 3 consecutive days with worsening symptoms should contact the site.

7.1.1.6 Medication Compliance

Subjects will record the times (morning and evening) of study drug dosing in the eDiary, except on the mornings of in-clinic dosing. Study drug compliance will be checked at all visits. Any issues identified (i.e., < 70% compliance) will be documented in the appropriate study file and reinstruction will be completed as necessary.

7.1.1.7 Major/minor Symptom Worsening Assessment and Alert System

Subjects will capture all major and minor symptoms of a worsening event in the eDiary for purposes of a 'symptom worsening alert'. In this way both the subject and the site can be notified of the potential for worsening symptoms that need further evaluation.

All questions regarding worsening of symptoms will have a 24-hour recall period. Questions pertaining to the severity of symptoms versus their usual state will have three 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 or Yes, I had a sore throat).

An alert will be triggered if two or more major symptoms (e.g., dyspnea, sputum volume, and sputum color) worsen for two consecutive days or if one major symptom and one minor symptom (e.g., sore throat, cold, fever without other cause, cough, and wheeze) worsen for at least two 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 the next 24 to 72 hours if he/she has not contacted the site for follow-up.

7.1.2 COPD Exacerbation

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

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

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

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

7.1.2.1 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 three 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.

7.1.2.2 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 either prescribed treatment. In order to ensure that the same event is not counted twice, concurrent moderate or severe COPD exacerbations with start and stop dates ≤ 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 on the set of worsened symptoms as recorded by the subject in the eDiary and stop date will be defined as the last day of worsened symptoms. In order to ensure the same event is not counted twice, mild COPD exacerbations with start and stop dates ≤ 7 days apart will be considered the same event.

7.1.2.3 Approach for Capturing COPD Exacerbations

All moderate or severe COPD exacerbations must be captured using the COPD Exacerbation eCRF. Mild COPD exacerbations will be captured based on symptoms as recorded by the subject in the eDiary. COPD exacerbations of any severity will be considered expected study endpoints and will not be reported as adverse events (AEs) unless considered a serious AE (SAE).

SYMPTOM REPORTING

An eDiary will be used 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.

7.1.2.4 Investigator-judged COPD Exacerbations

For events which do not meet the outlined symptom criteria for a COPD exacerbation and/or when symptoms have a shorter duration, the investigator must justify the decision for considering the event an exacerbation and record it on the appropriate eCRF. An example would be when symptoms of COPD warrant urgent treatment due to rapid onset or rapidly progressive symptoms. Such a situation does not allow enough time to fulfill the criteria of 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 do not strictly fulfill all symptom requirements, as defined earlier, but justification and clinical relevance must be documented in the eCRF.

7.1.3 Subject Questionnaires

Subject questionnaires to be completed on site utilizing study-supplied electronic questionnaire devices (not the subject's eDiary) at specified visits throughout the study are CAT, BDI/TDI, SGRQ, and EQ-5D-5L, described in detail below. Various language versions for each questionnaire will be utilized, as appropriate, for participating countries. Whenever BDI/TDI, SGRQ, and/or EQ-5D-5L are obtained at the same visit, it is recommended that the BDI/TDI be collected first followed immediately by the SGRQ and the EQ-5D-5L.

The EXACT questionnaire will be captured via the subject eDiary (refer to Section 7.1.1.4).

7.1.3.1 Chronic Obstructive Pulmonary Disease Assessment Test (CAT)

The CAT is a self-administered questionnaire designed to assess the condition of subjects and overall impact of COPD [Jones, 2009]. Studies have proven that the CAT questionnaire has good repeatability and discriminative properties, suggesting that it is sensitive to treatment effects at a group level. Since the CAT is designed to assess the impact of COPD on the subject by measuring overall impairment, it has moderate correlations with other instruments, such as the Modified Medical Research Council Dyspnea Scale, SGRQ, and the 6-minute walk test.

Subjects will complete the CAT (refer to Appendix 6) at Visit 1 and results are used as an entry criterion. The CAT score will describe the burden and symptomatic impact of COPD in subjects enrolled in the study.

7.1.3.2 Baseline Dyspnea Index and Transition Dyspnea Index (BDI/TDI)

Dyspnea is the primary symptom of COPD and its' relief is an important goal of therapy. In the evaluation of pharmacotherapy for COPD, several instruments are available to provide a discriminative and evaluative assessment of dyspnea. Among these are the BDI and TDI indices, which assess breathlessness in components related to functional impairment, magnitude of task and magnitude of effort.

As the name implies, BDI measures a subject's breathlessness at baseline, prior to initiation of study medication. The reliability and validity of the BDI assessment has been reported [Mahler,1984] and confirmed against other related measures [Witek, 2003]. The Interviewer-administered rating of severity of dyspnea at a single state provides a multidimensional measurement of dyspnea based on three components that evoke dyspnea in activities of daily living in symptomatic individuals. The BDI score ranges from 0 (very severe impairment) to 4 (no impairment) for each domain and are summed to determine the BDI focal score (0 to 12) (i.e., the lower the score, the worse the severity of dyspnea). The appropriate language version of the questionnaires will be used. The questionnaire can be found in Appendix 7.

The TDI measures changes in dyspnea severity, from baseline, as established at baseline by the BDI. The three components of the TDI are: Change in Functional Impairment, Change in Magnitude of Task, and Change in Magnitude of Effort. The TDI score ranges from -3 (major deterioration) to +3 (major improvement) for each component. The sum of all components yields the TDI focal score (-9 to +9) where a lower score reflects a greater deterioration in dyspnea severity.

The BDI/TDI questionnaire will be captured on the Sponsor-provided tablet and not in the eDiary. Always administer the BDI/TDI questionnaire prior to any other subject questionnaires, PFT assessments, and study drug administration to avoid influencing the subject's response. The BDI/TDI questionnaire is key outcome in many countries for marketing approval.

The BDI will be completed at Visit 3 prior to study drug administration. The TDI will be completed prior to study drug administration at each post-randomization visit and if the subject discontinues treatment/withdraws consent.

7.1.3.3 St. George's Respiratory Questionnaire (SGRQ)

The SGRQ 4-week recall tool will be used to provide the health status/health-related Quality of Life (QoL) measurements (refer to Appendix 8). The appropriate language version of the questionnaires will be available in each participating country. The subject should complete the questionnaire in a quiet area and be allowed to ask questions; however, site staff should take care not to influence the subject's responses. The subject will be instructed to provide the most accurate and best individualized response about how they felt regarding their health status/health-related QoL over the last four weeks (i.e., since the study visit). The questionnaire should be checked for completeness and collected prior to study drug administration. At subsequent visits, subjects may not review their previous responses.

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

The SGRQ will be captured on the Sponsor-provided tablet and not in the eDiary. It is to be completed prior to study drug administration at Visit 3 and at each post-randomization visit and if the subject discontinues treatment/withdraws consent.

7.1.3.4 European Quality-of-Life-5 Dimensions Questionnaire (EQ-5D-5L)

The EQ-5D-5L is a 5-level standardized instrument measuring health outcomes and is applicable to a wide range of health conditions/treatments, thereby providing a simple descriptive profile and a single index value for health status [EuroQol, 2014].

The EQ-5D-5L consists of two assessments, a descriptive system and a visual analogue scale (VAS). The descriptive system is comprised of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression where each dimension has five severity levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

The VAS records the subject's self-rated health on a 20-cm, 0-100 vertical scale with endpoints labeled "the best health you can imagine" and "the worst health you can imagine."

This score is used as a quantitative measure of QoL where a higher score corresponds to a better health state and vice versa.

The EQ-5D-5L (refer to Appendix 9) will be captured on the Sponsor-provided tablet and not in the eDiary. It is to be completed prior to study drug administration at Visit 3 and at each post-randomization visit and if the subject discontinues treatment/withdraws consent.

7.1.3.5 Exacerbations of Chronic Pulmonary Disease Tool (EXACT)

The EXACT is a 14-item instrument developed to assess the frequency, severity and duration of COPD exacerbations [Jones, 2011). This instrument was developed for daily, at home administration using a handheld electronic device. Respondents will be instructed to consider their experiences that day (i.e., today) when completing the diary every evening, prior to bedtime. The instrument includes assessments of breathlessness (5 items), cough and sputum (2 items), chest symptoms (3 items), and four additional items (difficulty with sputum, tired or weak, sleep disturbance, and psychological state).

The daily EXACT total score will be computed across the 14 items, with a range of 0-100 and where higher scores are indicative of greater severity. Total score changes are used to identify the onset and recovery from an EXACT-defined exacerbation event.

The E-RS is an 11-item sub-set of EXACT, which evaluates the severity of the respiratory symptoms associated with COPD [Leidy, 2014]. The E-RS was designed to be captured as part of the daily EXACT assessment. On [redacted] the EXACT-Respiratory Symptoms Scale was renamed the Evaluating Respiratory Symptoms (E-RS) measure. When referring specifically to its use in COPD, the proposed context of use for qualification, the full name is now "Evaluating Respiratory Symptoms in COPD (E-RS™: COPD). Summation of E-RS item responses produces a total score ranging from 0 to 40, with higher scores indicating greater severity. In addition to the total score, symptom domain scores can be calculated for breathlessness (5 items; score range: 0–17), cough and sputum (3 items; score range: 0–11) and chest symptoms (3 items; score range: 0–11) by summing the responses of items within a respective domain. As with the total score, higher domain scores indicate greater severity.

The EXACT (refer to Appendix 10) will be completed daily by the subject as part of the eDiary assessments.

7.2 Safety Assessments

Safety assessments for this study include physical examination findings, vital signs, ECGs, and clinical laboratory tests in addition to recording AEs and SAEs.

7.2.1 Medical/Surgical History and Physical Examination

Medical history, including specific cardiovascular history details, will be collected at Visit 1 and updated throughout the Screening Period.

The number of COPD exacerbations requiring oral steroids and/or oral antibiotics, or hospitalization within 12 months of Visit 1 will be collected.

A complete physical examination will be performed at Visits 1 and 9 or if the Subject discontinues treatment/withdraws consent, and include the following:

- General appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities and nervous system
- Weight will be measured at Visits 1 and 9, or at the Premature Discontinuation/Early Termination Visit; height will be measured at Visit 1 only

7.2.2 Vital Sign Measurements

All vital sign measurements, including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and temperature, will be obtained after the subject has rested for 5 minutes in either the supine or seated position. Vital signs will be measured as follows:

- Visit 1: a single measurement of vital signs will be collected
- Visit 2: a single measurement of vital signs measured 60 minutes pre- and 30 minutes post-bronchodilator (completed for Reversibility Testing)
- Visit 3: two vital sign measurements, at least five minutes apart, will be collected approximately 60 minutes pre-dose. A single measurement of post-dose vital signs will be obtained at 30 minutes and 4 hours after study drug dosing.
- All remaining in-clinic study visits (Visits 4 to 9):
  - A single vital sign measurement will be collected approximately 60 minutes pre-dose
  - A single measurement of post-dose vital signs will be obtained at 30 minutes
  - A single measurement of 4 hour post-dose vital signs will be collected at Visits 4, 6 and 9 (in addition to Visit 3 noted above).

Note: A single temperature reading will be collected at Visit 1 and pre-dose at all visits; temperature reading will not be repeated post-dose unless clinically indicated.

Subjects discontinuing treatment/withdrawing consent: a single vital sign measurement will be obtained at the Premature Discontinuation Visit.

PFT SUB-STUDY SUBJECTS ONLY

Subjects participating in the 12-hour PFT sub-study will follow vital sign measurements listed above, except vital signs will not be measured 4 hours after study drug dosing. Instead, a single set of vital signs will be measured following the final spirometry assessment (refer to Table 8-3).

7.2.3 12-Lead Electrocardiogram

To standardize ECG collection, all sites will be provided with identical ECG equipment [redacted] with customized study-specific software. All study staff responsible for performing ECG collection will receive identical, detailed training at the Investigator meeting 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 on study subjects. After each test has been performed, the ECG data will be transmitted electronically for centralized quality assurance review[redacted] Feedback on the quality of the ECGs will be provided to the investigational site via a site qualification form.

The ECG parameters to be assessed include HR, PR interval, QRS axis, QRS interval, and QT/QTcF interval.

QT intervals and calculated QTcF intervals will be reviewed and checked for gross inaccuracies by the Investigator or designated ECG reviewer. If the calculated QTcF intervals are > 500 msec, and have increased by 60 msec or more over the 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 must be recorded as an AE and reported to the Pearl Medical Monitor.

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

ECGs will be obtained throughout the conduct of the study.

A single ECG will be collected at Visit 1 and when the subject discontinues treatment/withdraws consent.

Timed ECGs will be obtained as follows:

- At Visit 3 only, pre-dose ECGs will be obtained **twice** at least 5 minutes apart and within 60 minutes of dosing
- Pre-dose ECGs will be obtained **once** and within 60 minutes before dosing at Visit 6 and Visit 9

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 procedures for the preparation and collection of blood and urine samples along with all containers needed for their collection.

All clinical laboratory tests (hematology, clinical chemistry, and urinalysis) will be collected at Visit 1 and within 60 minutes prior to dosing at Visits 3, 6, and 9, and if the subject withdraws consent/discontinues treatment.

7.2.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, eosinophils and platelet count will be collected at Visit 1 and 60 minutes prior to dosing at Visits 3, 6, and 9, and if the subject withdraws consent/discontinues treatment.

7.2.4.2 Clinical Chemistry

Albumin, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, total cholesterol, magnesium, phosphate, sodium, potassium, chloride, creatinine, gamma-glutamyl transferase, blood glucose, total protein, triglycerides, bicarbonate, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) will be collected at Visit 1 and

60 minutes prior to dosing at Visits 3, 6, and 9, and if the subject withdraws consent/discontinues treatment.

Refer to Table 7-1 for a list of study-associated laboratory tests.

Table 7-1 Clinical Laboratory Tests

Hematology	
Hemoglobin	Mean corpuscular hemoglobin
Hematocrit	Mean corpuscular hemoglobin concentration
White blood cell count with differential	Mean corpuscular volume
Red blood cell count	Eosinophils
Platelet count	
Clinical Blood Chemistry	
Liver Enzyme and Other Liver Function Tests	**Other Clinical Blood Chemistry**
Alanine aminotransferase	Albumin
Aspartate aminotransferase	Blood Urea Nitrogen (BUN)
Alkaline phosphatase	Calcium
Bilirubin, total	Chloride
Gamma-glutamyl transferase	Cholesterol
	Bicarbonate
	Creatinine
	Glucose
	Magnesium
	Potassium
	Phosphate
	Protein, total
	Sodium
	Triglycerides
Urinalysis	
Macroscopic examination including specific gravity, pH, protein, glucose, ketones, blood, and urobilinogen.	
Other Tests:	
Pregnancy test (women of childbearing potential only): serum hCG at Visit 1 and Visit 9 or Treatment Discontinuation	
Creatinine clearance will be estimated by the CKD-EPI formula [Levy, 2009]	

CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; hCG=human chorionic gonadotropin.

7.2.4.3 Urinalysis

Routine macroscopic urinalysis for specific gravity, pH, protein, glucose, ketones, blood, and urobilinogen will be measured. Based on macroscopic results, a microscopic examination may be performed, if warranted. Urinalysis will be collected at Visit 1 and prior to dosing at Visits 3, 6, and 9 and if the subject withdraws consent/discontinues treatment.

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 Visit 1 and Visit 9 or the Treatment Discontinuation/Withdrawal Visit. A urine pregnancy test will be performed on-site at Visit 3 and Visit 6 (Table 7-1).

7.3 Adverse Events

7.3.1 Performing Adverse Event (AE) Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's eCRF and on the AE Reporting Form. If the AE is unexpected, the Investigator should report the AE immediately to Pearl. In addition, certain AEs (as described in Section 7.3.10) are classified as 'serious' and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as a Serious Adverse Event (SAE) to Pearl or its designee.

In the case of SAEs, after discussing the details of the event, the Investigator and the Medical Monitor may discontinue the subject from treatment 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 is an AE (e.g., bleeding esophageal varices, dental caries)
- Overdose of either study drug or concurrent medication without any clinical signs or symptoms
- Abnormal laboratory values that are not clinically significant; if accompanied by signs/symptoms, the signs or symptoms are considered an AE.

7.3.3 Pre-Randomization AEs

AEs occurring from the time the subject signs informed consent until the subject is randomized will be summarized as medical history and not as an AE unless the event meets the definition of an SAE as defined in Section 7.3.10.

7.3.4 Severity

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

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

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

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

7.3.5 Relationship to Study Drug

The investigator will assess causal relationship between investigational product and each AE, and answer yes/no to the question. 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Any SAE that could be associated with a study procedure the causal relationship is implied as 'yes'.

7.3.6 Chronic Obstructive Pulmonary Disease Exacerbations

All moderate or severe COPD exacerbations must be captured using the COPD Exacerbation eCRF. Mild COPD exacerbations will be evaluated based on symptoms recorded by the subject in the eDiary. Exacerbation(s) of COPD is/are expected to occur as a progression of disease despite standardized drug treatment, or treatment(s) with combination therapies. As a result, Pearl has classified a COPD exacerbation as a protocol specified expected event and it is not to

be reported as an adverse event (AE) unless considered a serious AE (SAE). Subsequently, 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 further medical assessment by Pearl requires it.

7.3.7 AEs of Special Interest

Certain AEs have been identified as adverse events of special interest (AESIs) due to the class of drugs being studied. These AEs will be captured through spontaneous reports 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.

7.3.7.1 LABA Effects

Known effects of LABAs include cardiovascular and tremor effects.

7.3.7.2 Local Steroid Effects

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

7.3.7.3 Pneumonia

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

The criteria established to standardize the diagnosis of pneumonia is as follows:

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 results (infiltrate compatible with pneumonia) will be documented within the eCRF at sites. 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 x-ray (frontal and lateral) within 14 days of the date of pneumonia diagnosis.

7.3.7.4 Paradoxical Bronchospasm

Monitoring for paradoxical bronchospasm will occur at Visits 3, 4, 6 and 9 at 15 and 30 minutes post-dose. In this study, paradoxical bronchospasm is defined as a reduction in FEV_1 of >20% from baseline (i.e., the mean FEV_1 values obtained 60 and 30 minutes prior to study drug administration) that occurs within 30 minutes post-dosing with associated symptoms of wheezing, shortness of breath, or cough. Spontaneous reporting of paradoxical bronchospasm will occur at Visits 5, 7, and 8.

7.3.8 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 Charters. The CEC will review and adjudicate serious CCV events as MACE using the following definition:

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

Charters will be established to govern these processes prior to First Patient First Visit.

7.3.9 Clinical Laboratory Adverse Events

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

7.3.10 Serious Adverse Events (SAEs)

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 jeopardize the subject or 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 at immediate risk of death. It does not include an adverse reaction or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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

7.3.10.1 Reporting of Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for AE identification, documentation, grading, assignment of causality, and prompt notification of SAEs to Pearl Pharmacovigilance or designee. All SAEs must be reported to Pearl Pharmacovigilance or designee no later than 24 hours after the Investigator recognizes/classifies the event as an SAE. All SAEs should be documented and reported using the eCRF. 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 an SAE to Pearl Pharmacovigilance or designee within two working days after receiving the information. Follow-up information will be a detailed written report that may include copies of hospital records, case reports, autopsy reports, and other pertinent documents.

For subjects discontinuing study treatment (i.e., Treatment Discontinuation) but planning to continue study participation (i.e., planning to complete all remaining study visits), all AEs/SAEs will be collected through the last study visit or early termination visit.

Post-study SAEs following the last dose of study drug must be reported to Pearl Pharmacovigilance as described in Section 7.3.10.4.

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

7.3.10.2 Supplemental Investigations of SAEs

The Investigator and supporting personnel responsible for subject care should discuss with the Pearl Medical Monitor or designee any need for supplemental investigations of SAEs. If

additional assessments are conducted, results must be reported to Pearl. If a subject dies during study participation and if a post-mortem examination is performed, a copy of the autopsy report should be submitted to Pearl.

7.3.10.3 Post-Study Follow Up of Adverse Events

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

For subjects discontinuing study treatment (i.e., Treatment Discontinuation) but planning to continue study participation (i.e., planning to complete all remaining study visits), all AEs/SAEs will be collected up will be collected through the last study visit or early termination visit.

7.3.10.4 Notification of Post-Study Serious Adverse Events

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

For subjects discontinuing study treatment (i.e., Treatment Discontinuation) but planning to continue study participation (i.e., planning to complete all remaining study visits), all AEs/SAEs will be collected up will be collected through the last study visit or early termination visit.

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

The Investigator is responsible for promptly notifying her/his Institutional Review Board/Independent Ethics Committee (IRB/IEC) of all SAEs, including any follow-up information, occurring at their site and any SAE regulatory report, including any follow-up reports received from Pearl. Documentation of IRB/IEC submission must be retained for each safety report. The Investigator is also responsible for notifying Pearl if their IRB/IEC requires revisions to the ICF or other measures based on its review of an SAE Report.

7.3.10.6 Health Authority Safety Reports

Pearl or its representatives will submit a safety report to the appropriate regulatory agencies for any suspected adverse reaction that is both serious and unexpected within the timeframe specified by each regulatory agency.

Pearl or its representatives will send copies of each submitted safety report to Investigators actively participating in Pearl-sponsored clinical studies. Safety reports must also be submitted to the appropriate IRBs/IECs as soon as possible. Documentation of submission to the IRB/IEC must be retained for each safety report.

7.3.11 Overdose

An overdose is defined as any dose greater than the highest dose investigated in this study that results in clinical signs and symptoms. In the event of a study drug overdose, the Investigator should use their best clinical judgment in treating the overdose; and the Pearl Medical Monitor should also be contacted. Investigators 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 administered. Such document(s) may include, but not limited to: the Investigator's Brochure for BFF MDI and FF MDI and approved product labeling for open-label products.

7.3.12 Pregnancy

To ensure subject safety, each pregnancy from Visit 1 until study completion must be reported to Pearl within 24 hours of learning of its' occurrence. The pregnancy should be followed in its' entirety to ascertain 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 pregnancy paper form and should include possible relationship to the study drug in response to the pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

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 11 for further instructions in cases of combined increase of aminotransferase and TBL.

7.3.14 Use of Steroids during the Study

At each visit, subjects will be asked whether they have been administered oral, intramuscular, or intravenous corticosteroids since their last visit. Use of oral, IM, or IV corticosteroids for the management of COPD exacerbations or other conditions is not a reason for Treatment Discontinuation or Study Withdrawal. Use of corticosteroids, however, should be documented in the Concomitant Medications eCRF. Subjects who are being treated for a COPD exacerbation with OCS or have been treated for a COPD exacerbation with OCS within 14 days of a 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, IM, or IV corticosteroids for indications other than COPD, should still follow their regular visit schedule. If a subject requires intraocular corticosteroids, the Investigator should make a determination as to the suitability of the subject continuing in the study.

7.3.15 Clinical Endpoint Committees

An external Clinical Endpoint committee will be established for this study. The committee will consist of independent experts who will provide a centralized review, functioning

independently of Pearl. Three Clinical Endpoint Adjudication Charters will outline the clinical endpoints for adjudication.

- Cardio 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

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

7.3.15.2 Cause Specific Mortality Clinical Endpoint Adjudication Charter

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 death will be classified as MACE.

7.3.15.3 Pneumonia Clinical Endpoint Adjudication Charter

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

7.3.15.4 Data Monitoring Committee

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

7.4 Healthcare Resource Utilization

Healthcare resource utilization will be captured at Visits 4 through 9 and whenever treatment discontinued/ consent withdrawn. Data collected will include: number of missed work days; days primary caregiver missed work as a result of the subjects COPD; number and percentage of subjects with telephone calls to health care providers; number and percentage of subjects with visits to health care providers; number and percentage of subjects with Emergency Room (ER) visits; number and percentage of subjects hospitalized along with the corresponding number and percentage of days in the hospital, Intensive Care Unit (ICU), or Critical Care Unit (CCU); and number and percentage of subjects requiring ambulance transport.

7.5 Termination of the Study

An Investigator may choose to discontinue study participation at any time, for any reason and should provide sufficient notice 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 timeframe that is compatible with the subjects' wellbeing.

8 STUDY ACTIVITIES

Please refer to Section 7 for a complete and detailed description of all study procedures and their respective timing. A time and events schedule is provided in Table 8-1. Other detailed schedules are provided for timed assessments of all post-randomization visits in Table 8-2 (Post-randomization Visits 3-9) and Table 8-3 (Visit 6, PFT Sub-study Participants)

GENERAL CONSIDERATIONS

- Subjects who inadvertently took COPD medication(s) within six hours of the start of study procedures must be delayed (but not to exceed dosing by 10am) or rescheduled within the specified visit window.
- Subjects must not ingest xanthine and/or xanthine analogue (caffeine)-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit. Examples of such products include coffee, tea, chocolate, and cola. Decaffeinated beverages are acceptable.
- Subjects will be required to refrain from smoking (nicotine gums or patches are allowed) for at least four hours prior to each study visit and throughout the duration of each visit.
- Subjects will be required to return to clinic at approximately the same time as Visit 3 for all treatment visits (± 2 hours) and dosing time should not exceed 10:00AM. Subjects will be required to remain at clinic until completion of all protocol-defined assessments.
- In order to minimize diurnal variance, sites should make every effort to assess subjects at the same time throughout the study. Sites should discuss the importance of dosing at a consistent time linked to the time of dosing at randomization (e.g., if the initial dose at randomization is administered at 8 am, all subsequent doses should be administered at 8 am and 8 pm. In this case, all subsequent visits should be scheduled to support in-clinic dosing as close to 8 am [the timing of the initial dose at randomization] as possible).
- To ensure dosing time standardization, 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
  - To withhold all inhaled medications (oral and intranasal) for at least 6 hours prior to PFTs
  - Site personnel will instruct subjects not to take any COPD medications, without site personnel permission, during a visit until all study procedures have been completed, and the subject is discharged. Site personnel should take every precaution to prevent subject use of COPD medications during the test day. Site personnel may request the subject to surrender all COPD medications prior to the visit start 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.

Table 8-1 Overall Schedule of Study Events

	Screening[a]		Treatment Period							Follow-up TC
	Visit 1	Visit 2	Visit 3 (R)	Visit 4 Week 4	Visit 5 Week 8	Visit 6 Week 12	Visit 7 Week 16	Visit 8 Week 20	Visit 9 Week 24	14 (+2) Days after last dose
Study Day[b]	Day -28 to -8	Day -21 to -1	Day 1	Day 28±2	Day 56±5	Day 84±5	Day 112±5	Day 140±5	Day 168±5	Day 182
Procedures										
Informed Consent	X									
Inclusion/Exclusion Criteria	X	X	X	X	X	X	X	X	X	
Demographics and Medical/Surgical History Chest Image or MRI[c] CAT	X									
Physical Examination[d]	X								X[n]	
Prior/Concomitant Medications[e]	X	X	X	X	X	X	X	X	X[n]	X
Smoking Status	X	X	X	X	X	X	X	X	X	
Reversibility Testing[f]		X								
Vital Signs	X	X	X	X	X	X	X	X	X[n]	
Clinical Laboratory Testing	X		X			X			X[n]	
12-Lead ECG	X		X			X			X[n]	
Pregnancy Test[g]	X		X			X			X[n]	
Spirometry	X	X	X	X	X	X	X	X	X	
Adjust COPD Medications[h]	X								X[n]	
Adverse Events/COPD Exacerbations	X	X	X	X	X	X	X	X	X[n]	X
Inhalation Device and Dose Indicator Training	X	X	X							
Study Drug Dispensing/Collection	X[i]		X	X	X	X	X	X	X[n]	
eDiary: Dispense/Collect	X[j]								X[n]	
eDiary: Training/Review[k]		X	X	X	X	X	X	X	X[n]	
Study Drug Administration			X	X	X	X	X	X	X	
Questionnaries[l] BDI/TDI SGRQ EQ-5D-5L			X	X	X	X	X	X	X[n]	
HCRU				X	X	X	X	X	X[n]	X
Vital Status Check[m]									X	
PFT Sub-study						X				

BDI/TDI=Baseline Dyspnea Index/Transition Dyspnea Index; CAT=COPD Assessment Test; ECG=electrocardiogram; eDiary=electronic diary; EQ-5D=European Quality-of-Life-5 Dimensions; HCRU=Healthcare Resource Utilization; MRI=Magnetic resonance imaging; R=randomization; PFT=Pulmonary Function Test; SGRQ=St. George Respiratory Questionnaire

[a] Maximum Screening Period is 28 days after Visit 1.
Minimum Screening Period is 8 days after Visit 1 (7 days for LABA washout plus 1 day between Visit 2 and Visit 3) or 15 days if tiotropium washout.
Site should make every effort to maintain subjects within the scheduled visit window. Subjects who fall outside the visit window will be placed in the appropriate visit window at the next scheduled visit.

[b] Sites should call subjects 1-2 days before each scheduled visit to remind subject of visit and to bring all study assigned medications and eDiary.

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

[d] Includes evaluation of height at Visit 1 and weight at Visit 1 and Visit 9, or if subject discontinues study early.

[e] After Visit 1, time of last dose of short-acting bronchodilator and other COPD medications needs to be assessed; if < 6 hours, visit should be rescheduled.

[f] Subjects will be tested for reversibility within 30 minutes following 4 puffs of Ventolin HFA at Visit 2.

[g] Serum pregnancy test at Visit 1 and Visit 9; urine pregnancy test at Visit 3 and 6.

[h] Stop prohibited COPD medications. Subjects receiving an ICS/LABA will discontinue but continue the ICS component for the remainder of Screening Period. Subjects treated with an ICS as part of their inhaled maintenance therapy will continue their ICS for remainder of Screening Period. The ICS medications will be discontinued at Randomization. At the end of Visit 9, return subject to pre-study or other appropriate inhaled maintenance COPD medications.

[i] Sponsor-provided Ventolin HFA is dispensed only after subject determined to be eligible to proceed to Visit 2.

[j] Issue and train subjects on eDiary use, only after subject determined to qualify to proceed to Visit 2.

[k] EXACT included as part of subject diary review.

[l] The BDI/TDI, SGRQ, and EQ-5D-5L should be completed prior to any other visit procedures and in this order: BDI/TDI followed immediately by the SGRQ, then the EQ-5D-5L.

[m] Subjects discontinuing study early should still have vital status check 24 weeks after randomization.

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

Table 8-2 Timed Assessments at Visits 3 through 9

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

BDI/TDI=Baseline Dyspnea Index/Transition Dyspnea Index; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5 Dimensions Questionnaire; EXACT =Exacerbations of Chronic Pulmonary Disease Tool; FEF_{25-75}=forced expiratory flow between 25% to 75% of FVC; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; PEFR=peak expiratory flow rate; SGRQ=St. George's Respiratory Questionnaire

Note: Time point for dosing is regarded as "0 minutes". When data collection time-points are concurrent, variables should be collected in the following order: BDI/TDI, SGRQ, EQ-5D-5L, vital signs, ECG, clinical laboratory assessments, and spirometry.

[a] This is not a timed assessment. Sites should plan to perform these activities to allow for collection of timed spirometry.

[b] EXACT included as part of subject diary review.

[c] Vital signs should be started (approximately 5 to 10 minutes) ahead of the specified time point to ensure spirometry will be conducted as close to the specified time points as possible (i.e., spirometry should be conducted within ±15 minutes of specified time prior to study drug administration; ±5 minutes of specified time for the first 60 minutes after study drug administration; and ±15 minutes of specified time point for assessments obtained thereafter).

[d] Pre-dose vital signs (heart rate, blood pressure) will be collected twice, at least 5 minutes apart at Visit 3 only; at all remaining visits pre-dose vital signs will be collected once. Temperature will be obtained pre-dose and will not be repeated post-dose unless clinically indicated.

[e] Pre-dose ECG will be collected at least twice, 5 minutes apart at Visit 3 only; a single pre-dose ECG will be collected at Visits 6 and 9.

[f] All clinical laboratory tests (hematology, chemistry, and urinalysis) will be assessed within 60 minutes prior to dosing at Visits 3, 6, and 9.

[g] Every effort should be made to assess subjects pre-dose and post-dose FEV_1 at the same time throughout the study.

[h] 5 minutes post-dose spirometry assessment will **ONLY** be collected at Visit 3; remaining post-dose spirometry measurement to be completed at Visits, 3, 4, 6, and 9.

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

[j] Dispense study drug to subject for at-home use following the completion of all post-dose assessments. Study drug will not be dispensed for at home use at Visit 9.

[k] 4 hour post-dose vital signs will be collected at Visit 3, 4, 6 and 9 only.

Table 8-3 Timed Assessments for Subjects Participating in the PFT Sub-study (Visit 6)

	Pre-Dose		Post-Dose									
	Minutes		Minutes		Hours							
Clinical Variable	**-60**	**-30**	**15**	**30**	**1**	**2**	**4**	**6**	**8**	**10**	**11.5**	**12**
Questionnaires TDI SGRQ EQ-5D-5L	X[a]											
Review of Electronic Diary[b]	X[a]											
Vital Signs[c]	X[a,d]			X								X[e]
12-Lead ECG	X[a,f]											
Clinical Laboratory Testing[g]	X[a]											
Spirometry (FEV_1, FVC, PEFR, FEF_{25-75})[h]	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Collection[i]	X[a]											
Study Drug Dispensing[j]		X[a]										

ECG=electrocardiogram; EQ-5D-5L=EuroQol 5 Dimensions Questionnaire; EXACT =Exacerbations of Chronic Pulmonary Disease Tool; FEF_{25-75}=forced expiratory flow between 25% to 75% of FVC; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; PEFR=peak expiratory flow rate; SGRQ=St. George's Respiratory Questionnaire; TDI= Transition Dyspnea Index

Note: The time point at which dosing is to occur is regarded as "0 minutes". When data collection time-points are concurrent, it is recommended that variables be collected in the following order: BDI/TDI, SGRQ, EQ-5D-5L, vital signs, ECG, clinical laboratory assessments, and spirometry.

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

[b] EXACT included as part of subject diary review.

[c] Vital signs should be started (approximately 5 to 10 minutes) ahead of the specified time point to ensure spirometry will be conducted as close to the specified time points as possible (i.e., spirometry should be conducted within ±15 minutes of specified time prior to study drug administration; ±5 minutes of specified time for the first 60 minutes after study drug administration; and ±15 minutes of specified time point for assessments obtained thereafter).

[d] Pre-dose vital signs (heart rate, blood pressure) will be collected once during the PFT sub-study. Temperature will be obtained pre-dose and will not be repeated post-dose at subsequent time points unless clinically indicate

[e] To be completed after final spirometry assessment.

[f] A single pre-dose ECG will be collected within 60 minutes prior to dosing.

[g] All clinical laboratory tests (hematology, chemistry, and urinalysis) will be assessed within 60 minutes prior to dosing.

[h] Every effort should be made to assess subjects pre-dose and post-dose FEV_1 at the same time throughout the study.

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

[j] Dispense study drug to subject for at-home use following the completion of all post-dose assessments.

8.1 Visit 1 (Screening)

- Obtain informed consent
- Register the subject in IWRS to obtain subject screening number
- Obtain demographic data, including age, race, smoking history/status, medical/surgical history (including cardiovascular risk factors and history), and age of onset of COPD
- Review inclusion/exclusion criteria
- Obtain medication history, including COPD medications
- Conduct a serum pregnancy test for all female subjects unless it is documented in the medical history that the subject has been irreversibly surgically sterilized (hysterectomy, oophorectomy, or bilateral tubal ligation) or they are at least 2 years post-menopausal
- Conduct a complete physical examination (general appearance, skin, head, eyes, ears, nose, throat, neck [including thyroid], lymph nodes, chest, heart, abdomen, extremities, and nervous system)
- Record COPD exacerbations and AEs (if any).
  Note: Adverse events that occur during the Screening Period (Visit 1 to Visit 3, before study drug dosing) will be summarized as medical history and not as a study AE, unless the event meets the definition of an SAE
- Obtain height, weight, and vital signs (HR and blood pressure after being supine or seated for five minutes, and oral or tympanic temperature)
- Obtain a 12-lead ECG
- Obtain CAT
- Conduct spirometry assessments
- Confirm subject's ability to use MDI correctly (provide coaching as needed)
- If subject qualifies to continue to Visit 2 perform the following:
  - Obtain laboratory samples (hematology, chemistry, and urinalysis)
  - If Chest x-ray or CT within 6 months of Visit 1 (Screening Period) is not available, obtain a new Chest x-ray (frontal and lateral) except in countries with restrictive radiology assessment practice where only subjects who have had a chest x-ray or CT scan (thorax) performed outside of the study in the last 6 months are allowed to be enrolled. Alternatively, in these countries, an MRI may be used instead of a CT scan or chest x-ray as per local practice assessment
  - Stop prohibited COPD medications and change concurrent COPD medications, as specified in protocol (refer to Section 5.4)
  - Dispense Sponsor-provided Ventolin HFA for use as rescue medication during the Screening Period
  - Refer to Appendix 1Appendix 1 for detailed instructions for Ventolin HFA preparation, administration and cleaning.

- Distribute and train subject on eDiary use
- During the Screening Period, subjects receiving an ICS/LABA will discontinue the ICS/LABA, but will continue the ICS component for the remainder of the Screening Period. Similarly, subjects treated with an ICS as part of their inhaled maintenance therapy will continue their ICS for the remainder of the Screening Period. Ventolin® HFA (albuterol sulfate inhalation aerosol) will be provided by the Sponsor for rescue use throughout the study. The ICS medications will be discontinued at Randomization
- In order to allow for adequate washout of previous maintenance medications, subjects will undergo a Washout Period of at least 1 week (at least 2 weeks if taking Spiriva), but not greater than 26 days in duration prior to returning to the clinic for Visit 2.

- Schedule Visit 2
- Subjects will be instructed to bring their eDiary and all study-related drugs to the next scheduled clinic visit.
  Note: It is recommended that sites call subjects the day BEFORE their scheduled Visit 2 to remind them of these expectations

8.2 Visit 2 (Screening)

- Review subject diary entries and retrain subject if subject has not met diary compliance requirement of ≥ 70% subject completion of diary assessments. Review EXACT for completion as part of eDiary review
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if < 6 hours, Visit 2 must be rescheduled)
- Review inclusion/exclusion criteria and confirm subject eligibility to continue
- Review smoking status
- Record COPD exacerbations and AEs (if any)
  Note: Adverse events that occur during the Screening Period (Visit 1 to Visit 3, pre study drug dosing) will be summarized as medical history and not as a study AE unless the event meets the definition of an SAE.
- Review all prior medications and ensure adherence to COPD regimen
- Obtain vital signs
- Inhalation device and dose indicator training
- Obtain spirometry
- Perform reversibility test to Ventolin HFA (see Section 7.1.1.2 for instructions)
- Schedule Visit 3
  Note: Visit 3 can be scheduled a minimum of one day after Visit 2 but no later than 28 days after Visit 1
- Ensure subject has adequate supply of Sponsor-provided rescue Ventolin HFA

- Subjects will be instructed to bring their eDiary and all study-related drugs to the next scheduled clinic visit.
  Note: It is recommended that sites call subjects the day BEFORE their scheduled Visit 3 to remind them of these expectations

8.3 Visit 3 (Randomization Day 1)

- Review subject diary entries and screen fail subject if subject has not met diary compliance requirement of ≥ 70% subject completion of diary assessments in the last seven days preceding Visit 3. Review EXACT for completion as part of this review.
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if < 6 hours, Visit 3 must be rescheduled)
- Complete BDI questionnaire followed by SGRQ questionnaire, and EQ-5D-5L, before any other study procedures are performed
- Record COPD exacerbations and AEs (if any)
- Review smoking status
- Perform a urine pregnancy test in all women of childbearing potential
- Review all concomitant medications and ensure adherence to COPD regimen
- Collect Sponsor-provided Ventolin HFA dispensed during the Screening Period
- Review inclusion/exclusion criteria and confirm subject eligibility for randomization
- Obtain subject randomization number and treatment assignment information from IWRS.
  Note: The subject is to be considered randomized after receiving a randomization number.
- To allow for proper preparation of study drug, it is recommended that the seal around the study day treatment box be opened 15 to 30 minutes prior to dosing
  - Record/document the dose indicator reading. The dose indicator count recorded by the site staff will be dose indicator count observed after priming but prior to subject dosing. For new MDIs, the recorded count will be the count following the priming of the device but before the subject dose. Refer to Appendix 12 for more details.
- Complete all pre-dose assessments (refer to Table 8-2).
  - Train subject on inhalation device use and reading the dose indicator.
    See Section 6.7 and Appendices 2 and 3 (as applicable) for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
- Once study drug is primed and ready for use, provide assigned study drug to subject
  - Subject will administer first dose of randomized study drug at the clinic
- Perform all post-dosing assessments (refer to Table 8-2)
- Return eDiary to subjects and provide retraining if appropriate

- Subjects will be instructed to bring their eDiary and all issued study drug (including used study drug and rescue Ventolin HFA) to the next scheduled clinic visit
  Note: It is recommended that sites call subjects the day BEFORE their scheduled Visit 3 to remind them of these expectations.
- Schedule Visit 4 and ensure subject has adequate supply of study drug including rescue Ventolin HFA

8.4 Visits 4, 5, 6, 7, and 8 (Weeks 4, 8, 12, 16 and 20)

- Review subject eDiary for data collection compliance
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, visit must be rescheduled)
- Confirm the subject took their last dose of study medication as scheduled the prior evening. If the time of dosing was not in accordance with the protocol, the visit must be rescheduled
- Complete TDI questionnaire followed by SGRQ, and EQ-5D-5L before any other study procedures are performed
- Record COPD exacerbations and AEs (if any)
- Review smoking status
- At Visit 6 only, perform urine pregnancy test in women of childbearing potential
- Review all concomitant medications and ensure adherence to COPD regimen
- Confirm subject eligibility to continue
- Collect HCRU information
- Complete all pre-dose assessments (refer to Table 8-2)
- To allow for proper preparation of study drug, it is recommended the seal around the study day treatment box be opened 15 to 30 minutes prior to dosing
- Prior to dosing, site personnel will use IWRS to assign subjects adequate supply of study drug for in-clinic dosing and to continue dosing at home until the next scheduled visit
  - See Section 6.7 and Appendices 2 and 3 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
  - For new MDIs, the recorded count will be the count following the priming of the device but before the subject doses
  - Record/document the dose indicator readings of the used MDI and the replacement MDI
- Administer in-clinic study drug dose from the new kit assigned at the visit
- Perform all post-dosing assessments (refer to Table 8-2)
- Return eDiary to subjects and provide retraining if appropriate

- Subjects assigned to blinded study drug will be instructed to dose while at home from the site-primed MDI **only,** unless all of the following **replacement conditions** are met:
  - Dose indicator is in the red zone (Refer to Appendices 2 and 12 for dose indicator reading instructions)
  - The dose indicator registers ≤ 10 puffs remaining, **and**
  - Their next scheduled study clinic visit is not the following day

  If these replacement conditions are met, subjects will be instructed to open their replacement kit, prime the MDI and start using for at-home dosing until the next scheduled study clinic visit.
- Subjects will be instructed to bring their eDiary and all study drug (including used study drug and Sponsor-provided rescue Ventolin HFA) to the next scheduled clinic visit
  Note: It is recommended that sites call subjects the day BEFORE their scheduled visit to remind them of these expectations.
- Schedule next visit and ensure subject has adequate supply of study drug including rescue Ventolin HFA

FOR SUBJECTS PARTICIPATING IN THE PFT SUB-STUDY

- For subjects participating in the PFT sub-study, perform additional post-dose assessments at Visit 6 (refer to Table 8-3).

8.5 Final Visit (Visit 9; Week 24)

- Collect subject eDiary
- 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 study medication as scheduled the prior evening. If the time of dosing was not in accordance with the protocol, the visit must be rescheduled
- Complete TDI questionnaire followed by SGRQ, and EQ-5D-5L before any other study procedures are performed
- Record COPD exacerbations and AEs (if any)
- Review smoking status
- Perform serum pregnancy test in all female subjects unless it is documented in the medical history that the subject has been irreversibly surgically sterilized (hysterectomy, oophorectomy, or bilateral tubal ligation) or they are at least 2 years post-menopausal
- Perform all pre-dose assessments (refer to Table 8-2)
- Conduct a physical examination, including weight
- Collect HCRU information
- Review all concomitant medications and ensure adherence to COPD regimen

- Prior to dosing, site personnel will use IWRS to assign subjects a new kit of study drug for in-clinic dosing
  - See Section 6.7 and Appendices 2 and 3 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
  - Record/document the dose indicator readings of the used MDI and the replacement MDI
  - For the new MDI, the recorded count will be the count following the priming of the device but before the subject doses
- Administer in-clinic study drug dose from the new kit assigned at the visit, then collect kit for return.
- Perform all post-dosing assessments (refer to Table 8-2)
- Collect all study drugs including Sponsor-provided Ventolin HFA
- At completion of all Visit 9 assessments, return subject to pre-study or appropriate maintenance COPD medications
- For those subjects who discontinue study treatment but continue to participate in the study to complete all remaining study visits, all AEs/SAEs will be collected through the last study visit or early termination visit.
- Inform subject about reporting all SAEs up to 14 days following the last dose of study drug
- Schedule the follow-up TC at least 14 days from Visit 9

8.6 Procedures for Treatment Discontinuation and Study Withdrawal Subjects

Subjects who discontinue study treatment prior to Week 24 will be encouraged to remain in the study to complete all remaining study visits during the 24 week treatment period. Subjects who agree to continue to be followed post treatment discontinuation will sign an ICF addendum. All subjects who agree to continue study participation beyond treatment discontinuation will complete a Treatment Discontinuation/Study Withdrawal Visit (refer to Section 8.7) prior to transitioning back to regularly scheduled study visits. Subjects participating in a sub-study who choose to discontinue from treatment will only complete regularly scheduled visits and not complete any remaining sub-study assessments. Treatment discontinuation subjects will return to appropriate maintenance COPD medications, per the Investigator's discretion. For subjects recorded as Treatment Discontinuations that do not complete at least one post-treatment data collection, a telephone follow-up call is required at least 14 days after last study drug dose.

If a subject chooses not to continue with study assessments, at a minimum, the subject will complete the Treatment Discontinuation/Study Withdrawal Visit (refer to Table 8-1). These subjects will return to appropriate maintenance COPD medications, per the investigators discretion. A follow-up telephone call will be performed at least 14 days after the last study drug dose. In the event the Treatment Discontinuation/Withdrawal Visit is performed >14

days post last study drug dosing, a follow-up TC will not be required. These subjects will be followed for vital status at 24 weeks post randomization in accordance with the informed consent.

8.7 Unscheduled Visit and Treatment Discontinuation/Study Withdrawal Visit

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

The following minimum procedures will be completed for Treatment Discontinuation/Study Withdrawal Visits:

- Complete TDI questionnaire first; followed by SGRQ questionnaire and EQ-5D-5L before any other study procedures are performed
- Collect HCRU information
- Record COPD exacerbations and AEs (if any)
- Review concomitant medications
- Conduct a physical examination, including vital signs
- Perform ECG and collect blood samples for hematology, chemistry and urinalysis
- Collect a blood sample for pregnancy test for women of child-bearing potential
- Collect subject eDiary
- Collect all study drugs, including rescue medications
- Return subject to pre-study or appropriate maintenance COPD medications
- For subjects discontinuing study treatment (i.e., Treatment Discontinuation) but planning to continue study participation (i.e., planning to complete all remaining study visits), all AEs/SAEs will be collected up will be collected through the last study visit or early termination visit.
- Inform subject about reporting all SAEs up to 14 days following the last dose of study drug
- Capture the reason for treatment discontinuation

8.8 Follow-up Telephone Call

Subjects will be followed up through a TC at least 14 days after the last study drug dosing. The following information will be requested:

- Collect HCRU information
- Review previously on-going COPD exacerbations and AEs and record AEs (if any)
- Review concomitant medications

Note: For subjects who withdraw consent, schedule a follow-up TC at least 14 days after the last study drug dosing unless the visit is performed > 14 days post last study drug dosing, a

follow-up TC will not be required. For Treatment Discontinuation Subjects, a telephone follow-up call is not required as long as at least one post treatment study visit is completed.

8.9 24-Week Post-Randomization Vital Status Confirmation

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

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

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

8.10 Completion of the Study

The Investigator will document the study completion or the reason for early treatment discontinuation or study withdrawal by a subject in the eCRF. **Note:** The End of Study is defined as the date on which data are collected for the last subject's Follow-up Telephone Call.

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
- AE(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 (see Section 5)

9 PLANNED STATISTICAL METHODS

9.1 Introduction

This is a Phase III, randomized, double-blind, multicenter, parallel group, chronic dosing, 24-week lung function study in approximately 2,420 subjects with moderate to very severe COPD who remain symptomatic as measured by the COPD Assessment Test (CAT) while receiving one or more inhaled bronchodilators administered as maintenance treatments.

Subjects will be randomized in a 3:3:3:1:1 ratio to one of the following 5 treatment groups:

- BFF MDI 320/9.6 µg BID (N=660)
- BFF MDI 160/9.6 µg BID (N=660)
- FF MDI 9.6 µg BID (N=660)
- BD MDI 320 µg BID (N=220)
- Symbicort TBH 400/12 µg BID (N=220)

The primary objectives of this study are to assess the effects of BFF MDI relative to BD MDI and FF MDI on lung function. In addition, as secondary and other objectives, this study will assess the effects of BFF MDI relative to FF MDI, BD MDI, and Symbicort TBH on COPD symptoms, quality of life, pulmonary function, safety and tolerability, and HCRU.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

Refer to Section 3 for complete details on all efficacy endpoints.

9.2.2 Safety Endpoints

Refer to Section 3 for complete details on all safety endpoints.

9.2.3 Health Care Resource Utilization Endpoints

Refer to Section 3 for complete details on all HCRU endpoints.

9.2.4 Pulmonary Function Test Sub-study Endpoints

Refer to Section 3 for complete details on all PFT sub-study endpoints.

9.3 Efficacy Analysis

The primary, secondary, and other efficacy analyses will be performed for different estimands. Estimands and analysis populations are discussed in Section 9.12.

9.3.1 Primary Efficacy Analysis

9.3.1.1 Morning Pre-dose Trough FEV_1

Change from baseline in morning pre-dose trough FEV_1 will be analyzed using a linear repeated measures ANCOVA model. The model will include treatment, visit, and treatment-by-visit interaction, and ICS use at Screening as categorical covariates and baseline FEV_1, blood eosinophil count at Screening, 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 the randomization visit. An unstructured covariance matrix will be used to model within subject variability across time points. If this model fails to converge, a first order autoregressive [AR (1)] structure will be used instead. Contrasts will be used to obtain estimates of the treatment differences at Week 24, over Weeks 12 to 24, and over 24 weeks. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be produced for each treatment difference.

The primary efficacy analysis of the morning pre-dose trough FEV_1 will be defined differently by regulatory authority.

- For the US regulatory approach, the comparisons of BFF MDI vs. FF MDI at Week 24 will be a primary analysis.
- For the EU approach, BFF MDI vs. FF MDI over 24 weeks will be a primary analysis. Additionally, BFF MDI 320/9.6 µg vs. Symbicort TBH over 24 weeks will be evaluated for non-inferiority as a primary analysis.

The analysis of this endpoint will be conducted for the efficacy estimand using the mITT Population where only data obtained prior to subjects discontinuing from randomized treatment will be utilized. This population will provide an estimate of the efficacy of the treatments during treatment in the randomized population. Non-inferiority analyses to Symbicort TBH will conducted for the per protocol (PP) estimand. Secondary analyses in this endpoint will be conducted for the attributable estimand.

Supportive Analysis: Analyses will also be conducted for the treatment policy estimand in the ITT Population where all observed data will be utilized regardless of whether subjects remain on randomized treatment. The use of this population will provide an estimate of the treatment strategy effectiveness.

9.3.1.2 FEV_1 AUC_{0-4}

Change from baseline in FEV_1 AUC_{0-4} at Week 24 and over 24 weeks will be analyzed in a similar manner as for morning pre-dose trough FEV_1. The area under the curve (AUC) will be calculated using the trapezoidal rule and will be normalized by dividing by the time (in hours) from dosing to the last measurement included (typically 4 hours). For the mITT Population analysis, only one non-missing, post-dose value is required for the calculation of AUC. For the PP Population, the AUC will be calculated provided that there are at least 2 non-missing values during the first 4 hours post-dose. Actual time from dosing will be used in the calculation if available, otherwise scheduled time will be used.

The primary efficacy analysis of FEV_1 AUC_{0-4} will be defined differently by regulatory authority:

- For the US regulatory approach, the comparisons of BFF MDI vs. BD MDI at Week 24 will be a primary analysis.
- For the EU approach, BFF MDI vs. BD MDI over 24 weeks will be a primary analysis. Additionally, BFF MDI 320/9.6 µg vs. Symbicort TBH over 24 weeks will be evaluated for non-inferiority as a primary analysis.

Like morning pre-dose trough FEV_1, the analysis of this endpoint will be conducted for the efficacy estimand using the mITT Population. Non-inferiority analyses to Symbicort TBH will conducted for the PP estimand. Secondary analyses in this endpoint will be conducted for the attributable estimand.

Supportive Analysis: Analyses will also be conducted for the treatment policy estimand using the ITT Population where all observed data will be utilized regardless of whether subjects remain on randomized treatment. The use of this population will provide an estimate of the treatment strategy effectiveness.

9.3.2 Secondary Efficacy Analyses

9.3.2.1 Time to First Moderate or Severe COPD Exacerbation

The time to first moderate or severe COPD exacerbation will be analyzed to Week 24 using a Cox regression model. Treatment comparisons will be performed using the model, adjusting for percent predicted post-bronchodilator FEV_1, baseline eosinophil count, baseline COPD exacerbation history (Yes/No), country, and ICS use at Screening (Yes/No). Estimated adjusted hazard ratios relative to the comparator for each treatment comparison will be displayed along with the associated Wald two-sided 95% CIs and p-values.

9.3.2.2 Time to Clinically Important Deterioration

For the EU approach, time to clinically important deterioration will be analyzed to Week 24 as a secondary efficacy analysis using a Cox regression model. The model will include treatment, baseline post-bronchodilator percent predicted FEV_1, baseline eosinophil count, baseline COPD exacerbation history (Yes/No), country, and ICS use at Screening (yes/no).

Clinically important deterioration is defined as ≥ 100 mL decrease from baseline in trough FEV_1, or ≥ 4 points increase from baseline in SGRQ total score, or a TDI focal score of -1 point or less, or treatment-emergent moderate-or-severe COPD exacerbation occurring up to Week 24.

9.3.2.3 Saint George's Respiratory Questionnaire (SGRQ)

Responder analyses will be performed where responders are defined as an improvement of ≥4.0 points on average at Week 24, over Weeks 12 to 24, and over 24 weeks. Logistic

regression will be used to compare the treatment groups with baseline SGRQ Score, blood eosinophil count at Screening, baseline post-bronchodilator percent predicted FEV1, and percent reversibility to Ventolin HFA as continuous covariates. Treatment and ICS use at baseline will be categorical covariates. P-values and odds ratios with 95% CIs will be produced for each treatment comparison.

The secondary efficacy analysis of SGRQ will be defined differently by regulatory authority:

- For the US regulatory approach, the comparisons of BFF MDI vs FF MDI and BFF MDI vs BD MDI at Week 24 will be classified as secondary analyses.
- For the EU Approach, BFF MDI vs FF MDI and BFF vs BD MDI over 24 weeks will be classified as secondary analyses. Additionally, BFF MDI 320/9.6 µg vs Symbicort TBH over 24 weeks will be evaluated for non-inferiority as a secondary analysis.

9.3.2.4 Morning Pre-Dose Trough FEV_1

In addition to being a primary efficacy endpoint, morning pre-dose trough FEV_1 will also be a secondary efficacy endpoint. The analysis of morning pre-dose trough FEV_1 will use the same modeling specifications and strategy as with the primary efficacy analysis.

The secondary efficacy analysis of morning pre-dose trough FEV_1 will be defined differently by regulatory authority:

- For the US regulatory approach, the comparisons of BFF MDI vs BD MDI at Week 24 will be classified as a secondary analysis.
- For the EU Approach, BFF MDI vs BD MDI over 24 weeks will be classified as a secondary analysis.

9.3.2.5 Peak Change from Baseline in FEV_1

Peak change from baseline in FEV_1 within four hours post-dosing at Week 24, over Weeks 12 to 24, and over 24 weeks will be evaluated as a secondary efficacy analysis. This analysis will use the same modeling specifications and strategy as with morning pre-dose trough FEV_1.

The secondary efficacy analysis of peak change from baseline in FEV_1 will be defined differently by regulatory authority:

- For the US regulatory approach, the comparisons of BFF MDI vs BD MDI at Week 24 will be classified as a secondary analysis.
- For the EU Approach, BFF MDI vs BD MDI over 24 weeks will be classified as a secondary analysis.

9.3.2.6 Rescue Ventolin HFA Usage

The number of puffs of rescue medication use taken in the previous 12 hours will be recorded in the subject diary in the morning and evening. Diary data recorded during the last 7 days of the Screening Period will be used to calculate the baseline. The mean daily number of puffs of rescue medication use will be calculated overall and for each of the 4-week intervals

during the Treatment Period. 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.

A linear repeated measures ANCOVA model will be used to analyze change from baseline in average daily rescue Ventolin HFA use. The model will include treatment, the number of the relevant 4-week interval (1-6), and the treatment by 4-week interval interaction, and ICS use at Screening as categorical covariates and blood eosinophil count at Screening, baseline rescue Ventolin HFA use, baseline FEV_1, and percent reversibility to Ventolin HFA as continuous covariates. An unstructured correlation matrix will be used to model additional autocorrelation within subject. If this model fails to converge, an AR(1) structure will be used instead; for this model, subject will be considered a random effect. Contrasts will be used to obtain estimates of the treatment differences over 24 weeks. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference.

The secondary efficacy analysis of change from baseline in average daily rescue Ventolin HFA use will be defined differently by regulatory authority:

- For the US regulatory approach, BFF MDI vs BD MDI over 24 weeks will be classified as a secondary analysis.
- For the EU Approach, BFF MDI vs BD MDI over 24 weeks will be classified as a secondary analysis.

9.3.2.7 Transition Dyspnea Index

Assessments of dyspnea will be obtained using the BDI/TDI.

At Randomization, the severity of dyspnea at baseline will be assessed using the BDI. At subsequent visits, change from baseline will be assessed using the TDI. Scoring and handling of missing items will be conducted in accordance with the user's guide for the TDI score. TDI will be analyzed using a RM linear model. Data from all study treatments will be included in the modeling.

The linear RM ANCOVA model will include treatment, visit, and the treatment by visit interaction, and ICS use at Screening as categorical covariates and blood eosinophil count at screening, BDI, baseline post-bronchodilator percent predicted FEV_1, and percent reversibility to Ventolin HFA as continuous covariates. An unstructured correlation matrix will be used to model additional autocorrelation within subject. If this model fails to converge, an AR(1) structure will be used instead; for this model, subject will be considered a random effect. Contrasts will be used to obtain estimates of the treatment differences over 24 weeks. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference.

The secondary efficacy analysis of TDI will be defined differently by regulatory authority:

- For the US regulatory approach, the analysis of TDI is not considered a secondary efficacy analysis.
- For the EU Approach, BFF MDI vs FF MDI and BFF MDI vs BD MDI over 24 weeks will be classified as secondary analyses. Additionally, BFF MDI 320/9.6 µg vs

Symbicort TBH over 24 weeks will be evaluated for non-inferiority as a secondary analysis.

9.3.2.8 Evaluating Respiratory Symptoms in COPD (E-RS: COPD) total score (RS-Total Score)

Mean change from baseline in the daily Evaluating Respiratory Symptoms in COPD (E-RS: COPD) total score (RS-Total Score) will be calculated over 24 weeks. The last 7 days of the Screening Period will be used to calculate the baseline. The mean change from baseline in RS-Total Score will be analyzed using a similar RM model as for TDI to estimate treatment effects over 24 weeks, but using the RS-Total Score baseline mean score instead of the BDI as a covariate. Instead of visit, the number of the relevant 4-week interval (1-6) will be used as a categorical covariate in the model.

The secondary efficacy analysis of RS-Total Score will be defined differently by regulatory approach:

- For the US regulatory approach, the analysis of RS-Total Score is not considered a secondary efficacy analysis.
- For the EU Approach, BFF MDI vs FF MDI and BFF MDI vs BD MDI over 24 weeks will be classified as secondary analyses. Additionally, BFF MDI 320/9.6 µg vs Symbicort TBH over 24 weeks will be evaluated for non-inferiority as a secondary analysis.

9.3.2.9 FEV_1 AUC_{0-4}

In addition to being a primary efficacy endpoint, FEV_1 AUC_{0-4} will also be a secondary efficacy endpoint. The analysis of FEV_1 AUC_{0-4} will use the same modeling specifications and strategy as with the primary efficacy analysis.

The secondary efficacy analysis of FEV_1 AUC_{0-4} will be defined differently by regulatory authority:

- For the US regulatory approach, the analysis of FEV_1 AUC_{0-4} is already defined as a primary efficacy analysis.
- For the EU Approach, the analysis of FEV_1 AUC_{0-4} is already defined as a primary efficacy analysis.

9.3.2.10 Time to Onset of Action

The onset of action for BFF MDI will be evaluated on Day 1 by comparing BFF MDI vs BD MDI in the mean change from baseline in FEV_1 at the 5 minute post-dose timepoint. To perform this analysis, a linear model with repeated measures will be fit to the Day 1 post-baseline data. This model will include baseline FEV_1, percent reversibility to Ventolin HFA, and baseline eosinophil count as continuous covariates and time point, treatment, the treatment by time point interaction, and ICS use at screening as categorical covariates.

Responder analyses will be performed where responders are defined as an improvement of a 100 ml increase from baseline. The percentage of responders at each time point before Hour 1 post-dose will be summarized by treatment, and the difference in response rates versus BD MDI will be presented along with two-sided p-values and the 95% CI of the difference. The median time to response will also be presented by treatment.

9.3.3 Other Efficacy Analysis

9.3.3.1 Additional Spirometry Assessments

FEV_1, FVC, PEFR, and FEF_{25-75} will be collected throughout the study. For each parameter, if not already defined as a primary or secondary analysis, the following analyses will be performed over 24 weeks, over Weeks 12 to 24, and at each post-randomization visit:

- Change from baseline at each time point
- Change from baseline in morning pre-dose trough value
- AUC_{0-4}
- Peak change from baseline within 4 hours of dose

Similar to the primary and secondary analyses, linear repeated measures ANCOVA models will be built to analyze FVC, PEFR, and FEF_{25-75} over 24 weeks, over Weeks 12 to 24, and at Week 24.

9.3.3.2 FEV_1 Response at Day 1

The proportion of subjects achieving a peak improvement from baseline on Day 1 in FEV_1 will be summarized by treatment. The thresholds for improvement are as follows:

- $\geq$ 10% improvement from baseline
- $\geq$ 12% improvement from baseline
- $\geq$ 15% improvement from baseline
- $\geq$ 100 mL improvement from baseline
- $\geq$ 200 mL improvement from baseline
- $\geq$ 12% and $\geq$ 200 mL improvement from baseline

Further analyses will be detailed in the SAP.

9.3.3.3 Rate of COPD Exacerbations

The rate of COPD exacerbations of any severity and moderate-to- severe COPD exacerbations will be analyzed with a negative binomial regression model. Details will be provided in the SAP.

9.3.3.4 Time to Event Analyses

All of the following variables will be analyzed using a Cox regression model:

- Time to treatment failure
- Time to treatment discontinuation for any cause
- Time to CID
- Time to sustained CID
- Time to death

Treatment failure is defined as a moderate or severe COPD exacerbation or discontinuation from treatment for any reason or death. Subjects who do not experience a treatment failure will be censored at their Week 24 Visit or Day 168, whichever comes first.

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

For time to death (all causes), subjects will be censored at the date of last contact. A Cox regression model will be used to compare the treatments, adjusted for baseline percent predicted post bronchodilator FEV_1 and baseline age as covariates. For this endpoint, the primary population will use the ITT Population. This analysis will only be conducted if there are 30 or more deaths in the study.

9.3.3.5 Exacerbations of Chronic Pulmonary Disease Tool (EXACT)

In addition to the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) total score (RS-Total Score) secondary analysis, the RM ANCOVA model will be used to evaluate the difference between treatments in mean change from baseline in: the daily EXACT Total Score, the 11-item RS-Total Score, as well as 3 subscale scores- RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms over 24 weeks, and over each 4-week interval of the 24-week Treatment Period.

9.3.3.6 TDI Focal Score

In addition to the TDI secondary analyses, the RM ANCOVA model will be used to evaluate the difference between treatments over 24 weeks, Weeks 12 to 24, and at each of the individual visits. Similar analyses will be performed for the individual components of the TDI: functional impairment, magnitude of task, and magnitude of effort over 24 weeks, Weeks 12 to 24, and at each post-randomization visit.

Responder analyses will be performed for TDI focal score where responders are defined as a response of 1.0 points or more on average over 24 weeks and over Weeks 12 to 24. Logistic regression will be used to compare the treatment groups with BDI and blood eosinophil count at Screening, percent reversibility to Ventolin HFA as continuous covariates and treatment, and ICS use at Screening as a categorical covariate. P-values and odds ratios with 95% CIs will be produced for each treatment comparison.

9.3.3.7 St. George's Respiratory Questionnaire (SGRQ)

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

The difference between treatments at each of the individual visits will also be evaluated and summarized. Individual domains of the SGRQ will also be analyzed in a similar fashion as the overall score.

The percentage of subjects achieving an MCID of 4 units or more on average in SGRQ total score at Week 24, over 24 weeks, and over Weeks 12 to 24 will be evaluated with a model similar to the one used on the secondary analysis of SGRQ responders.

9.3.3.8 EuroQoL (ED-5D) Dimensions Questionnaire (EQ-5D-5L)

Data from the EQ-5D-5L will be analyzed.

The data will be weighted to calculate an index score based upon subjects' responses to the 5 dimensions. The visual analogue scale (VAS) will be scored from 0 (worst imaginable health state) through 100 (best imaginable health state) to represent the subject's self-report concerning how bad or how good their health was during that day.

EQ-5D will be presented in three different ways:

1. Presenting results from the EQ-5D-5L descriptive system as a health profile at baseline, at all visits, and at EoT (%, n) by domain
2. Presenting results of the VAS as a measure of overall self-rated health status - baseline scores, scores at each visit, changes from baseline at each visit, and mean VAS score over the treatment period
3. Presenting results from the EQ-5D-5L index score (using UK value set) at baseline, each visit, changes from baseline to each visit, and the mean index score over the treatment period.

Further details may be found in the SAP.

The compliance of completing the EQ-5D-5L questionnaires will be described by post-randomization visit, by the number and percentage of subjects who were assessed at that visit.

9.3.4 Type I Error Control

The same general Type I error control strategy will be employed for the US and EU regulatory approaches. In each approach, Type I error will be controlled for the following analyses:

- The primary analyses for the efficacy estimand
- The secondary analysis of the primary endpoints for the attributable estimand
- The remaining secondary analyses

9.3.4.1 US Approach

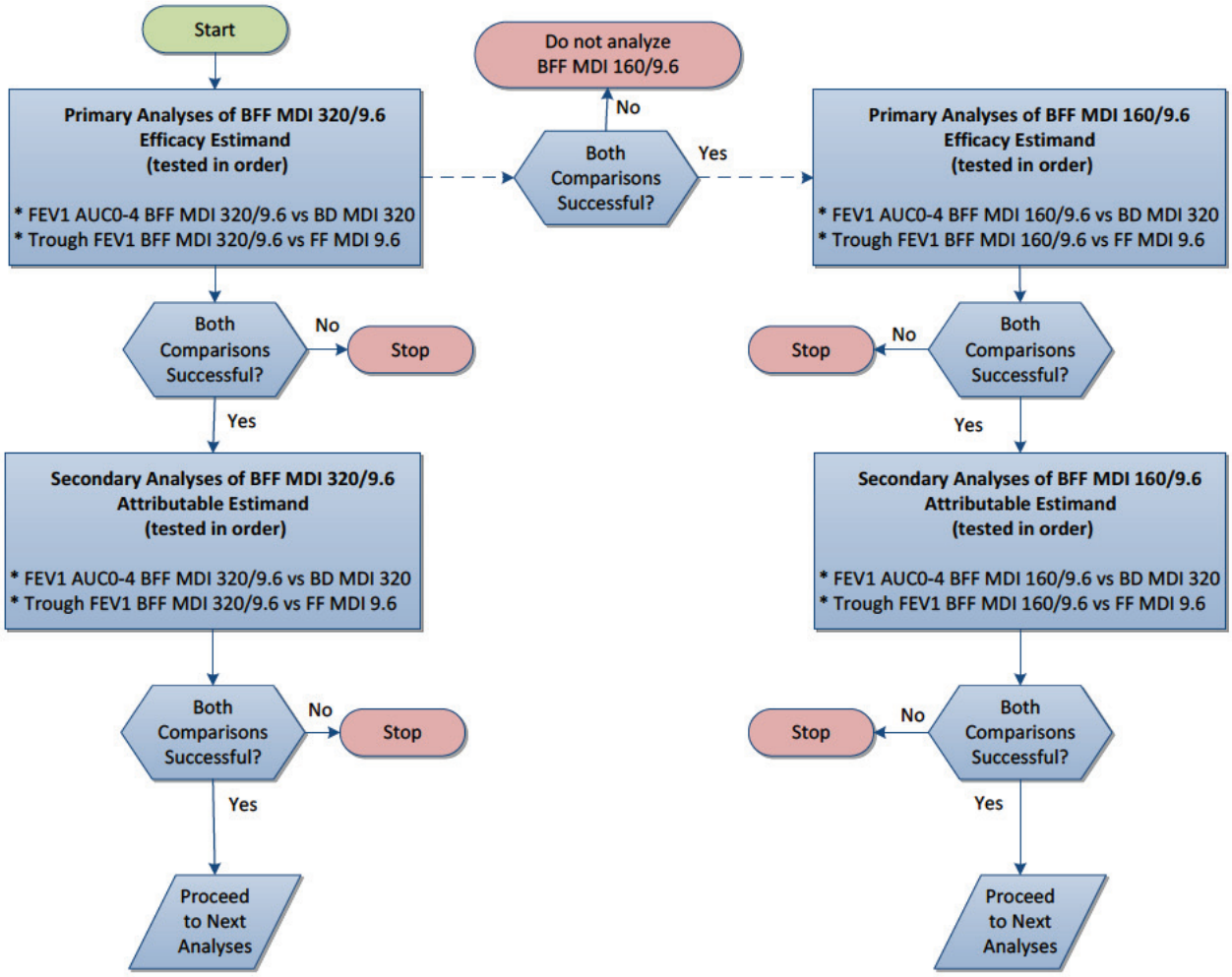
The Type I error rate will be controlled within the primary and secondary efficacy analyses. The primary analyses associated with BFF MDI 160/9.6 will proceed only if all of the primary analyses associated with BFF MDI 320/9.6 are successful (Figure 9-1). The secondary analysis of the primary endpoints for the attributable estimand and remaining secondary analyses for each BFF dose will proceed only if the primary analyses associated with that dose of BFF MDI are successful.

For ease of review, the set of planned analyses has been divided into two groups:

Group 1: The primary analyses for the efficacy estimand and the secondary analysis of the primary endpoints for the attributable estimand.

Group 2: The remaining secondary analyses for the efficacy estimand.

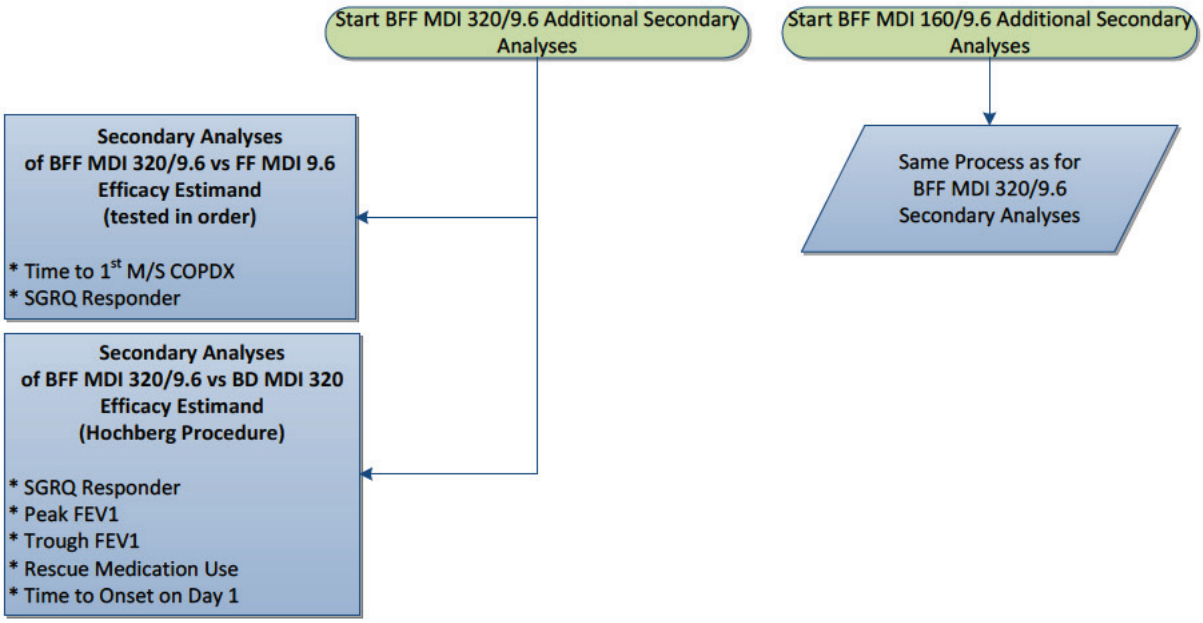
Figure 9-1 Group 1: Type I Error Control for the Analyses of the Primary Endpoints (US Approach)



In Group 1, a sequential multiplicity approach will be used in the analysis of the primary endpoints (See Figure 9-1). In this approach, the analyses of the primary endpoints are listed in a pre-specified order in which they will be tested. Each hypothesis will be tested at the 2-sided 0.05 level. If a p-value is less than 0.05, then that hypothesis is rejected and the next hypothesis is tested. If a primary hypothesis is not rejected, then testing will stop. However, it is noted that p-values will still be calculated for all subsequent analyses for descriptive purposes.

Group 2 analyses are presented in Figure 9-2.

Figure 9-2 Group 2: The Analysis of the Additional Secondary Endpoints (US Approach)

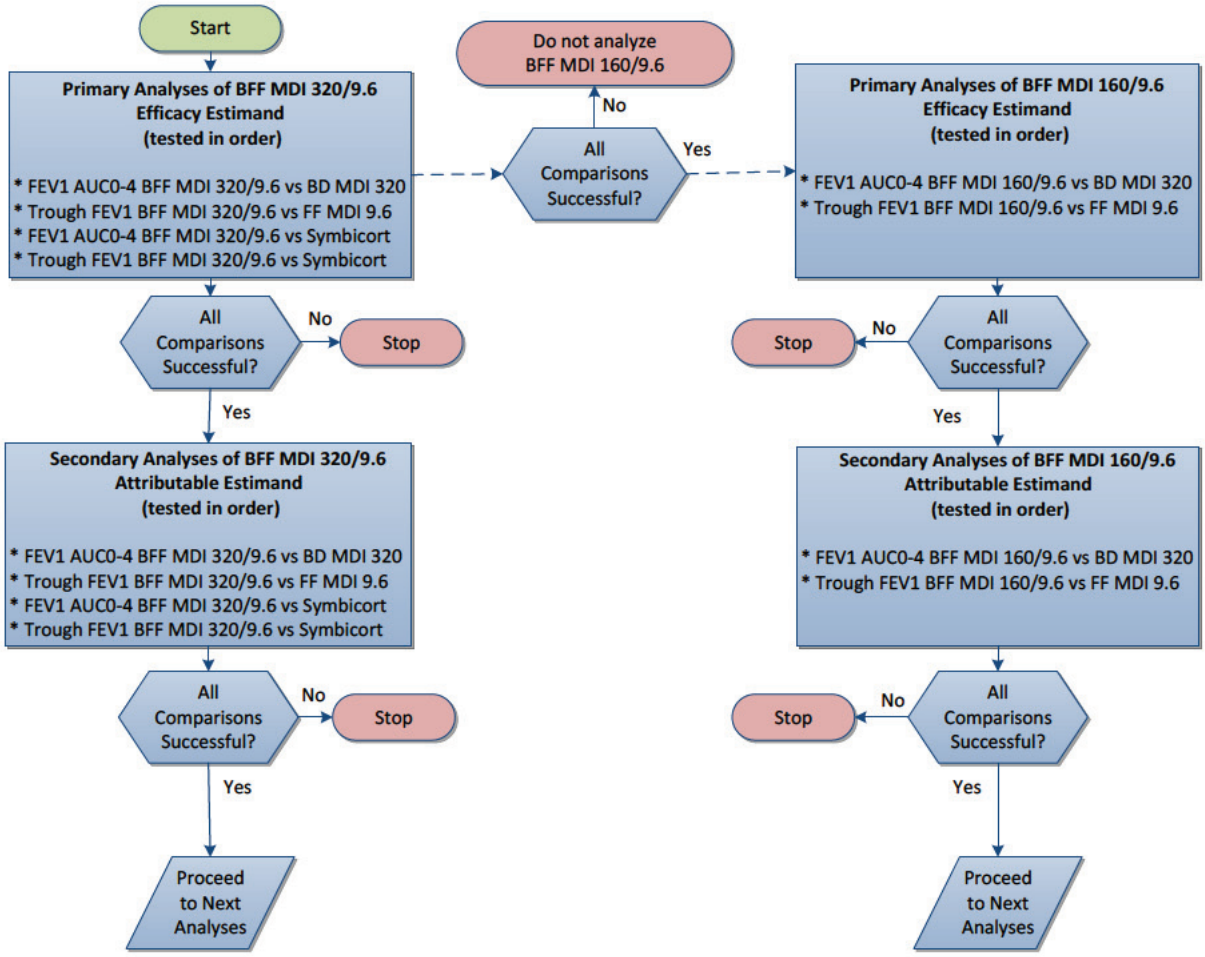


In Group 2, the secondary comparisons to the mono-component control arms will be treated as separate families of hypotheses. The Type I error in each family of secondary analyses will be controlled to alpha with either a sequential testing method or the Hochberg procedure.

9.3.4.2 EU Approach

The EU Approach will follow a similar general strategy as the US Approach. The control of Type I error in the EU Approach differs from the US Approach in the need to compare BFF MDI 320/9.6 µg to Symbicort for non-inferiority and the number of secondary endpoints being evaluated. Otherwise, the Type I error control strategy is similar. The graphical representations of the primary, secondary, and subgroup analyses are presented in Figure 9-3 and Figure 9-4.

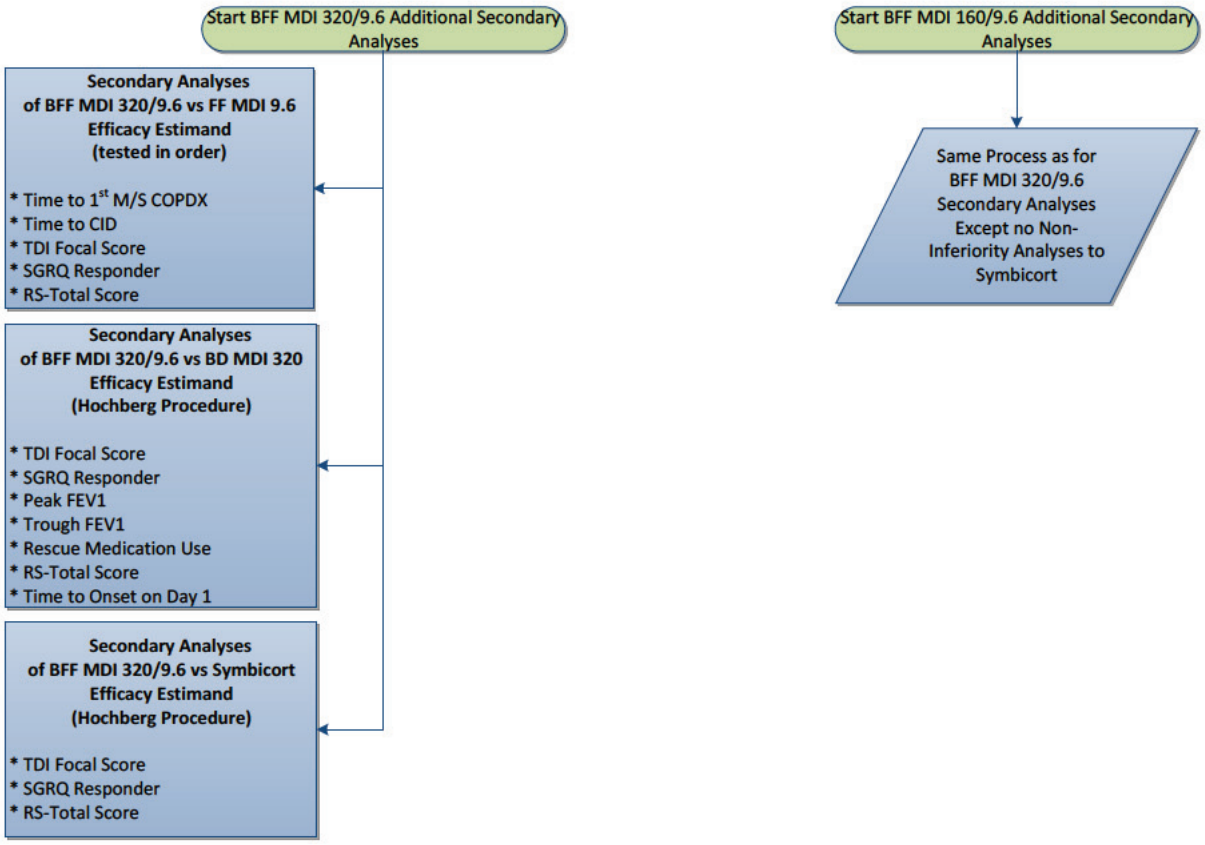
Figure 9-3 Group 1: Type I Error Control for the Analyses of the Primary Endpoints (EU Approach)



If the Group 1 analyses are successful within a BFF MDI dose, the analysis of the remaining secondary endpoints for that BFF MDI dose (Group 2) will proceed under the efficacy estimand.

Group 2 analyses are presented in Figure 9-4.

Figure 9-4 Group 2: The Analysis of the Additional Secondary Endpoints (EU Approach)



9.4 Safety Analysis

9.4.1 Adverse Events

Adverse events during each treatment period will be summarized by the number of subjects experiencing an event. They will be tabulated at the level of the Medical Dictionary for Regulatory Activities (MedDRA) preferred term, and the MedDRA system organ class. The version of MedDRA current at the time the first subject is randomized will be used throughout the study. Tabulations will be broken down by severity, seriousness, AEs leading to discontinuation, and by relationship to study drug. No hypothesis tests will be performed.

9.4.1.1 Adverse Events of Special Interest

AEs of special interest will be tabulated by treatment group. Additional analyses may be performed and will be detailed in the SAP.

9.4.1.2 Clinical Laboratory Measurements

Summary statistics (mean, median, standard deviation [SD], and range) of change from baseline values will be tabulated for each treatment and each assessment time. For clinical

laboratory measurements, baseline will be defined as the last available value prior to Randomization. Potentially clinically significant values will be identified and summarized.

9.4.1.3 Vital Signs

Summary statistics (mean, median, SD, and range) of change from baseline will be tabulated by vital sign parameter and treatment for each scheduled assessment time. For vital signs, baseline will be defined as the average of the values prior to dosing on the day of Randomization. In addition, potentially clinically significant values will be identified and summarized.

9.4.1.4 ECGs

Summary statistics (mean, median, SD, and range) for absolute values and change from baseline will be tabulated by ECG parameter and treatment for each scheduled assessment time. For ECG parameters, baseline values will be defined as the average of the pre-dose measurements taken prior to the start of treatment at the randomization visit (Visit 3). In addition, potentially clinically significant values will be identified and summarized.

9.5 HCRU Analyses

HCRU endpoints will be descriptively summarized by treatment group. Additional analyses may be performed which will be specified in the SAP.

9.6 PFT Sub-Study Analyses

Change from baseline in FEV_1 AUC_{0-12} at Week 12 will be analyzed by treatment. The SAP will contain details of the planned analyses. Data from the PFT sub-study will be descriptively summarized by treatment with tables and figures.

9.7 Randomization

Subjects will be randomized in a 3:3:3:1:1 scheme. Approximately 2,420 subjects will be randomized. Approximately 660 subjects each will be randomized to the BFF MDI 320/9.6 µg, BFF MDI 160/9.6 µg, and FF MDI 9.6 µg treatment groups. Approximately 220 subjects each will be randomized to the BD MDI 320 µg and Symbicort TBH treatment groups. Randomization will be stratified by reversibility to Ventolin (≥ 12% and 200ml or < 12%, measured at Visit 2), post-bronchodilator FEV_1 (< 50% or 50% to < 80% predicted, measured at Visit 2), blood eosinophil count (< 150 or ≥ 150 cells per mm^3), and country. Enrollment will be targeted to achieve a 2:1 ratio for the blood eosinophil strata with twice as many randomized subjects in the ≥ 150 cells per mm^3 category.

9.8 Experimental Design

This study is a multi-center, double-blind, parallel-group, active-controlled design.

9.9 Sample Size Consideration

Assumptions regarding variability for the primary endpoints are based on Pearl Therapeutics' experience with Phase IIb and III clinical studies.

For trough FEV_1, a standard deviation (SD) of 200 mL for the change from baseline at each visit has been assumed. Based on the repeated measures and anticipated dropout of approximately 20%, an effective SD for the change over 24 weeks of 157 mL is assumed. An effective SD for the change over 12 to 24 weeks of 175 mL is assumed.

A SD of 220 mL for FEV_1 AUC_{0-4} at Week 24 is assumed. A SD of 200 mL for FEV_1 AUC_{0-4} over 24 weeks is assumed.

US APPROACH:

It is estimated that a sample size of 2,420 subjects (660 per arm in each of the BFF MDI and FF MDI groups and 220 per arm in the BD MDI and Symbicort TBH groups) will provide approximately 90% power to detect a difference of 40 mL between BFF MDI and FF MDI in morning pre-dose trough FEV_1 at Week 24 with Type I error controlled at a two-sided alpha level of 0.05 and approximately 99% power to detect a difference between BFF MDI and BD MDI of 100 mL in FEV_1 AUC_{0-4} at Week 24 with Type I error controlled at a two-sided alpha level of 0.05. The above calculations assume a 20% dropout rate.

EU APPROACH:

It is estimated that a sample size of 2,420 subjects (660 per arm in the BFF MDI and FF MDI groups and 220 per arm in the BD MDI and Symbicort TBH groups) will provide approximately 99% power to detect a difference of 40 mL between BFF MDI and FF MDI in morning pre-dose trough FEV_1 over 24 weeks and approximately 99% power to detect a difference between BFF MDI and BD MDI of 100 mL in FEV_1 AUC_{0-4} over 24 weeks. In both cases, Type I error is controlled at a two-sided alpha level of 0.05, and a 20% dropout rate is assumed.

With the same sample size, there is 96% power to declare BFF MDI non-inferior to Symbicort TBH in morning pre-dose trough FEV_1 over 24 weeks with Type I error controlled at a two-sided alpha level of 0.05 and a non-inferiority margin of 50 mL. There is 99% power to declare BFF MDI non-inferior to Symbicort TBH in FEV_1 AUC_{0-4} over 24 weeks with Type I error controlled at a two-sided alpha level of 0.05 and a non-inferiority margin of 75 mL.

9.10 Data Validation and Transformation

In general, the distribution of spirometry measures is well approximated by a normal distribution. Under some circumstances, however, (for example during a COPD exacerbation, unrelated to treatment) extreme and atypical values can arise. Such values have high influence on estimation of variance parameters and on standard errors of fixed effect estimates. The distribution of residuals, and influence statistics will be examined to identify such cases. In the event that a single or small number of such outlying values are found to exist and found to be highly influential, the effects may be ameliorated either by

transformation or by removal of the outlier. Transformations to be considered may include the logarithmic transformation, or normal rank transformations. Where outliers are removed, sensitivity analyses including those values will be reported.

Changes in spirometry measures from baseline, and from time point to time point will be examined graphically before data base lock, and before unblinding, as part of data quality management. This will include production of normal probability plots, kernel density estimates, and normal order outlier statistics.

9.11 Analysis Plan

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

9.12 Analysis Populations and Estimands

9.12.1 Analysis Populations

The following analysis populations are defined in this study:

- The **Intent-To-Treat (ITT) Population** is defined as all subjects who are randomized to treatment and receive any amount of the study treatment. Subjects will be analyzed according to the treatment they were assigned at randomization. Data obtained after discontinuation of treatment, but prior to withdrawal from the study, will be included.
- The **Modified Intent-to-Treat (mITT) Population** is a subset of the ITT Population, defined as all subjects with post-randomization data obtained prior to discontinuation from treatment. Any data collected after completion of or discontinuation from randomized study medication will be excluded from the mITT analysis but will still be included in the ITT analysis. Subjects will be analyzed according to randomized treatment group. (Note that a subject who used a study treatment, but took less than one full dose of treatment will qualify for this population). Data obtained after treatment discontinuation will be excluded. The mITT Population will be the primary population for all efficacy analyses except for the non-inferiority analyses. Note: The knowledge that a subject did not have a COPD exacerbation constitutes an efficacy assessment.
- Differences in rescue Ventolin HFA usage are expected across the study including some subjects who used virtually no rescue medication at study entry. In order to represent the population of patients who may benefit from study treatment and reduce their use of rescue medication, the **Rescue Ventolin User (RVU) Population** is defined as all subjects in the ITT Population with mean baseline rescue Ventolin use of $\geq$ 1.0 puff/day.
- The **PP Population** is a subset of the ITT Population, defined as all subjects with post-randomization data obtained prior to any major protocol deviations. Data obtained after any major protocol deviation or discontinuation from treatment will be excluded. Since receiving the wrong treatment is a major protocol deviation, subjects in the PP population will be analyzed as randomized (which for this population is identical to analysis by actual treatment received). Any evaluability criteria with a potential impact on efficacy

results will be identified in a blinded fashion from review of data listings prior to unblinding. Major protocol deviations (protocol violations), therefore, can result in exclusion of all data from a particular subject from the PP population or require exclusion of data from a specific time point and/or subsequent time points for an endpoint.

- The **Safety Population** is defined as all subjects who are randomized to treatment and receive at least one dose of the study treatment. However, subjects will be analyzed according to treatment received rather than randomized. If a subject received more than 1 randomized treatment, they will be analyzed and included in summaries according to the treatment they received the most. Subjects receiving no study treatment will be excluded, as will subjects who have no post-dose safety assessments. A subject who used a study treatment, but took less than 1 full dose of treatment will qualify for this population. Note: The statement that a subject had no AEs also constitutes a safety assessment.
- Analyses will be performed as follows:
  - Demographics will be summarized for the mITT, PP, RVU, Safety, and Non-Randomized Populations, as well as for subjects participating in the 12-hr PFT sub-study.
  - Extent of exposure will be summarized for the Safety Population. The Safety Population will be used to summarize safety.
  - Efficacy analyses will be performed for the ITT, mITT, and PP Populations. In general, the mITT Population will be considered the primary population for the efficacy analyses, with the ITT and PP populations being considered supportive.

9.12.2 Estimands

Four estimands of interest are defined for this study: efficacy estimand, attributable estimand, treatment policy estimand, and per protocol estimand.

The efficacy estimand is the primary estimand of interest and is the effect of the randomized treatments in all subjects assuming continuation of randomized treatments for the duration of the study regardless of actual compliance. The primary analysis for the efficacy estimand will be conducted using the mITT Population where only data obtained prior to subjects discontinuing from randomized treatment will be utilized. This assumes that efficacy observed on treatment is reflective of what would have occurred after discontinuation of randomized treatment had they remained on treatment.

The attributable estimand is the effect of treatment in subjects attributable to the randomized treatment. For this estimand, discontinuation of randomized medication for reasons such as tolerability or lack of efficacy is considered a bad outcome. Analyses of the attributable estimand will be conducted using the mITT Population. Data that are missing due to treatment discontinuation will be imputed based on the 5^{th} or 95^{th} percentile of the reference arms' distribution if the reason is reasonably attributable to tolerability or lack of efficacy. The 5^{th} percentile applies to an endpoint for which a higher value is a better outcome; however the 95^{th} percentile applies to an endpoint for which a higher value is a worse outcome. For this purpose, FF MDI and BD MDI are considered the reference arms. The

estimated average of the two reference means will be used. Other missing data are to be imputed using the observed data model, i.e. assumed to be missing at random (MAR).

The treatment policy estimand is the effect of randomized treatment over the study period regardless of whether randomized treatment is continued. Analyses of the treatment policy estimand will be conducted using the ITT Population, in which all observed data will be utilized regardless of whether subjects remain on randomized treatment.

The per protocol estimand is the effect of treatment on subjects who are compliant with the protocol (i.e., no major protocol deviations), including the use of randomized medication. Analysis of this estimand will use the PP Population.

9.13 Subgroup Analyses

Subgroup analyses will be performed for change from baseline in morning pre-dose trough FEV_1, FEV_1 AUC_{0-4}, and the rate of moderate or severe COPD exacerbations (efficacy estimand only). The following subgroups will be considered:

- History of Moderate or Severe COPD Exacerbation in the last 12 Months:
  - Yes
  - No
- Baseline Eosinophil Count:
  - <150 cells per mm^3
  - ≥150 cells per mm^3
- Country

Each subgroup will be analyzed separately using the same model that was used for the overall (combined subgroups) analysis. Estimates for the treatment effect and for the treatment differences will be displayed in the efficacy endpoint tables for each subgroup.

For each subgroup analysis, a test for the treatment-by-subgroup interaction will be performed using the same model that was used for the overall (combined subgroups) analysis but with the addition of terms for subgroup and the treatment-by-subgroup interaction. A table will be provided with the p-value for the test of the treatment-by subgroup interaction.

Eosinophil Cut Point Exploration

Subgroup analyses of trough FEV_1 will be conducted in the baseline eosinophil count-high (≥150 cells per mm^3) and the baseline eosinophil count-low (<150 cells per mm^3) subgroups. It is acknowledged 150 cells per mm^3 may not ultimately be the appropriate threshold for evaluation of treatment benefit. Thus, additional analyses will evaluate alternative thresholds, and the results from these analyses could then inform thresholds for future clinical studies. This exploration will include using additive mixed models that combine nonparametric

regression for the relationship of eosinophil levels to trough FEV_1 as well as potentially using subgroups defined by different cut points.

9.14 Handling of Missing Data

Pre-dose spirometry values will use the average of the non-missing -60 minutes and -30 minutes values. Weekly averages for eDiary-based parameters will use all non-missing values.

9.15 Statistical Software

Data processing, statistical screening, descriptive reporting and analysis of the efficacy and safety data will be performed using [redacted] Graphs may also be produced using [redacted].

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

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

10.2 Ethical Conduct of the Study and IRB or IEC Approval

This study is to be conducted in accordance with Good Clinical Practice (GCP). These standards respect the following guidelines:

- Guideline for GCP E6 (R1): Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- US CFR dealing with clinical studies (21 CFR parts 50, 54, 56, and 312).
- Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects) http://www.wma.net/en/10home/index.html.
- Any additional regulatory requirements.

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

Pearl will provide the Investigator with relevant document(s)/data necessary for IRB/IEC review 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, when 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. IRB/IEC approval of an amended ICF/other information must be promptly forwarded to Pearl or its' designee.

10.3 Subject Information and Consent

This 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 Pearl prior to initiation of the study.

The Investigator will be responsible for obtaining written informed consent from potential subjects prior to any study-specific Screening. A copy of the signed ICF will be provided to the subject and the original will be retained by the Investigator.

10.4 Confidentiality

10.4.1 Confidentiality of Data

By signing this protocol, the Investigator affirms that information furnished to the Investigator by Pearl will be maintained in confidence. Information relating to this study will be divulged to an IRB/IEC or similar expert committee, affiliated institution, or employees only under an appropriate understanding of confidentiality with said person(s). Data generated by this study will be considered confidential by the Investigator except to the extent that it is included in a publication.

10.4.2 Confidentiality of Subject/Patient Records

By signing this protocol, the Investigator agrees that Pearl (or its' representative), IRB/IEC, 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 agrees to this process. If study documents are photocopied during the process of verifying worksheet/CRF information, the subject will be identified by a unique code; 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), rules and regulations.

10.5 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 a clinical study.

10.6 Data Management

Data management procedures and information for this protocol will be provided by Pearl.

10.7 Study Monitoring

In accordance with applicable regulations, GCP, and Pearl procedures, clinical monitors will contact the site prior to subject enrollment to review the protocol and data collection procedures with site staff. In addition, the monitor will periodically contact the site, including conducting on-site visits. The extent, nature, and frequency of on-site visits will be based on 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

These reviews 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 concerns. Upon completion of the study, the monitor will conduct the following activities in conjunction with the Investigator or site staff, as appropriate:

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

After the final review of the study files, the files should be secured for the appropriate time period as specified in Section 10.8. The Investigator will also permit inspection of the study files by Pearls' Quality Assurance auditors, or designees, including representatives from AstraZeneca, and authorized representatives of the and authorized representatives of the FDA or other applicable regulatory agencies.

10.8 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 Pearls' Quality Assurance auditors and by all applicable regulatory authorities. The period of time these documents must be maintained is governed by county-specific 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-related documents to allow Pearl to make alternate storage arrangements.

10.9 Financial Disclosure

The Principal Investigator or sub-Investigators named on the Form FDA 1572 will need to complete a financial disclosure form prior to study initiation, at any time during the study 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.

10.10 Investigator's Final Report

Following completion of the study, the Investigator will submit a final written report to Pearl.

10.11 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. In addition, Pearl recognizes and adheres to the precepts of the International Society for Medical Publications Professionals (ISMPP), which provides guidance to the preparation of publications, disclosure of conflicts of interest, and the protection of intellectual property. 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:** Pearl, 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, etc. 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 Trials Results:** To provide transparency in the conduct and reporting of randomized clinical trials, Pearl reports clinical findings based on the guidance of The CONsolidated Standards of Reporting Trials (CONSORT) Statement [Mohler, 2010] and a 25-item checklist which is intended to improve the reporting of a randomized controlled trial, facilitate reader understanding of the trial design, conduct, analysis and interpretation, and to support their ability to assess the validity of its results.
7. **Internet Clinical Trial Listing:** In addition, also consistent with the recommendations of the ICMJE, Pearl Therapeutics will make available appropriate information regarding the study via the internet. This will include registration and listing of the study on www.clinicaltrials.gov, the US National Institutes of Health listing of clinical trials.

11 REFERENCE LIST

Celli B, MacNee W, ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004; 23(6):932-46.

Dellamary LA, Tarara TE, Smith DJ, et al. Hollow porous particles in metered dose inhalers. Pharm Res. 2000;17(2):168-74.

EuroQol Group. EQ-5D. Accessed at http://www.euroqol.org/about-eq-5d/how-to-use-eq-5d.html (November, 2014).

Global strategy for the diagnosis, management, and prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016. http://www.goldcopd.org. Accessed 3 March 2016.

Hirst, PH, Pitcairn GR, Weers JG, et al. In vivo lung deposition of hollow porous particles from a pressurized metered dose inhaler. Pharm Res. 2002;19(3):258-64.

Japanese Respiratory Society (JRS). Guidelines for the Diagnosis and Treatment of COPD, 4th edition, 2013.

Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD assessment test. Eur Respir J. 2009;34(3):648-54.

Jones PW, Chen W-H, Wilcox TK, et al. Characterizing and Quantifying the Symptomatic Features of COPD Exacerbations. Chest 2011;139(6)1388-94.

Leidy NK, Sexton CC, Jones et al. Measuring respiratory symptoms in clinical trials of COPD: reliability and validity of a daily diary. Thorax May 2014;69(5):424-30.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest. 1984;85(6):751-58.

Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-338.

Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg. 2012;10(1):28-55. doi: 10.1016/j.ijsu.2011.10.001. Epub 2011 Oct 12. Review.

[redacted]

Witek TJ, Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. Eur Respir J. 2003;21:267-272.