Revised Clinical Study Protocol

Study Code	PT009003
NCT #	NCT02727660
Version	Ver. 4 Amendment 3
Date	08 January 2018

A Randomized, Double-Blind, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT009 compared to PT005 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	09 February 2016
Version 2, Amendment 1	15 July 2016
Version 3, Amendment 2	15 December 2016
Version 4, Amendment 3	08 January 2018

Clinical Trial Protocol: PT009003-03

Study Title:	A Randomized, Double-Blind, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT009 compared to PT005 in Subjects With Moderate to Very Severe COPD
Study Number:	PT009003
Study Phase:	III
Product Name:	Budesonide and Formoterol Fumarate Inhalation Aerosol (PT009, BFF MDI) Formoterol Fumarate Inhalation Aerosol (PT005, FF MDI)
IND Number:	122166
EudraCT Number:	2016-000155-28
Indication:	Chronic Obstructive Pulmonary Disease (COPD)
Investigators:	
Sponsor:	
Sponsor Contact:	

	Version Number	Date
Original Protocol	Version 1.0	09 February 2016
Amended Protocol	Version 2.0	15 July 2016
Amended Protocol	Version 3.0	15 December 2016
Amended Protocol	Version 4.0	08 January 2018

SUMMARY OF CHANGES TO AMENDED PROTOCOL PT009003-02 VERSION 3.0, DATED 15 DECEMBER 2016

The current amended study protocol, PT009003-03 (Version 4.0), includes the following edits:

Sections/Description of Changes	Rationale
Synopsis/Sections 3.2, 3.3, 9.3.3.3 • Amendment clarifies that "time to first clinically important deterioration in COPD" is a secondary endpoint for the ex-US approach and an "other" endpoint for the US approach. • Definition of sustained CID was moved to Section 9.3.3.3.	• Previous version of the protocol mistakenly listed "time to first clinically important deterioration in COPD" as a secondary endpoint in the US approach. It was meant to be a secondary endpoint in the ex-US approach only.
Sections 3.3 and 7.1.4.5 • Amendment renames "EXACT Respiratory Symptoms (E-RS) Total Score" to be "Evaluating Respiratory Symptoms in COPD (E-RS: COPD) Total Score".	• This change was made to reflect the current name of the instrument.
Section 3.4 • Amendment removes temperature from the list of safety endpoints.	• Summaries of mean changes in temperature by treatment are not expected to be informative of patient safety. Abnormal temperature changes at the patient level will be captured as adverse events and summarized.
Section 3.5 Modifications to the list of HCRU endpoints: • New text clarifies that "the number of days missed from work" pertains to the number of days 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.	• The list of HCRU endpoints was updated to align across the PT009 and PT010 development programs.
Table 8-1 and Section 8.5 • Amendment clarifies that smoking status will be evaluated at each study visit.	• This change to the table and text reflects what is currently being performed in the study.

Section 9.3.1.1 New text clarifies the following: • The efficacy estimand will be the primary analysis • 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 and communicates the hierarchy of the estimand analyses.
Sections 9.3.1.1, 9.3.2, and 9.11 • Amendment removes the per protocol population as an analysis population. All references to the per protocol population are removed.	• The per protocol population is only required for non-inferiority analyses. No non-inferiority analyses are specified at this time.
Section 9.3.2.2 • "Country" was added to the statistical model. • The definition of CID was amended to include a condition for TDI.	• The statistical model and definition of CID were updated to align across the PT009 and PT010 development programs.
Section 9.3.2.6 • Language regarding the use of unscheduled visit data was removed.	• The text was removed to align across the PT009 and PT010 development programs.
Section 9.3.3.1 • Language regarding an ITT analysis was removed.	• "Other" endpoints will be analyzed only for the efficacy estimand in the mITT population, as this is the primary estimand of interest.
Section 9.3.3.3 • 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 revamps the Type I Error control strategy to account for new secondary endpoints and the analysis of the primary endpoint under the attributable estimand.	• New secondary endpoints and the inclusion 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 9.11 • Section 9.11 was renamed to be "Analysis Populations and Estimands" • Two subsections, 9.11.1 and 9.11.2, were created to define "analysis populations" and "estimands," respectively. • Language was added to the beginning of Section 9.3 to reference Section 9.11.	• This section was reconfigured to describe both estimands and analysis populations in the same section.
Section 9.11.1 • New text provides more detail for the mITT population definition. • New text defines a Rescue Ventolin User (RVU) population. • New text for safety population was inserted.	• New text clarifies the mITT population definition. • 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 safety population is inserted to make the definition consistent across the clinical development program, which resulted in no material change in the definition. • New text makes it easier to understand what analyses will be performed in what populations.
Section 9.11.2	

• 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 9.12 • 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)
200 Cardinal Way, 2nd Floor
Redwood City, CA 94063

Name of Finished Product
Budesonide and Formoterol Fumarate Inhalation Aerosol (PT009, BFF MDI)
Formoterol Fumarate Inhalation Aerosol (PT005, FF MDI)

Name of Active Ingredient
Budesonide and Formoterol Fumarate
Formoterol Fumarate

Study Title
A Randomized, Double-Blind, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT009 compared to PT005 in Subjects With Moderate to Very Severe COPD

Study Number: PT009003-02

Study Phase: III

Primary Objective
- To assess the effects of BFF MDI relative to FF MDI on lung function

Secondary Objectives
- To assess the effects of BFF MDI relative to FF MDI on COPD exacerbations
- To assess the effects of BFF MDI relative to FF MDI on symptoms of COPD
- To assess the effects of BFF MDI relative to FF MDI on quality of life

Safety Objective
- To assess the safety of BFF MDI and FF MDI

Study Population
Approximately 1,860 subjects with moderate to very severe COPD will be enrolled to provide approximately 1,581 completed subjects. This study will be conducted in approximately 275 sites with each site enrolling 6 to 10 subjects.

To be eligible for the study, subjects must:
- be receiving 1 or more inhaled maintenance bronchodilators at for at least 6 weeks prior to Visit 1
- score ≥ 10 on the CAT at Visit 1
- exhibit FEV_1 ≥ 25 - < 80% of the predicted normal value calculated using appropriate reference equations at Visit 2
- have a documented history of at least 1 moderate or severe COPD exacerbation in the previous 12 months

Study Design
This is a Phase III randomized, double-blind, parallel group, multi-center, variable length efficacy and safety study with BFF MDI (320/9.6 µg and 160/9.6 µg) compared to FF MDI 9.6 µg administered BID.

Subjects will undergo a 1- to 4-week Screening Period. In instances where a COPD exacerbation has occurred during the Screening Period, the Screening Period may be extended to a maximum of 10 weeks (to account for a course of oral corticosteroids and/or antibiotics of up to 2 weeks in duration and a 4-week period of washout after treatment).

In order to allow for adequate washout of previous COPD maintenance medications, subjects will undergo a Washout Period of 1 week or longer, depending on their specific medication(s), but no greater than 26 days prior to returning to clinic for Visit 2.

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

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

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

- BFF MDI 320/9.6 µg BID (N= 620)
- BFF MDI 160/9.6 µg BID (N= 620)
- FF MDI 9.6 µg BID (N= 620)

Randomization will be stratified by exacerbation history (1 or ≥ 2 moderate or severe exacerbations), post-bronchodilator FEV_1 (25% to < 50% predicted or 50% to < 80% predicted, measured at Visit 2), blood eosinophil count (< 150 cells per mm^3 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. Reversibility of FEV_1 to Ventolin will be tested at Visit 2 for characterization purposes only. Following randomization, subjects will enter the Randomized Treatment Period and undergo up to 10 additional treatment visits over 52 weeks.
Subjects who discontinue randomized study treatment prior to the end of study will be encouraged to remain in the study to complete all remaining study visits.

Test Product, Dose, and Mode of Administration

Investigational materials will be provided by the Sponsor, as shown below:

Product Name & Dose	Product Strength	Dosage Form/Fill Count	Administration
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
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 Take as needed throughout screening and treatment periods

BID = Twice Daily; BFF MDI = Budesonide and Formoterol Fumarate Inhalation Aerosol; FF MDI = Formoterol Fumarate Inhalation Aerosol; HFA = Hydrofluoroalkane; MDI = Metered Dose Inhaler
[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 the Sponsor.

Duration of Treatment

Following randomization, each subject is planned to receive randomized treatment for at least 12. The study will end when the last remaining randomized subject completes 12 weeks on randomized treatment or completes the Final Study Visit.

Duration of Study
The duration of the study is variable, and will end when the last remaining randomized subject completes 12 weeks on randomized treatment or completes the Final Study Visit. The study is anticipated to last approximately 18 months and is not expected to exceed 22 months.

Efficacy Endpoints (US regulatory approach)
Primary

- Morning pre-dose trough FEV_1 at Week 12

Secondary

- Time to first moderate or severe COPD exacerbation
- Change from baseline in average daily rescue Ventolin HFA use over 12 weeks
- Percentage of subjects achieving an MCID of 4 units or more in Saint George's Respiratory Questionnaire (SGRQ) total score at Week 12

Additional efficacy endpoints, including those for the Ex-US regulatory approach, are described in Section 3**)**
Refer to Section 7.1.3 for the COPD Exacerbation definition.

Safety Endpoints

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

Statistical Methods
Planned Analyses
The primary efficacy endpoint of morning pre-dose trough FEV_1 will be analyzed using a linear repeated measures ANCOVA model. The primary efficacy analyses will be conducted on the mITT Population. Further information about the primary efficacy analyses along with all other planned analyses are presented in Section 9.

Sample Size
For the analysis of morning pre-dose trough FEV_1 at Week 12 (US Regulatory Approach), the proposed sample size of 1,860 subjects with 15% dropout will provide 90% power to detect a difference of 40 mL between BFF MDI and FF MDI. The Type I error rate will be controlled at a two-sided alpha level of 0.05. Further information about the sample size calculations and the US vs ex-US regulatory approaches are presented in Section 9.

Data Monitoring Committee
An independent, external Data Monitoring Committee (DMC) will be set up to review all serious adverse events (including deaths and all hospitalizations) and pre-defined cardiovascular events. Members of the DMC will review these data generated externally and independently of the Sponsor at predetermined intervals. Based on the safety implications of the data, the DMC may recommend study modification or termination of the study.

Clinical Endpoint Committee
A blinded, independent, external clinical endpoint committee has been implemented for this study. The committee will review, approve, and operate according to three Clinical Endpoint Adjudication Charters that have been established for this study.

- 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: 09 February 2016
Date of Amended Protocol: 08 January 2018

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AR(1)	Autoregressive Order 1
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
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)
CONSORT	CONsolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computerized Tomography
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
e.g.	*Exempli Gratia*, For Example
ERS	European Respiratory Society
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
IBS	Irritable Bowel Syndrome
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
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
QID	*Quarter In Die*, Four Times Daily
QTcF	QT Corrected Using Fridericia's Formula (QT/[RR $^{1/3}$])
RVU	Rescue Ventolin User
SABA	Short-Acting Beta 2 Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SBP	Systolic Blood Pressure
SD	Standard Deviation
TDI	Transition Dyspnea Index
US	United States
VC	Vital Capacity

TRADEMARK INFORMATION

SAS®

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1 INTRODUCTION

The Sponsor 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). The Sponsor is also developing the individual product, Formoterol Fumarate Inhalation Aerosol (PT005; hereafter referred to as formoterol fumarate metered dose inhaler [FF MDI]), as a BID maintenance bronchodilator treatment in subjects with COPD.

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]. COPD exacerbations are characterized by worsening respiratory symptoms beyond normal day-to-day variations, which leads to a change in medication. Exacerbations and co-morbidities contribute to the overall severity in individual patients.

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are β_2-agonists, 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 1 second (FEV_1) value of < 60% of predicted. Withdrawal from treatment of ICS may lead to exacerbations in some patients [GOLD, 2016].

1.2 BFF MDI

The Sponsor 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 Sponsor formulations will provide highly efficient, reproducible administration of therapeutics from MDIs in a wide dosing range [Hirst 2002; Dellamary 2000]. The Sponsor is developing a broad range of MDI-based inhalation products using its porous particle technology platform.

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objectives

- To assess the effects of BFF MDI relative to FF MDI on COPD exacerbations
- To assess the effects of BFF MDI relative to FF MDI on symptoms of COPD
- To assess the effects of BFF MDI relative to FF MDI on quality of life

2.3 Safety Objective

- To assess the safety of BFF MDI and FF MDI

2.4 Healthcare Resource Utilization (HCRU) Objective

- To assess overall and COPD-specific HCRU of BFF MDI and FF MDI

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 two different registration approaches in this study. The registration approaches will be called: (1) US and (2) Ex-US. The US approach is for countries or regions such as the United States where the primary and secondary endpoints are generally evaluated at a point in time. The Ex-US approach is for registration purposes in countries or regions such as Europe where the primary and secondary endpoints are generally evaluated over a period of time.

3.1 Primary Efficacy Endpoint

- Morning pre-dose trough FEV_1 at Week 12 (over 24 weeks Ex-US)

3.2 Secondary Efficacy Endpoints

- Time to first moderate or severe COPD exacerbation
- Time to first clinically important deterioration in COPD (Ex-US)
- Change from baseline in average daily rescue Ventolin HFA use over 12 weeks (over 24 weeks Ex-US)
- Percentage of subjects achieving an MCID of 4 units or more in Saint George's Respiratory Questionnaire (SGRQ) total score at Week 12 (over 24 weeks Ex-US)
- Change from baseline in the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) total score over the treatment period (Ex-US)
- Transient Dyspnea Index (TDI) focal score over 24 weeks (Ex-US)

3.3 Other Efficacy Endpoints

Unless already listed as a secondary efficacy endpoint above, the following will be categorized as other efficacy endpoints:

- Rate of moderate or severe COPD exacerbations over the treatment period
- Change from baseline in morning pre-dose trough FEV_1, forced vital capacity (FVC), peak expiratory flow rate (PEFR), and forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}) over 12, 24 and 52 weeks, and at each post-randomization in-clinic visit
- Rate of COPD exacerbations of any severity
- Time to first COPD exacerbation of any severity
- Rate of severe COPD exacerbation
- Time to first severe COPD exacerbation
- Rate of COPD exacerbations treated with systemic steroids
- Rate of COPD exacerbations treated with antibiotics
- Time to first COPD exacerbation treated with systemic steroids
- Time to first COPD exacerbation treated with antibiotics
- Time to first clinically important deterioration in COPD

- Time to first sustained clinically important deterioration in COPD
- Time to treatment failure (treatment discontinuation for any cause, moderate or severe exacerbation, or death)
- Time to death, all cause
- Time to death, respiratory
- Change from baseline in EXACT total score, Evaluating Respiratory Symptoms in COPD (E-RS: COPD) total score (RS-Total Score), and symptom domain scores for breathlessness, cough and sputum, and chest symptoms over 24 weeks and 52 weeks, and over each 4-week interval of the 52-week treatment period
- Change from baseline in average daily rescue Ventolin HFA use over 12, 24, and 52 weeks and over each 4-week interval of the 52-week period
- Percentage of days with "no rescue Ventolin HFA use"
- TDI focal score over 12, 24 and 52 weeks, and at each post-randomization in-clinic visit
- Individual components of the TDI (functional impairment, magnitude of task, and magnitude of effort) over 12, 24 and 52 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 over 12, 24 and 52 weeks in TDI focal score
- Change from baseline in SGRQ total score over 12, 24 and 52 weeks, and at each post-randomization in-clinic visit
- Change in individual domains of the SGRQ (Symptoms, Activity, and Impacts) over 12, 24 and 52 weeks, and at each post-randomization in-clinic visit
- Percentage of subjects achieving an MCID of 4 units or more on average in SGRQ total score over 12, 24, and 52 weeks, and at each post-randomization in-clinic visit
- EuroQoL (EQ-5D) Dimensions Questionnaire (EQ-5D-5L) variables including the EQ-5D index score, the EQ-5D Visual Analog Score (VAS), and five dimension single item 5-level responses at each post-randomization in-clinic visit

3.4 Safety Endpoints

- 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 health-care 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 health-care 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 the ICU
- The percentage of subjects in the ICU
- The mean number of days in the 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

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a phase III, randomized, double-blind, parallel group, multi-center, variable length efficacy and safety study comparing BFF MDI (320/9.6 µg and 160/9.6 µg) to FF 9.6 µg MDI administered BID, in subjects with moderate to very severe COPD. Eligible subjects must have a history of COPD exacerbations, and remain symptomatic, as measured by the COPD Assessment Test (CAT), while receiving one or more inhaled maintenance bronchodilators.

Subjects will undergo a 1- to 4-week Screening Period. In instances where a COPD exacerbation occurs during the Screening Period, the Screening Period may be extended to a maximum of 10 weeks (to account for a course of oral corticosteroids and/or antibiotics of up to 2 weeks duration followed by a 4-week washout period).

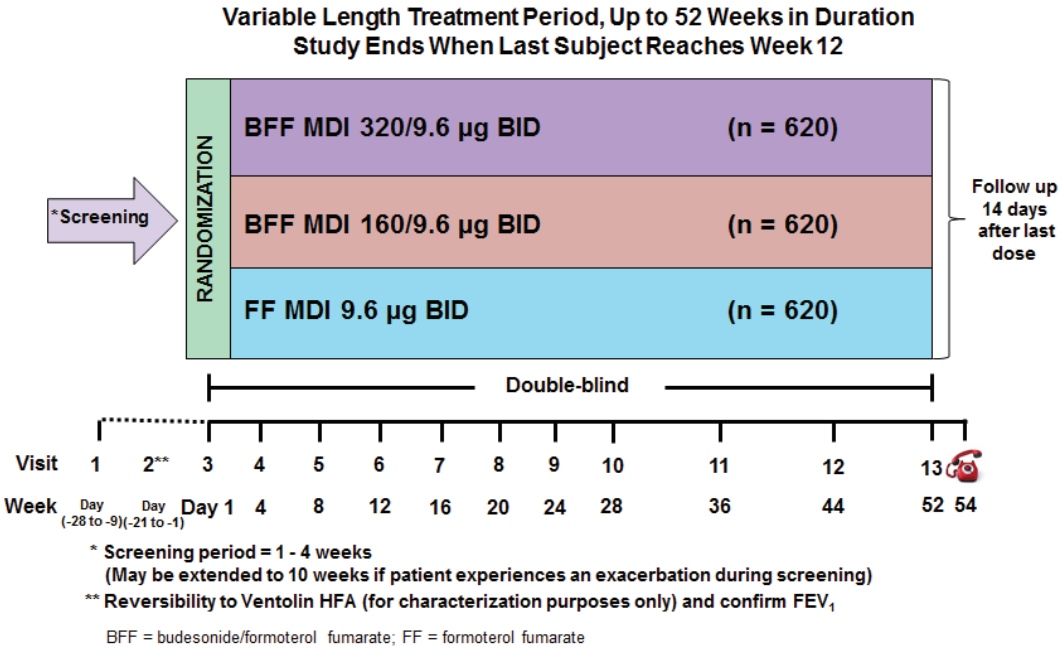
Subjects meeting the inclusion criteria and none of the exclusion criteria will be randomized into the study. Randomization will be stratified by exacerbation history, post-bronchodilator FEV_1, blood eosinophil count, and country. Enrollment will be targeted to achieve a 2:1 ratio for the blood eosinophil strata with twice as many randomized subjects in the ≥ 150 cells per mm^3 category.

Following randomization, subjects will enter the Randomized Treatment Period. The study is variable in length, with a planned minimum of 12 weeks and a maximum of 52 weeks on randomized treatment. The study will end when the last remaining randomized subject completes 12 weeks on randomized treatment or completes the Final Study Visit.

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 overall study design is illustrated in Figure 4-1.

Figure 4-1 Study Design



This international study will be conducted at approximately 275 sites, contributing approximately 6 to 10 subjects per site. It is planned that approximately 1,860 subjects will be randomized to provide approximately 1,581 subjects to complete the study.

4.2 Rationale of Study and Study Design

4.2.1 Overall Study

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 reducing exacerbations and 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 efficacy and safety of BFF MDI compared with FF MDI on lung function, as well as COPD exacerbations, subject-reported symptom outcomes, and health status.

4.2.2 Population

This study will evaluate a patient population with moderate to severe COPD that remains symptomatic despite treatment with one or more inhaled maintenance medications. Symptomatic patients with COPD, demonstrated by a CAT $\geq$ 10, while receiving maintenance medications and history of exacerbation within the last 12 months will be studied because patients with these qualities are at the highest risk for a new exacerbation within the study period [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 3 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 improving lung function and reducing COPD exacerbations. Including two doses of BFF MDI may demonstrate a dose ordering effect on lung function and COPD exacerbation reduction.

4.2.5 Study Duration

The study was originally designed as a 52-week COPD lung function and exacerbation study with a patient population enriched to increase the probability of observing COPD exacerbations. Since the PT009003 protocol was implemented in April 2016, regulatory requirements for the approval of dual and triple inhalation combination products have been refined and the study design has been modified accordingly. In the revised design, the study infrastructure will remain intact; however, the study will end when the last remaining

randomized subject completes 12 weeks on randomized treatment or completes the Final Study Visit. This will ensure that the study will remain fully powered to demonstrate a lung function benefit, as measured by pre-dose trough FEV_1, of the dual- vs. mono-product (i.e., BFF MDI vs. FF MDI) at Week 12. The modified study is also expected to demonstrate a numerical trend on COPD exacerbations.

5 STUDY POPULATION SELECTION AND ELIGIBILITY

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 ≥ 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 ≥ 25% to < 80% predicted normal value
   - 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 1 or more inhaled bronchodilators as maintenance therapy for the management of their COPD for at least 6 weeks prior to Screening
   - **Notes:** the following are included:
     - Scheduled SABA and/or scheduled SAMA
     - Nebulized COPD maintenance medications as long as they are discontinued at Visit 1, and are not used for the remainder of the study
6. History of Exacerbations: (See Section 7.1.3 for COPD exacerbation definition)
   - Subjects must have a documented history of at least 1 moderate or severe COPD exacerbation in the previous 12 months

   Important Notes:
   - Subject's verbal reports are not acceptable
   - Prior use of antibiotics and/or oral corticosteroids alone does not qualify as a COPD exacerbation history unless the use was associated with treatment of worsening COPD symptoms of COPD (e.g. increased dyspnea, increased sputum volume, or a change in sputum color)
   - Antibiotics or corticosteroids used for the treatment of URI with no lower respiratory symptoms do not qualify for the treatment of COPD exacerbation
7. 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)]

8. Willing and, in the opinion of the investigator, able to adjust current COPD therapy, as required by protocol
9. Agree to one of the following to prevent pregnancy:
   - Non-childbearing potential [i.e., physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal, or surgically sterile (defined as having a bi-lateral oophorectomy, hysterectomy or tubal ligation)]

     Note: for purposes of this protocol, menopausal women are 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 a sexually active 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 2 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, diaphragm plus spermicide or condom plus spermicide)
     - Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy
   - If a woman of childbearing potential, have a negative serum pregnancy test
   - Male subjects who are sexually active must agree to use a double barrier method of contraception (condom with spermicide) from the first dose of randomized treatment until 2 weeks after their last dose, and must not donate sperm during their study participation period.
10. Screening Lab Tests must be acceptable to the Investigator
11. Screening 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 at Visit 1, 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
14. Demonstrate correct MDI administration technique

5.2 Exclusion Criteria

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

1. 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 6 weeks prior to Visit 1
g. Lower respiratory tract infections that required antibiotics within 6 weeks prior to Visit 1
h. Treatment with systemic corticosteroids and/or antibiotics (for criteria 1f or 1g above), within 4 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 7 days or 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
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 at least one of the pre-bronchodilator assessments at Visit 2 (-60 minute or -30 minute) and at the post-bronchodilator assessment at Visit 2

Note: Subjects who have met all of the inclusion criteria but have failed to meet spirometry acceptability or repeatability criteria at Visit 1 may continue to Visit 2. Provided these subjects meet all spirometry criteria at Visit 2, including acceptability and repeatability, they are eligible to continue to Visit 3. Subjects who fail to meet acceptability and repeatability criteria at Visit 2 must be considered as screen failed.

- 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

2. 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) with irregular ventricular response, atrial flutter, ventricular tachycardia)
        Note: Clinically stable AF that is appropriately treated with anticoagulation and rate controlled therapies (i.e., selective β-blocker, calcium channel blocker, digoxin, ablation therapy) for at least 6 months is allowed. At pre-randomization visits, resting ventricular rate must be < 100 beats per minute (bpm).
      - Corrected QT interval for heart rate, using Fridericia's formula (QTcF): ≥ 500 milliseconds (msec) with QRS < 120 msec; or ≥ 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)
   e. Uncontrolled hypertension despite pharmacological treatment, as deemed by Investigator
3. 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 ≥ 4 weeks or altered at any point during the Screening Period, or exceeds maximum labeled dose
   c. Cerebrovascular accident (CVA) within 6 months
4. Renal
   a. Underlying significant renal disease that may place subject at risk, as deemed by Investigator

5. Endocrine
   a. Uncontrolled hypo- or hyperthyroidism, hypokalemia, or hyperadrenergic state
   b. Uncontrolled Type I or II diabetes
6. 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
7. 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
8. Cancer
   a. Not in complete remission for at least five years
      Note: subjects with 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
9. Women who are pregnant or lactating, planning to become pregnant during the study course, or of childbearing potential not using acceptable contraception method
10. Hypersensitivity to β2-agonists or corticosteroids or any component of the MDI
11. Significantly abuse alcohol or drugs
12. Unable to abstain from protocol-defined prohibited medications during Screening and Randomized Treatment period (refer to Section 5.4)
13. Using any herbal products either by inhalation or nebulization within 2 weeks and does not agree to stop for the duration of the study
14. Received a live attenuated vaccination within 7 days
15. 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
16. Study Investigators, Sub-investigators, and Coordinators, and their employees or immediate family members
17. Hospitalized for psychiatric disorder or attempted suicide within one year
18. History of psychiatric disease, intellectual deficiency, poor motivation, or other conditions limiting informed consent validity
19. 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
20. Previously randomized in any PT009 or PT010 study conducted or sponsored by the Sponsor

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 policies, availability, and affordability [GOLD, 2016]. 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

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 use of any of the listed medications should be discontinued from randomized treatment but encouraged to continue in the study and complete all 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
LAMAs	7 days: aclidinium, glycopyrronium, umeclidinium 14 days: tiotropium
LABAs (inhaled)	7 days: salmeterol, formoterol, vilanterol 14 days: indacaterol, olodaterol
Fixed-combinations of LABA/LAMA	7 days: umeclidinium/vilanterol 14 days: glycopyrronium/indacaterol, tiotropium/olodaterol
Fixed-combinations of LABA/ICS	7 days
Fixed-combinations of SABAs and SAMAs	6 hours
SABAs[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 antagonists

[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 4 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
- Subjects treated with an ICS as part of their inhaled maintenance therapy will continue their ICS for the remainder of the Screening Period
- Discontinue all other COPD maintenance "as needed" medications as indicated in Table 5-1
- Initiate Sponsor-provided Ventolin HFA to be administered as needed, up to 8 inhalations per day, for control of COPD symptoms
- Subjects receiving phosphodiesterase inhibitors (e.g., roflumilast) at stable doses for at least 4 weeks prior to Visit 1, may continue on these medications throughout the Screening and Randomized 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.

Subjects meeting entry criteria at Visit 1 who are being treated with any of the medications listed in Table 5-2 need to discontinue these medications and observe the minimum washout

requirement before returning for Visit 2. These medications, however, are permitted during the Randomized 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.

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 antagonists (e.g., zafirlukast, montelukast, and zilueton)	7 days
Cromoglycate	7 days
Nedocromil	7 days
Ketotifen [a]	7 days

[a]Ketotifen eye drops are allowed

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 providing they have met the minimum Washout Period prior to Visit 1. These medications are prohibited throughout the course of the study, and, should a subject require use of any of the listed medications, the investigator should evaluate the appropriateness of continuing the subject in the study.

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

Prohibited Medications	Minimum Cessation 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 antiarrhythmics Class Ia, III	7 days, unless amiodarone then 3 months
Anticonvulsants for seizure disorder[b]	Allowed if stable dose for 12 months and free of seizures for 1 year
Tricyclic antidepressants[c]	14 days
Monoamine oxidase inhibitors	14 days
Anti-tumor necrosis factor α antibodies (e.g., infliximab and any other members of this class of drugs)	30 days or 5 half-lives, whichever is longer
Monoclonal antibodies	30 days or 5 half-lives, whichever is longer
Antipsychotic drugs[c]	30 days
Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors, and cimetidine	30 days
Systemic anticholinergics[d]	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])*[e]	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] Anticonvulsants for conditions other than seizures may be started and stopped at any time prior to the study and throughout the randomized treatment period.
[c] Tricyclic antidepressants and antipsychotic agents used for previously diagnosed underlying medical conditions are allowed if, in the opinion of the Investigator, there are no concerns regarding patient safety, and if the patient has been on a stable dose for at least 6 weeks.
[d] If systemic anticholinergics are used for treatment of Irritable Bowel Syndrome or overactive bladder and the treatment has been constant for at least 1 month, they are allowed.
[e] Requires case-by-case review by the Investigator to determine appropriate wash-out 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, 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 the start of Screening (Visit 1) to the end of the Follow-up TC or to whenever the subject withdraws from the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented and the subject will be discontinued at the discretion of the Investigator. Medical marijuana is not an exclusionary drug if used for medical purposes, and there is no change in the dose or frequency of consumption.

5.5.2 Dietary Restrictions

Subjects must not ingest xanthine and/or xanthine analogue (caffeine)-containing foods and beverages and caffeine containing medications for at least six 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 13 (Week 52 or Final Study Visit), 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 13 (Week 52 or Final Study Visit) 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 and electronic cigarettes) for at least 4 hours prior to each in-clinic 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

5.7.1 Reasons for Treatment Discontinuation

Subjects requiring any of the prohibited medications listed in Sections 5.4.2 and 5.4.3 (other than study-provided medication and COPD exacerbation medication), should be withdrawn from randomized treatment but encouraged to continue in the study and complete all study visits.

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

- Calculated QTcF intervals > 500 msec which has increased by ≥ 60 msec from pre-dose baseline value obtained at Randomization
  EU-specific regions only - Calculated QTcF intervals ≥ 500 msec OR ≥ 60 msec from pre-dose baseline value obtained at Randomization
- 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 in the 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
  EU-specific regions only - 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
  EU-specific regions only - 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 obtained at Randomization as determined by the Investigator.
- A decrease in creatinine clearance to a value ≤ 30 mL/minute using the CKD-EPI formula or a clinically relevant change from pre-dose baseline obtained at Randomization as determined by the Investigator.
  EU-specific regions only - A decrease of 33% in calculated creatinine clearance from pre-dose baseline obtained at Randomization using CKD-EPI

5.7.2 Reasons for Study Withdrawal

If a subject becomes pregnant during the course of the study, she will discontinue randomized treatment, and must be withdrawn from the study and followed until delivery or final outcome. (Please see Section 7.3.12 for additional procedures.)

Subjects may be withdrawn from the study at their own request or upon the request of the Investigator or the Sponsor at any time and for any reason. (Please see Sections 8.7 and 8.8 for additional procedures.)

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 the Sponsor as summarized in Table 6-1 below. The Sponsor will provide open-label Ventolin® HFA and manufacturer's instructions for drug administration are provided in Appendix 4.

Table 6-1 Product Descriptions

Product Name & Dose	Product Strength	Dosage Form/Fill Count	Administration
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
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 Take as needed for duration of study

BFF MDI = Budesonide and Formoterol Fumarate Inhalation Aerosol; BID = Twice Daily; FF MDI = Formoterol Fumarate Inhalation Aerosol; HFA = Hydrofluoroalkane; MDI = Metered Dose Inhaler
[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 the Sponsor

6.3 Primary Packaging and Labeling

Investigational materials will be packaged by the Sponsor.

Blinded Supplies: Each BFF 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 HFA will be provided as an individually labeled MDI with a single label on the actuator and a foil pouch containing the Ventolin canister.

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

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

ID = identification; # = number

6.4 Secondary Packaging and Labeling

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

Table 6-2 Description of Boxes

Drug Supplies	Individual Box Contents
Blinded	1 MDI
Ventolin (albuterol sulfate) HFA[a]	1 MDI

HFA = hydrofluoroalkane; MDI = metered dose inhaler

[a]The 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.

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

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

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 Sponsor Medical Monitor or other appropriate Sponsor study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the Investigator must notify the Sponsor 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 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.

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 and FF MDI

Treatment Dispensing
Individual BFF 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 four (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 (two puffs in the morning and two 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 3 for additional instructions on the administration and cleaning of the BFF MDI and FF MDI.

6.7.2 Ventolin HFA® (Albuterol Sulfate)

Refer to Appendix 4 for instructions on the administration 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.

6.8 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 the Sponsor, 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 Sponsor 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 the Sponsor.

Sites should check with the Sponsor's 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 Sponsor's 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 the Sponsor or designee.

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

All product complaints (including device malfunctions) must be reported to the Sponsor or the Sponsor's representative using the Product Complaints Form provided in each site's regulatory binder. The Sponsor 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.

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 in accordance with ATS criteria (refer to Appendix 1) [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 2).

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 2).

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 PFTs on each test day.

In the event that it is not logistically possible to provide such equipment in a specific country, the 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 minimum performance recommendations of the ATS (refer to Appendix 2).

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 the Sponsor or designee for central data management.

For exact spirometry, collection and specifications please see Table 8-1 Schedule of Events and Section 8.1 through Section 8.8.

- 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

- At all remaining in-clinic visits (i.e., Visits 3, 4, 6, 9, 11, and 13 [Week 52 or Final Study Visit]), spirometry will be conducted 60 and 30 minutes prior to study drug administration.

Subjects will be required to return to the clinic 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: Spirometry must meet both acceptability and repeatability criteria at Visit 2 to proceed to Visit 3 (refer to exclusion criteria, Section 5.2).

7.1.1.1 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 30 minutes after the administration of Ventolin

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

7.1.1.2 FEV_1 Baseline Stability Criteria

All comparisons will be made to the baseline (mean of 60 and 30 minutes prior to dosing) values obtained at Visit 3 (Randomization). It is important to ensure that the baseline FEV_1 is stable and reflective of the subject's 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.

7.1.2 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, which 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, is noncompliance with the eDiary, 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. The Sponsor may also instruct a site to discontinue a subject based on consistent noncompliance

7.1.2.1 Rescue Medication Use

Use of rescue medication (i.e., 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.

Note: Subjects requiring more than eight puffs per day on three consecutive days with worsening symptoms should contact the site.

7.1.2.2 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 will be documented in the appropriate study file and reinstruction will be completed as necessary.

7.1.2.3 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.

7.1.3 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.

7.1.3.1 Severity of COPD Exacerbation

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

Exacerbations will be considered moderate if they result in:

- Use of systemic corticosteroids and/or antibiotics for at least 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.

7.1.3.2 Duration of COPD Exacerbation

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

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

7.1.3.3 Approach for Capturing COPD Exacerbations

All moderate or severe COPD exacerbations occurring after Visit 3 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.

7.1.3.4 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 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.

7.1.4 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. 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 7.1.2).

7.1.4.1 Chronic Obstructive Pulmonary Disease Assessment Test (CAT)

The CAT is a self-administered questionnaire designed to assess the condition of subjects and overall impact of COPD [Jones, 2009]. 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 5) 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.

7.1.4.2 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 have 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 in Appendix 6.

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 study drug administration and before any other subject questionnaires to avoid influencing the subject's response. The BDI/TDI questionnaire is a 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 in-clinic, visit and if the subject discontinues treatment/withdraws consent.

7.1.4.3 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 7). 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 in-clinic, post-randomization visit and if the subject discontinues treatment/withdraws consent.

7.1.4.4 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" (100) and "the worst health you can imagine" (0). 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 8) 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 in-clinic, post-randomization visit and if the subject discontinues treatment/withdraws consent.

7.1.4.5 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 [Jones, 2011]. The E-RS was designed to be captured as part of the daily EXACT assessment. On 07 March 2016, the EXACT-Respiratory Symptoms Scale was renamed the Evaluating Respiratory Symptoms (E-RS) measure. When referring specifically to its use in COPD, the proposed context of use for qualification, the full name is now "Evaluating Respiratory Symptoms in COPD (E-RS™: COPD). Summation of E-RS item responses produces a total score ranging from 0 to 40, with higher scores indicating greater severity. In addition to the total score, symptom domain scores can be

calculated for breathlessness (5 items; score range: 0–17), cough and sputum (3 items; score range: 0–11) and chest symptoms (3 items; score range: 0–11) by summing the responses of items within a respective domain. As with the total score, higher domain scores indicate greater severity.

The EXACT (refer to Appendix 9) will be completed daily by the subject as part of the eDiary assessments.

7.2 Safety Assessments

Safety assessments for this study are 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 13 (Week 52 or Final Study Visit), or if the subject discontinues treatment/withdraws consent, and includes 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 13 (Week 52 or Final Study Visit) only, or the Treatment Discontinuation/Study Withdrawal 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 and 30 minutes post-dose
- All remaining in-clinic study visits (Visits 4 to 13 [Week 52 or Final Study Visit]): one vital sign measurement will be collected approximately 60 minutes pre-dose and 30 minutes post-dose

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.

For subjects who have not reached Week 52 when the study ends, and for subjects who discontinue randomized treatment/withdraw consent: a single measurement of vital signs will be obtained at the Final Study Visit and Treatment Discontinuation/Study Withdrawal Visit, respectively.

7.2.3 12-Lead Electrocardiogram

To standardize ECG collection, all sites will be provided with identical ECG equipment (Global Instrumentation M12R Recorder or Global Instrumentation M12R Lite Recorder, Global Instrumentation, Syracuse, New York, US) 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 Sponsor 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 Sponsor Medical Monitor must be contacted immediately.

ECGs will be obtained throughout the conduct of the study as follows:

- 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 (Randomization Visit), pre-dose ECGs will be obtained twice at least 5 minutes apart within 60 minutes of dosing
- At Visits 4, 9 and 13 (Week 52 or Final Study Visit), pre-dose ECGs will be obtained once within 60 minutes prior to dosing

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 prior to dosing at Visits 3, 4, 9 and 13 (Week 52 or Final Study Visit), or 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 prior to dosing at Visits 3, 4, 9 and 13 (Week 52 or Final Study Visit), or 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 prior to dosing at Visits 3, 4, 9 and 13 (Week 52 or Final Study Visit), or 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[a]
Bilirubin, total	Chloride[a]
Gamma-glutamyl transferase	Cholesterol
	Bicarbonate
	Creatinine[a]
	Glucose[a]
	Magnesium
	Potassium[a]
	Phosphate
	Protein, total
	Sodium[a]
	Triglycerides
Urinalysis	
Macroscopic examination including specific gravity, pH, protein, glucose, ketones, blood, and urobilinogen.	
Other Tests:	
Pregnancy test (women of childbearing potential only): serum hCG at Visit 1 and Visit 13 (Week 52 or Final Study Visit) or Treatment Discontinuation/Study Withdrawal Visit	
Creatinine clearance will be estimated by the CKD-EPI formula [Levey, 2009].	

Abbreviations: CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; hCG=human chorionic gonadotropin
[a] Parameters included in the Basic Metabolic Panel.

7.2.4.3 Urinalysis

Routine macroscopic urinalysis for specific gravity, pH, protein, glucose, ketones, blood, and urobilinogen will be measured. 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, 4, 9 and 13 (Week 52 or Final Study Visit), or 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 Visit 1 and Visit 13 (Week 52 or Final Study Visit), or the Treatment Discontinuation/Study 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 the Sponsor. 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 the Sponsor 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 randomized treatment.

7.3.2 AE 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. Note that for SAEs that could be associated with any 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, the Sponsor 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 the Sponsor 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, tremor, glucose, and potassium effects.

7.3.7.2 Local Steroid Effects

Local steroid effects include oral candidiasis, hoarseness, 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, the Clinical Endpoint Committee will review all adverse events and serious 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 are 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 Clinical Endpoint Committee will be empowered to request any additional information, including copies of chest X-rays or CT scans if needed, to confirm the pneumonia diagnosis.

Radiographs will be evaluated locally and the results (infiltrate compatible with pneumonia) will be documented within the eCRF at the 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 through spontaneous reporting.

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 Clinical

Endpoint Committee will review and adjudicate serious CCV events as MACE using the following definition:

- Cardiovascular death
- Non-fatal Myocardial Infarction (MI)
- Non-fatal stroke

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 the14 day follow up telephone call.

Post-study SAEs following the last dose of study drug must be reported to Pearl Pharmacovigilance as described in Section 7.3.10.3.

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 Sponsor Medical Monitor or designee any need for supplemental investigations of SAEs. If additional assessments are conducted, results must be reported to the Sponsor. 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 the Sponsor.

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. The Sponsor retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

7.3.10.4 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 the Sponsor, whether or not the event is attributable to study drug. All SAEs must be reported to the Sponsor no later than 24 hours after the Investigator recognizes/classifies the event as an SAE.

7.3.10.5 Institutional 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 the Sponsor. Documentation of IRB/IEC submission must be retained for each safety report. The Investigator is also responsible for notifying the Sponsor 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

The Sponsor 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.

The Sponsor 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 Sponsor Medical Monitor should 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 are 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 the Sponsor 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 Paternal Exposure

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

7.3.14 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 10 for further instructions in cases of combined increase of aminotransferase and TBL.

7.3.15 Use of Steroids during the Study

At each visit, subjects will be asked whether they have been administered oral, intramuscular, or intravenous corticosteroids since 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.

7.3.16 Clinical Endpoint Committee

An external Clinical Endpoint committee will be implemented for this study. The committee will consist of independent experts outside of the Sponsor who are not involved in the study conduct. Committee members will be blinded with respect to the subject's study medication. At regular intervals, the Committee will review narratives, discharge summaries, and medical records, as available. The committee will review, approve, and operate according to three Clinical Endpoint Adjudication Charters that will be established for this study.

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 as major adverse cardiovascular events (MACE). The Committee will review the program-wide selected MACE events to ensure that they are correctly classified. At regular intervals, the Committee will review narratives, discharge summaries, and medical records, as available, to determine whether the events presented meet the MACE criteria.

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 for cardiovascular and respiratory related events. At regular intervals, the Committee will review narratives, discharge summaries, and medical records, as available, to determine the most likely cause of death, in particular for cardiovascular and respiratory related deaths.

Pneumonia Clinical Endpoint Adjudication Charter

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

7.3.17 Data Monitoring Committee

An independent, external Data Monitoring Committee (DMC) will be set up to review all SAEs (including deaths and all hospitalizations) and cardiovascular events. Members of the DMC will review summaries of these safety data generated externally and independently of the Sponsor in a semi-blinded or unblinded manner 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.

7.4 Healthcare Resource Utilization

Healthcare resource utilization will be captured at Visits 4 through 13 (Week 52 or Final Study Visit) and whenever treatment is 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 of days and percentage of subjects 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 the Sponsor.

The Sponsor 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 the Sponsor, 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.

A time and events schedule is provided in Table 8-1. Other detailed schedules are provided for timed assessments for all post-randomization in-clinic visits.

General Considerations

- Subjects who inadvertently took COPD medication(s) within 6 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 4 hours prior to each study visit and throughout the duration of each study visit.
- In order to minimize diurnal variance, sites should make every effort to assess subjects at the same time throughout the study. 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).
- Subjects will be required to return to the clinic 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.
- To ensure standardization of dosing times, it is recommended that sites encourage subjects to maintain a dosing schedule consistent with their in-clinic dosing time and that sites call the subject on the day before a scheduled visit to remind the subject of the following:
  - To take their last dose the evening before the scheduled visit
  - To bring their study medications and eDiary with them to the clinic
  - To withhold all inhaled medications (oral and intranasal) and any oral medications 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 start of the visit before performing any study procedures and return the COPD medications to the subject at the end of the visit when all study procedures are completed. Subjects will be asked to abstain wherever possible from using rescue Ventolin HFA during study visits. If a subject is experiencing severe symptoms and requires Ventolin HFA for relief of COPD symptoms at any time during a test day, site personnel must note the time and justification of use in the subject's chart and all subsequent spirometry assessments should be stopped. However, safety assessments should be continued at the discretion of the Investigator.
- When the last subject is randomized, all active subjects will be managed as follows:

- Subjects who have not yet completed 12 weeks in the study will continue active participation until 12 weeks of treatment have been completed, at which time sites will perform all required Final Study Visit procedures as noted in Table 8-1.
- For subjects who have completed 12 weeks of treatment and have a scheduled visit within 4 to 8 weeks after the last subject is randomized, their next scheduled visit will be their Final Study Visit. Final Study Visit procedures will be followed for this visit (see Table 8-1).
- Subjects who have exceeded 12 weeks of treatment will complete the Final Study Visit 6 to 8 weeks after the last subject is randomized.
  - For subjects with a scheduled visit within 4 to 8 weeks after the last subject is randomized, their scheduled visit will be their Final Study Visit. Final Study Visit procedures will be followed for this visit (see Table 8 -1).
- The Sponsor will initiate administrative closure activities for the study once the last subject has been randomized. The study will end when the last remaining randomized subject completes 12 weeks on randomized treatment or completes the Final Study Visit (plus the 2-week follow-up telephone call).

Table 8-1 Overall Schedule of Study Events

	Screening		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	Visit 10 Week 28	Visit 11 Week 36	Visit 12 Week 44	Visit 13 Week 52 or Final Study Visit	14 (+2) Days after last dose
Study Day[a]	Day -28 to -9	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 196±5	Day 252±5	Day 308±5	Day 365±5	Day 379
In-Clinic	X	X	X	X		X			X		X		X	
Telephone Contact					X		X	X		X		X		X
Procedures														
Informed Consent	X													
Eligibility Criteria	X	X	X											
Verify Continued Eligibility		X	X	X		X			X		X		X	
Reversibility Testing[b]		X												
Demographics and Medical/Surgical History	X													
Smoking Status	X	X	X	X	X	X	X	X	X	X	X	X	X	
CAT[c]	X													
Prior/Concomitant Medications[d]	X	X	X	X	X	X	X	X	X	X	X	X	X[n]	X
Spirometry	X[d1]	X	X	X		X			X		X		X	
Physical Examination[e]	X												X[n]	
Vital Signs	X	X	X	X		X			X		X		X[n]	
12-Lead ECG	X		X	X					X				X[n]	
Pregnancy Test[f]	X		X			X							X[n]	
Clinical Laboratory Testing	X		X	X					X				X[n]	
Chest Image or MRI[g]	X													
Adjust COPD Medications[h]	X												X[n]	
Adverse Events/COPD Exacerbations.	X	X	X	X	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]	
Study Drug Administration			X	X		X			X		X		X	
BDI/TDI[j]			X	X		X			X		X		X[n]	
SGRQ[j]			X	X		X			X		X		X[n]	
EQ-5D-5L[j]			X	X		X			X		X		X[n]	
HCRU				X	X	X	X	X	X	X	X	X	X[n]	X

	Screening		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	Visit 10 Week 28	Visit 11 Week 36	Visit 12 Week 44	Visit 13 Week 52 or Final Study Visit	14 (+2) Days after last dose
Study Day[a]	Day -28 to -9	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 196±5	Day 252±5	Day 308±5	Day 365±5	Day 379
In-Clinic	X	X	X	X		X			X		X		X	
Telephone Contact					X		X	X		X		X		X
Procedures														
eDiary Dispensing/Collection[k]	X												X[n]	
eDiary Training / Re-Training[k]	X	X												
eDiary Review[l]		X	X	X	X	X	X	X	X	X	X	X	X	
Vital Status Check[m]													X	

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

a. Scheduling Visits: The maximum Screening Period is 28 days; the earliest a subject can be randomized from Visit 1 date is 8 days (7 days for LABA washout plus 1 day between Visit 2 and Visit 3) or 16 days if subject is washing off of tiotropium; The minimum Screening Period (between 1 and 4 weeks in duration) can be extended to a maximum of 10 weeks in case of an exacerbation during the Screening Period. Site should make every effort to maintain subjects within the scheduled visit window. Subjects who fall outside the visit window will be placed in the appropriate visit window at the next scheduled visit.

b. Subjects will be tested for reversibility within 30 minutes following 4 puffs of albuterol (Ventolin HFA) at Visit 2.

c. Subjects will complete the CAT at Visit 1 and as an entry criterion.

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

d1. **Note**: Subjects who have met all of the inclusion criteria but have failed to meet acceptability or repeatability criteria at Visit 1, may continue to Visit 2. Provided these subjects meet all spirometry criteria at Visit 2, including acceptability and repeatability, they are eligible to continue to Visit 3. Subjects who fail to meet acceptability and repeatability criteria at Visit 2 must be screen failed.

e. Includes evaluation of weight at Visit 1 and Visit 13 (Week 52 or Final Study Visit) only, or the Discontinuation/Early Termination Visit and evaluation of height at Visit 1 only.

f. Serum pregnancy test will be performed at Visit 1 and at Visit 13 (Week 52 or Final Study Visit). At Visit 3 and 6 (Week 12), a urine pregnancy test will be performed.

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

h. At Visit 1, stop prohibited COPD medications and change COPD medications. At the end of Visit 14, return subject to pre-study or other appropriate inhaled maintenance COPD.

i. Ventolin HFA is dispensed only after a subject is determined eligible to proceed to Visit 2 (i.e., only if subject meets COPD definition following spirometry assessments at Visit 1).

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

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

l. Subjects will be asked to maintain a daily record of their study drug dosing and rescue medication use. EXACT will be reviewed at each visit as part of the e Diary review.

m. Vital status check for all subjects. For subjects who withdraw from the study, the vital status check will be conducted 4 to 6 weeks after the last subject is randomized.

n. These are the minimum procedures that should be completed at a Treatment Discontinuation/Study Withdrawal Visit.

Table 8-2 Timed Assessments for all Post-randomization In-clinic (Visits 3, 4, 6, 9, 11, and 13 (Week 52 or Final Study Visit])

Clinical Variable	Pre-dose		Post-dose
	- 60 minutes	-30 minutes	30 minutes
Review of Electronic Diary[a]	X		
Vital Signs[b]	X		X
Spirometry	X	X	
12-Lead ECG[c]	X		
Clinical Laboratory Testing[d]	X†		
Study Drug Collection[e]	X†		
BDI/TDI	X†		
SGRQ	X†		
EQ-5D-5L	X†		

Abbreviations: BDI/TDI=Baseline Dyspnea Index/Transition Dyspnea Index; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5 Dimensions Questionnaire; SGRQ=St. George's Respiratory Questionnaire

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, and clinical laboratory assessments.

† 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 vital signs and ECGs.

a. EXACT will be reviewed at each visit as part of the subject diary review. Refer to Section 7.1.2 for details on subject diary review.

b. Temperature will be obtained pre-dose at all visits and will not be repeated post-dose at subsequent time points unless clinically indicated. Refer to Section 7.2.2 for vital signs assessments and specific time points.

c. ECGs will be performed at Visits 3, 4, 9, and 13 (Week 52 or Final Study Visit) only (Day 1, and Weeks 4, 24, and 52); see Table 8-1. Refer to Section 7.2.3 for ECG assessments and specific time points.

d. Clinical laboratory tests will be performed at Visits 3, 4, 9 and 13 (Week 52 or Final Study Visit) only (Day 1, and Weeks 4, 24, and 52); see Table 8-1. All clinical laboratory tests (hematology, chemistry, and urinalysis) will be assessed within 60 minutes prior to dosing at these visits. Females of childbearing potential will undergo a urine hCG screening at in-clinic Visits 3 and 6 (Day 1, Week 12). Refer to Section 7.2.4 for clinical laboratory assessments and specific time points.

e. 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.

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 5 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) is not available, obtain a new Chest x-ray 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)
  - Obtain subject assignment information of Ventolin HFA from IWRS and provide subjects with study drug as assigned by IWRS
  - Dispense and train subject on eDiary use
  - During the Screening Period, subjects that are receiving an ICS/LABA will discontinue the ICS/LABA, but will continue the ICS component for the remainder of the Screening Period. Similarly, subjects treated with an ICS as part of their inhaled maintenance therapy will also be permitted to continue their ICS for the remainder of

the Screening Period. Ventolin® HFA (albuterol sulfate inhalation aerosol) will be provided for rescue use throughout the study

- 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. In instances where an exacerbation has occurred during the Screening Period, the Screening Period may be extended to a maximum of 10 weeks (to account for a course of OCS of up to 2 weeks in duration and a 4-week period after treatment for exacerbation)

- Inhalation Device and Dose Indicator Training (See Appendices 3 and 11)
- Schedule Visit 2
  - Adverse events and COPD exacerbations must be recorded during the Screening Period, that is, from the time of consent to the start of study treatment
  - It is recommended that sites call subjects on the day before their scheduled Visit 2 and remind them of these expectations for the upcoming visit
- Subjects will be instructed to bring their eDiary and Sponsor-provided Ventolin HFA to the next scheduled clinic visit

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
- 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 AEs unless the event meets the definition of an SAE
- Review all prior medications and ensure adherence to COPD regimen
- Obtain vital signs 60 minutes pre-bronchodilator and 30 minutes post-bronchodilator
- Perform reversibility test to Ventolin HFA (sees Section 7.1.1.1 for instructions) and confirm if subject continues to meet entry criteria based on pre- and post-dose spirometry quality (see Section 5.2, Exclusion Criterion 1.t.), and post-dose spirometry values
- Obtain spirometry pre-bronchodilator 60 and 30 minutes and 30 minutes post bronchodilator
- Inhalation Device and Dose Indicator Training (See Appendices 3 and 11)
- Schedule Visit 3
  Note: Visit 3 can be scheduled a minimum of 1 day after Visit 2 and no later than 27 days after Visit 1 (Screening). In instances where an exacerbation has occurred during

the Screening Period, the Screening Period may be extended to a maximum of 10 weeks (to account for a course of oral corticosteroids of up to 2 weeks in duration and a 4-week period after treatment of the exacerbation).

- Ensure subject has adequate supply of Sponsor-provided rescue Ventolin HFA
- Provide subjects with Ventolin
- Subjects will be instructed to bring their eDiary and Sponsor-provided Ventolin HFA to the next scheduled clinic visit

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 7 days preceding Visit 3
- Have subject 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
- A urine pregnancy test will be performed for women of childbearing potential
- Review all concomitant medications and ensure adherence to COPD regimen
- Collect Sponsor-provided Ventolin HFA dispensed during the Screening Period
  - Ventolin HFA will be provided for rescue use throughout the study
- 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.
- Complete all pre-dose assessments (refer to Table 8-2)
  - Obtain central laboratory tests
  - Obtain vital signs and ECGs twice at least five minutes apart 60 minutes pre-dose
- Perform spirometry assessments -60 and -30 minutes pre-dose (see Table 8-2)
- To allow for proper preparation of study drug, it is recommended that the seal around the study day treatment box is opened 15 to 30 minutes prior to dosing and the instructions for administration of study drug followed
- Refer to Appendix 4 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits
- Record/document the dose indicator reading. The dose indicator count recorded by the site staff will be dose indicator count observed after priming but prior to subject dosing. For new MDIs, the recorded count will be the count following the priming of the device but before the subject dose
- Subject will administer first dose of randomized study drug at the clinic
- Perform all post-dosing assessments (see Table 8-2)

- Obtain vital signs 30 minutes post-dose

- 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
- Inhalation Device and Dose Indicator Training (see Appendices 3and 11)
- Provide subjects with study drug as assigned by IWRS
- Schedule Visit 4 and ensure subject has adequate supply of study drug including rescue Ventolin HFA

8.4 In-Clinic Visits 4, 6, 9, and 11 (Weeks 4, 12, 24, and 36)

- 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)
- Review smoking status
- A urine pregnancy test will be performed for women of childbearing potential at Visit 6 only
- Confirm subject eligibility to continue
- Confirm the subject took their last dose of randomized study drug as scheduled the prior evening. If the time of dosing was not in accordance with the protocol, then the visit must be rescheduled.
- At each in-clinic post-randomization visit, have subject complete TDI questionnaire followed by SGRQ, and EQ-5D-5L questionnaires, if applicable, before any other study procedures are performed
- Collect HCRU information
- Record COPD exacerbations and AEs (if any)
- Review all concomitant medications and ensure adherence to COPD regimen
- Perform all pre-dose assessments (see Table 8-2)
  - Obtain central laboratory tests at Visits 4 and 9
  - Obtain vital signs 60 minutes pre-dose at each in-clinic visit
  - Obtain ECGs 60 minutes pre-dose at Visits 4 and 9
  - Perform spirometry assessments -60 and -30 minutes pre-dose (see Table 8-2)
  - Return eDiary to subjects and provide retraining if appropriate
- 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 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 new MDIs, the recorded count will be the count following the priming of the device but before the subject doses

- Administer in-clinic study drug dose from the new kit assigned at the visit
- Perform all post-dosing assessments (refer to Table 8-2)
  - Obtain vital signs 30 minutes post-dose
- Subjects will be instructed to track study drug dosing in their eDiary between study clinic visits
- Subjects will be instructed to dose while at home from the site-primed MDI **only**, until all of the following **replacement conditions** are met:
  - Dose indicator is in the red zone (See Appendix 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 conditions are met, subjects will be instructed to open their supplemental kit, prime the MDI and start using it for at home dosing until the next scheduled study clinic visit
- Provide subjects with study drug as assigned by IWRS
- 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
- Schedule next visit and ensure subject has adequate supply of study drug including Sponsor-provided rescue Ventolin HFA
- For subjects who discontinue study treatment (randomized study medication) and continue in the study, the scheduled study visit, data collection, and procedures will be done according to the study protocol see Sections 8.7 and 8.8

8.5 Telephone Contact at Visits 5, 7, 8, 10, and 12 (Weeks 8, 16, 20, 28, and 44)

- Collect HCRU information
- Record COPD exacerbations and AEs (if any)
- Review all concomitant medications and ensure adherence to COPD regimen
- Review smoking status
- Subjects will be instructed to track study drug dosing in their eDiary between study clinic visits
- 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
- Schedule next visit and ensure subject has adequate supply of study drug including a Sponsor-provided rescue Ventolin HFA
- For subjects who discontinue treatment (randomized study medication) and continue in the study, the scheduled study visit, data collection, and procedures will be completed according to the study protocol see Sections 8.7 and 8.8

8.6 Visit 13 (Week 52 or Final Study Visit)

- Review subject eDiary for data collection compliance
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if < 6 hours, the visit must be rescheduled)
- Review smoking status
- 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
- Confirm subject eligibility to continue
- Confirm the subject took their last dose of randomized study drug as scheduled the prior evening. If the time of dosing was not in accordance with the protocol, then the visit must be rescheduled
- Perform all pre-dose assessments (see Table 8-2)
  - Obtain central laboratory tests
  - Obtain vital signs and ECGs 60 minutes pre-dose
- Perform spirometry assessments -60 and -30 minutes pre-dose (see Table 8-2)
- Conduct a physical examination, including weight
- Have subject complete TDI questionnaire followed by SGRQ and EQ-5D questionnaires before any other study procedures are performed
- Collect HCRU information
- Record COPD exacerbations and AEs (if any)
- Review all concomitant medications and ensure adherence to COPD regimen
- 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 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits
  - Record/document the dose indicator readings of the used MDI and the replacement MDI
  - For the new MDI, the recorded count will be the count following the priming of the device but before the subject doses
- Administer in-clinic study drug dose from the new kit assigned at the visit
- Perform all post-dosing assessments (refer to Table 8-2)
  - Obtain vital signs 30 minutes post-dose
- Collect subject eDiary
- Collect all study drugs including Sponsor-provided Ventolin HFA
- At completion of all Visit 13 (Week 52 or Final Study Visit) assessments, return subject to pre-study or appropriate maintenance COPD medications
- Inform subject about reporting all SAEs up to 14 days following the last dose of study drug

- Schedule the follow-up TC at least 14 days from Visit 13 (Week 52 or Final Study Visit)

8.7 Procedures for Treatment Discontinuation and Study Withdrawal Subjects

Subjects who discontinue study treatment prior to the end of the study will be encouraged to remain in the study to complete all remaining study visits during the randomized 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 8.8) prior to transitioning back to regularly scheduled study visits. Treatment discontinuation subjects will return to appropriate maintenance COPD medications, per the Investigators discretion. 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 the14 day follow up telephone call.

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. All AEs/SAEs will be collected through the14 day follow up telephone call.

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. All AEs/SAEs will be collected through the14 day follow up telephone call. In the event the Treatment Discontinuation/ Study 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 within 4 to 6 weeks after the last subject has been randomized into the study in accordance with the informed consent.

8.8 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
- Perform all pre-dose assessments (see Table 8-2)
  - Obtain central laboratory tests
  - Obtain vital signs and ECGs 60 minutes pre-dose
- Perform all pre-dose assessments (see Table 8-2)

  - Obtain central laboratory tests
  - Obtain vital signs 60 minutes pre-dose
  - Obtain ECGs 60 minutes pre-dose
- Conduct a physical examination, including weight
- Collect a blood sample for pregnancy test for women of child-bearing potential
- Collect subject eDiary
- Collect all study drugs, including rescue medications
- Return subject to pre-study or appropriate maintenance COPD medications
- Inform subjects all AEs/SAEs will be collected through the 14 day follow up telephone call visit.
- Capture the reason for treatment discontinuation

8.9 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
- Review and record AEs/SAEs (if any)
- Review concomitant medications

8.10 Vital Status Confirmation

All subjects who withdraw from the study prior to the end of the study will have their vital status confirmed within 4 to 6 weeks after the last subject has been randomized into the study.

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

- The first and second attempts may be conducted as telephone follow-up call to the subject within 2 weeks after 52 weeks post-randomization
- The third attempt will be by certified mail to the subject's address provided at the time of informed consent within 3 weeks after 52 weeks post-randomization
- The fourth attempt will be made as a telephone follow-up call to the next of kin/emergency contact provided at the time of informed consent within 4 weeks after 52 weeks post-randomization
- A fifth attempt will be made through a certified letter to the next of kin/emergency contact provided at the time of informed consent within 5weeks after 52 weeks post-randomization
- After the fifth attempt, the study site will contact the national death registries (if available in that country) to confirm date and cause of death

8.11 Completion of 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
- AEs/SAEs
- 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 double-blind, parallel group study evaluating the efficacy and safety of three treatment groups over a variable length 12-to-52-week treatment period in approximately 1,860 subjects (620 per treatment group) with moderate to very severe COPD who have a history of COPD exacerbations.

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

- BFF MDI 320/9.6 µg BID
- BFF MDI 160/9.6 µg BID
- FF MDI 9.6 µg BID

The primary objective of this study is to assess the effects of BFF MDI relative to FF MDI on lung function in subjects with a history of COPD exacerbations. In addition, this study will assess the effects of BFF MDI relative to FF MDI on COPD exacerbations and symptoms, disease-related health status, 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 HCRU Endpoints

Refer to Section 3 for complete details on all HCRU 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 9.11.

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 (yes/no) as categorical covariates and baseline FEV_1 and baseline blood eosinophil count, and percent reversibility to Ventolin HFA as continuous covariates. 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 12 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 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. Secondary analyses of this endpoint will be conducted for the attributable estimand.

Supportive Analyses: 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.

9.3.2 Secondary Efficacy Analysis

9.3.2.1 Time to First Moderate or Severe COPD Exacerbation

The time to first moderate or severe COPD exacerbation will be analyzed using a Cox regression model. The model will include treatment, baseline post-bronchodilator percent predicted FEV_1, baseline COPD exacerbation history (1, ≥2), baseline blood eosinophil (EOS) count, country, and ICS use at Screening (yes/no). Estimated adjusted hazard ratios relative to the comparator will be displayed along with the associated Wald two-sided 95% confidence interval (CI) and p-values for all treatment comparisons. Time to first moderate or severe COPD exacerbation will be displayed graphically for each treatment group using a Kaplan-Meier curve and analyzed using a log-rank test to compare the curves between the treatments as a supportive analysis. Subjects who did not experience a COPD exacerbation and completed the study on treatment will be censored at the date of study completion. Subjects who discontinued treatment early and did not experience a COPD exacerbation will be censored at the day after last dose for discontinuation of treatment or study withdrawal depending on the estimand in use.

9.3.2.2 Time to First Clinically Important Deterioration

The time to first clinically important deterioration (CID) will be analyzed using a Cox regression model. The model will include treatment, baseline post-bronchodilator percent predicted FEV_1, baseline COPD exacerbation history, baseline blood eosinophil count, country, and ICS use at Screening. Estimated adjusted hazard ratios relative to the comparator will be displayed along with the associated Wald two-sided 95% confidence interval (CI) and p-values for all treatment comparisons. Time to first CID will be displayed graphically for each treatment group using a Kaplan-Meier curve and analyzed using a log-rank test to compare the curves between the treatments as a supportive analysis. Subjects who did not experience a CID and completed the study will be censored at the date of study completion. Subjects who discontinued treatment early and did not experience a COPD exacerbation will be censored at the day after last dose for discontinuation of treatment or study withdrawal depending on the estimand in use.

A clinically important deterioration is defined as one or more of the following events occurring:

- A decrease from baseline of 100 mL or more in trough FEV_1
- A change from baseline of 4 or more in SGRQ

- A TDI focal score of -1 point or less
- An occurrence of a moderate or severe COPD exacerbation

9.3.2.3 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 over 12 and 24 weeks. For every period of time for which the mean number of puffs of rescue will be calculated, missing values will be ignored in both the numerator and denominator. As such, the denominator will be adjusted based on the number of days (including half days) with non-missing values.

The linear repeated measures ANCOVA model will include treatment, the number of the relevant 4-week interval (1-13), the treatment by 4-week interval interaction, and ICS use at Screening as categorical covariates and baseline blood eosinophil count, 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 the treatment period. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference.

9.3.2.4 Exacerbations of Chronic Pulmonary Disease Tool (EXACT)

The EXACT is a 14-item patient reported outcome (PRO) daily diary which will be used to measure the effect of treatment on exacerbations and on the severity of respiratory symptoms. Mean change from baseline in the daily EXACT Total Score will be calculated over the treatment period. 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 the treatment period, but using the EXACT baseline mean score instead of the BDI as a covariate. Instead of visit, the number of the relevant 4-week interval (1-13) will be used as a categorical covariate in the model.

9.3.2.5 St. 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 12 and over 24 weeks. Logistic regression will be used to compare the treatment groups with baseline SGRQ score, baseline blood eosinophil count, baseline post-bronchodilator percent predicted FEV_1, and percent reversibility to Ventolin HFA as continuous covariates. Treatment and ICS use at Screening will be categorical covariates. P-values and odds ratios with 95% CIs will be produced for each treatment comparison.

9.3.2.6 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 an 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 baseline blood eosinophil count, 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.

9.3.3 Other Efficacy Analysis

9.3.3.1 Rate of COPD Exacerbations

The rate of COPD exacerbations of any severity, moderate or severe COPD exacerbations, severe COPD exacerbations, COPD exacerbations treated with systemic steroids, and COPD exacerbations treated with antibiotics will be analyzed with negative binomial regression.

The ratio of the rates of COPD exacerbations will be analyzed using negative binomial regression. COPD exacerbations will be considered separate events if more than 7 days are between the recorded stop date of the earlier event and start date of the later event. Time at risk of experiencing an exacerbation will be used as an offset variable in the model. Time during an exacerbation or in the 7 days following an exacerbation will not be included in the calculation of exposure. Treatments will be compared adjusting for baseline post-bronchodilator percent predicted FEV_1, baseline COPD exacerbation history, baseline blood EOS count, and ICS use at Screening.

The number and percentage of subjects with exacerbations in each treatment group will be tabulated.

The analysis 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.

Duration of COPD Exacerbation

The duration of COPD exacerbation definition is located in Section 7.1.3.2.

In order to not double count exacerbations that are moderate or severe, eDiary data from dates within 7 days of a moderate or severe exacerbation will not be included as additional mild COPD exacerbations. This implies that continuing worsened symptoms that meet the definition of a mild exacerbation would need to be present at least 2 days prior to the 7-day period immediately preceding the start date of a moderate or severe COPD exacerbation in order to be considered a separate event. Similarly, worsened symptoms would need to be present for at least 2 days after the 7-day period immediately following a moderate or severe COPD exacerbation to be considered a separate event.

Analyses of each severity of exacerbation will account for the time that subjects are at risk of having an exacerbation of that severity or greater. Time during or immediately following an

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

9.3.3.2 Spirometry Parameters: Change from Baseline in Morning Pre-Dose Trough Values

Change from baseline in morning pre-dose trough FEV_1, forced vital capacity (FVC), peak expiratory flow rate (PEFR), and forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}) over 12, 24, and 52 weeks and at each post-randomization in-clinic visit will be evaluated by treatment. Models similar to the one built for the primary analysis of FEV_1 will be used. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be produced for each treatment difference. The parameter-specific baseline covariate will be used.

9.3.3.3 Time to Event Analyses

All of the following variables will be analyzed in a manner similar to the time to first moderate or severe COPD exacerbation as defined under secondary efficacy analysis (Section 9.3.2.1):

- Time to first COPD exacerbation of any severity
- Time to first severe COPD exacerbation
- Time to first COPD exacerbation treated with systemic steroids
- Time to first COPD exacerbation treated with antibiotics
- Time to treatment failure
- Time to CID
- Time to Sustained CID
- Time to death (all causes, respiratory)

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 date of discontinuation or Day 365, whichever comes first.

Time to first sustained CID (which is an "other endpoint") will be analyzed in a manner similar to time to first CID.

A sustained CID is defined as follows:

- the same component of CID occurs in two or more consecutive visits at least 4 weeks apart
- 50% or more of the subsequent scheduled visits are categorized as being a CID.
- An occurrence of a moderate or severe COPD exacerbation will be categorized as a sustained CID.

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, analyses will be conducted for the treatment policy estimand in the ITT population.

Data permitting, these analyses will be repeated for time to death from respiratory causes. The Sponsor and the Clinical Endpoint Committee will agree on search terms (based on the prevailing version of the MedDRA dictionary) to identify mortalities due to possible respiratory causes. Only those deaths identified as being due to respiratory causes by the Clinical Endpoint Committee will be considered as events for this analysis.

The analysis of time to death will be conducted contingent upon having at least 30 events of death. Otherwise, the analysis will be limited to counts and listings

9.3.3.4 Exacerbations of Chronic Pulmonary Disease Tool (EXACT)

In addition to the EXACT secondary analyses, 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 RS-Total Score, as well as the 3 symptom domain scores breathlessness, cough and sputum, and chest symptoms will be evaluated over 24 and 52 weeks, and over each 4-week interval of the Treatment Period.

9.3.3.5 Rescue Ventolin HFA Usage

In addition to the secondary analyses for rescue medication usage, the RM ANCOVA model will be used to evaluate the treatment difference over 12, 24, and 52 weeks and for each 4-week interval of the Treatment Period. Daytime rescue Ventolin HFA use and nighttime rescue medication use will be evaluated and summarized in a similar fashion. Two-sided p-values and point estimates with 2-sided 95% CIs will be produced for each treatment difference.

The percentage of days with ‘no rescue Ventolin HFA use’ over 12, 24, and 52 weeks, and for each 4-week interval of the Treatment Period will be evaluated with an ANOVA model. A ‘day with no rescue use’ is defined as any day where the subject reported zero puffs of rescue Ventolin HFA. The rescue Ventolin HFA usage diary data from days where rescue Ventolin HFA usage data is non-missing will be used to ascertain the days with “no rescue Ventolin HFA use”. The ANCOVA model will evaluate treatment differences and include baseline rescue Ventolin HFA use and reversibility to Ventolin HFA as continuous covariates and region, smoking status at baseline, and ICS use at Screening as categorical covariates.

9.3.3.6 Transition Dyspnea Index

In addition to the TDI secondary analyses, the RM ANCOVA model will be used to evaluate the difference between treatments over 12, 24, and 52 weeks 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 12, 24, and 52 weeks, 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 unit or more on average over 12, 24, and 52 weeks. Logistic regression will be used to compare the treatment groups with BDI and baseline blood eosinophil count, and 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 12, 24, and 52 weeks of treatment and at each post-randomization in-clinic visit 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 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 over 12, 24 and 52 weeks and at each post-randomization in-clinic visit 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.

9.3.4 Type I Error Control

The same general Type I error control strategy will be employed for the US and Ex-US 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 endpoint for the attributable estimand

- The secondary analyses
- A subgroup analysis of patients with 2 or more moderate or severe COPD exacerbations in the previous 12 months

9.3.4.1 US Approach

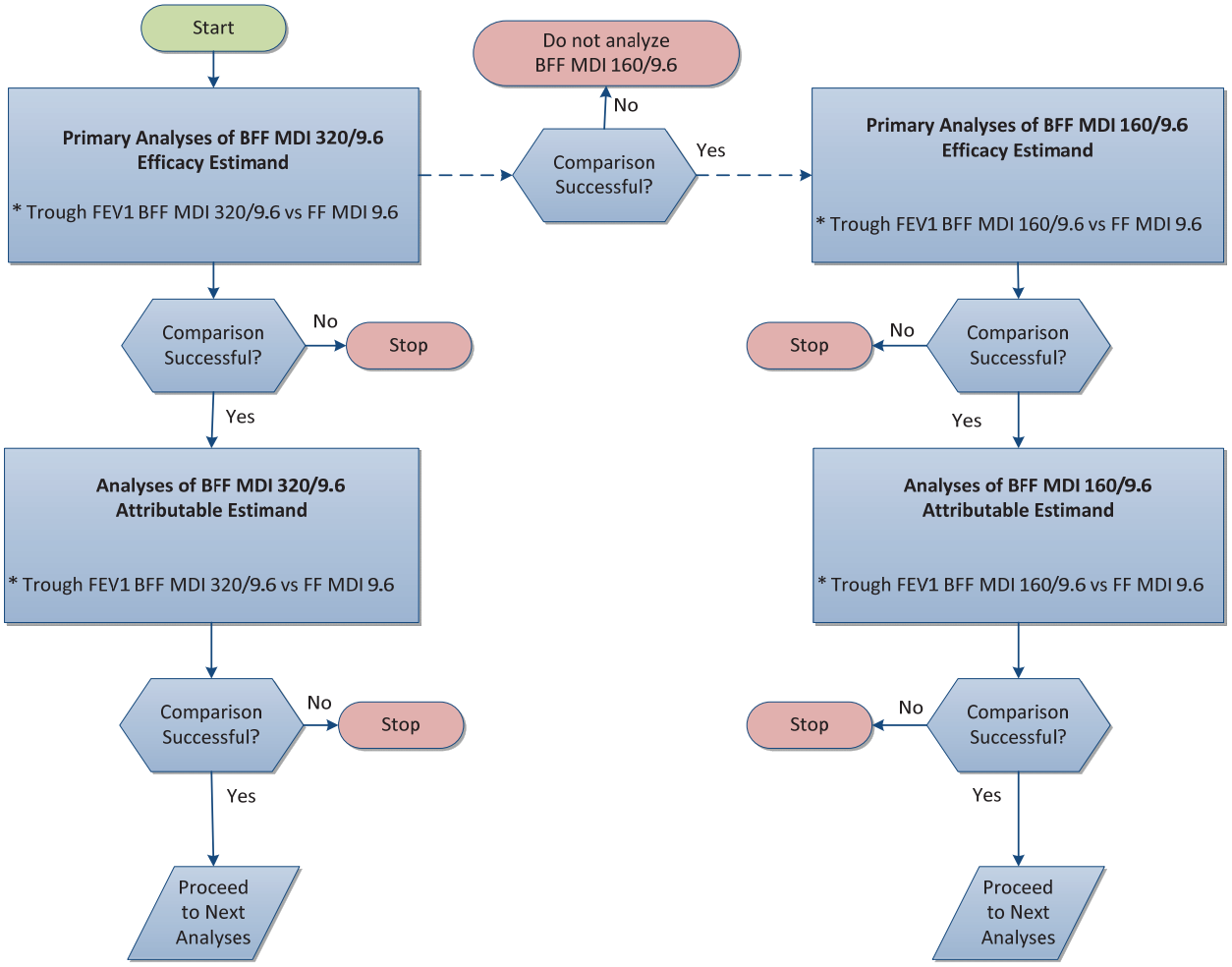
The Type I error rate will be controlled within the primary, secondary, and subgroup efficacy analyses. The primary analyses associated with BFF MDI 160/9.6 will proceed only if the primary analysis associated with BFF MDI 320/9.6 is successful. The analysis of the primary endpoint for the attributable estimand, secondary analyses, and subgroup analysis for each BFF MDI dose will proceed only if the primary analysis associated with that dose of BFF MDI is 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 analysis of the primary endpoints for the attributable estimand.

Group 2: The secondary and subgroup analyses for the efficacy estimand.

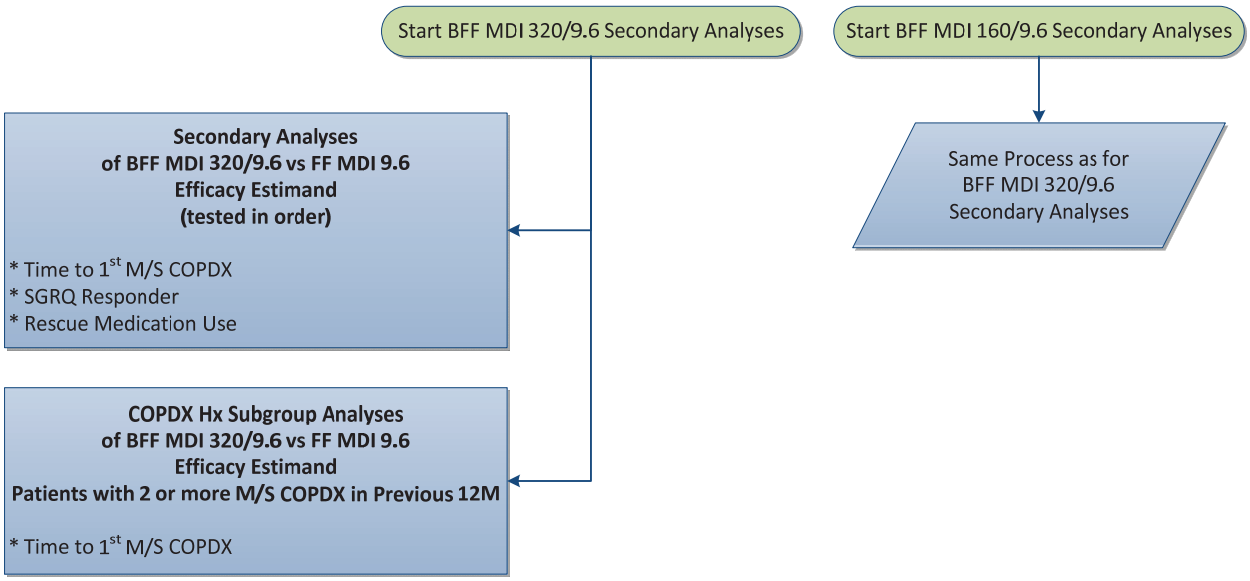
Figure 9-1 Group 1: Type I Error Control for the Analyses of the Primary Endpoints (US Approach)



In Group 1, a sequential multiplicity approach will be used in the analyses of the primary endpoint (Figure 9-1). In this approach, the analyses of the primary endpoint 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 the 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 Secondary Endpoints (US Approach)

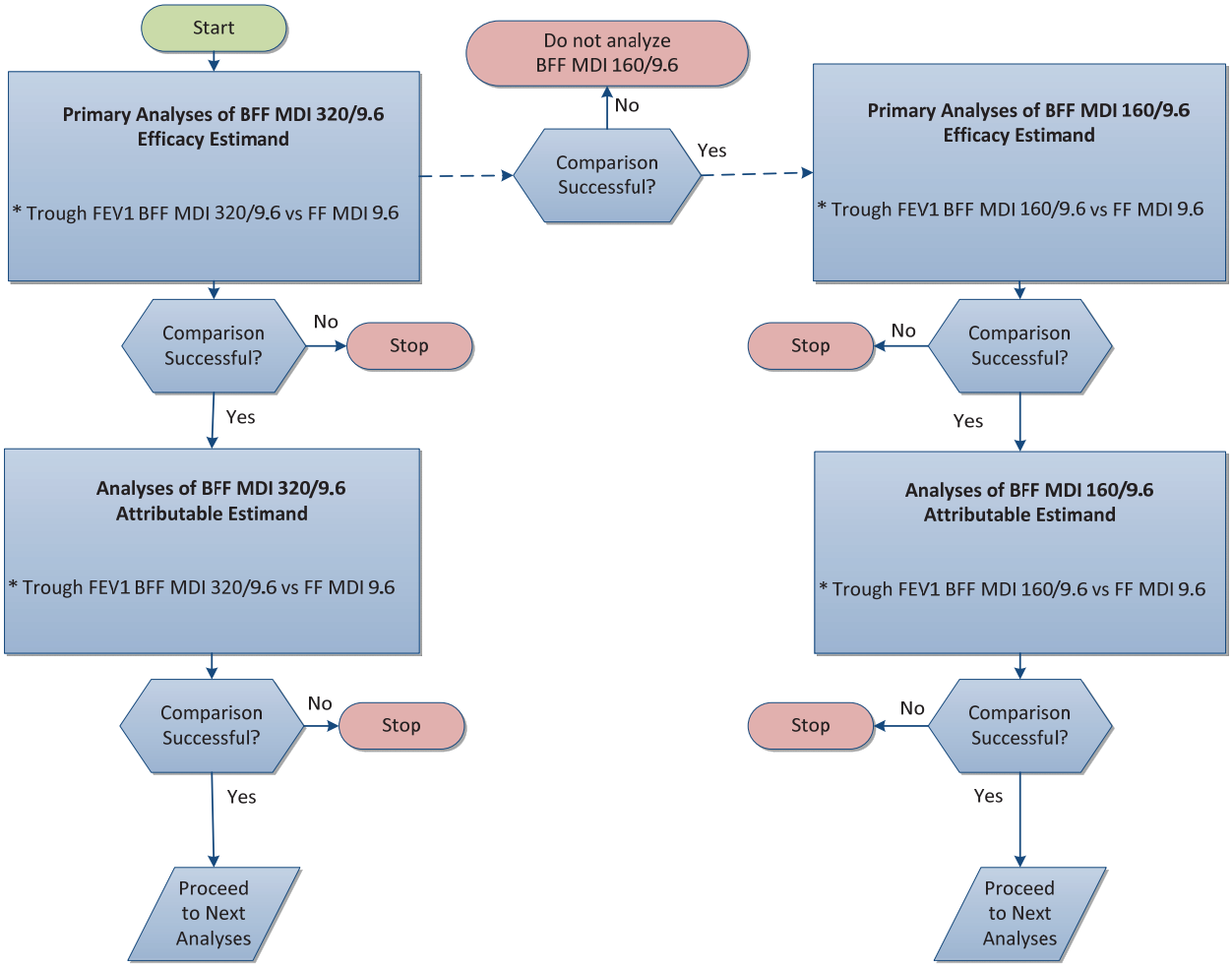


In Group 2, the secondary analyses and the subgroup analysis will be treated as separate families of hypotheses. The Type I error in each family of secondary analyses will be controlled to alpha.

9.3.4.2 Ex-US Approach

The Ex-US approach will follow a similar general strategy as the US approach. The control of Type I error in the Ex-US approach differs from the US approach in 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.

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



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

Group 2 analyses are presented in Figure 9-4.

Figure 9-4 Group 2: The Analysis of the Secondary Endpoints (Ex-US 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 relationship to study drug. No hypothesis tests will be performed.

9.4.1.1 Paradoxical Bronchospasm

Paradoxical bronchospasm will be considered an AE of special interest and will be tabulated separately.

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 Randomization

Subjects will be randomized in a 1:1:1 scheme. Approximately 620 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. Randomization will be stratified by exacerbation history (1 or ≥ 2 moderate or severe exacerbations), post-bronchodilator FEV_1 (25% to < 50% predicted or 50% to < 80% predicted), blood eosinophil count (< 150 cells per mm^3 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.

9.7 Experimental Design

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

9.8 Sample Size Consideration

For morning pre-dose trough FEV_1, the expected standard deviation (SD) for the change from baseline at each visit is 200 mL. The expected SD over 24 weeks is 158 mL. This assumes a correlation of 0.55 over the six post-randomization visits to Week 24.

For the analysis of morning pre-dose trough FEV_1 at Week 12 (the US Approach), the proposed sample size of 1,860 subjects (620 per arm in the BFF MDI and FF MDI groups) with 15% drop-out will provide approximately 90% power to detect a difference of 40 mL between BFF MDI and FF MDI. The Type I error will be controlled at a two-sided alpha level of 0.05.

For the analysis of morning pre-dose trough FEV_1 over 24 weeks (the ex-US Approach), with 30% dropout the same proposed sample size will provide approximately 96% power to detect a difference of 40 mL between BFF MDI and FF MDI. The Type I error will be controlled at a two-sided alpha level of 0.05.

Based on a review of the literature and data from a recent COPD exacerbation study of a budesonide and formoterol fumarate combination therapy, the percentage of patients with at least one moderate or severe COPD exacerbation in the BFF MDI 320/9.6 µg and FF MDI 9.6 µg groups is estimated to be 28.3% and 34.0%, respectively. This represents a hazard ratio (HR) of approximately 80% for BFF MDI compared to FF MDI. The projected numbers of patients with at least one moderate or severe COPD exacerbation in this variable length

study are 195 and 234, respectively, for the BFF MDI 320/9.6 µg and FF MDI 9.6 µg groups. This would provide 64% power to detect an HR of 80% or lower. The probability of detecting a numerical trend in the analysis of time to first moderate or severe COPD exacerbation is estimated to be 87%, where numerical trend is defined as the observed HR between a BFF MDI dose and FF MDI being below 0.90. If the criterion for numerical trend is raised to 0.95, the probability of detecting a numerical trend is estimated to be 94%.

9.9 Data Validation and Transformation

In general, the distribution of spirometry measures is well approximated by a normal distribution. Under some circumstances, however (for example during a COPD exacerbation, unrelated to treatment), extreme and atypical values can arise. Such values have high influence on estimation of variance parameters and on standard errors of fixed effect estimates. The distribution 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 by either transformation or 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 database 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.

9.10 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.

9.11 Analysis Populations and Estimands

9.11.1 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. 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). The mITT

Population will be the primary population for all efficacy 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 ≥ 1.0 puff/day.
- 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, RVU, Safety, and Non-Randomized Populations.
  - Extent of exposure will be summarized for the Safety Population. The Safety Population will be used to summarize safety.
  - Efficacy analyses will be performed for the ITT and mITT Populations. In general, the mITT Population will be considered the primary population for the efficacy analyses, with the ITT population being considered supportive.

9.11.2 Estimands

Three estimands of interest are defined for this study: efficacy estimand, attributable estimand, and treatment policy 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 in 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 from the two reference arms' distributions 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 in the ITT Population, in which all observed data will be utilized regardless of whether subjects remain on randomized treatment.

9.12 Subgroup Analyses

Subgroup analyses will be performed for change from baseline in morning pre-dose trough FEV_1 and 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:
  - 1
  - ≥2
- 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 that 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. A similar analysis will also be conducted for the rate of moderate or severe COPD exacerbations.

9.13 Handling of Missing Data

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

9.14 Statistical Software

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

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

The Sponsor 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 the Sponsor, 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.

The Sponsor 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 the Sponsor 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 the Sponsor prior to initiation of the study.

The Investigator will be responsible for obtaining written informed consent from potential subjects prior to any study-specific Screening. 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 the Sponsor 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 the Sponsor (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 the Sponsor. 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

The Sponsor 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 the Sponsor.

10.7 Study Monitoring

In accordance with applicable regulations, GCP, and Sponsor 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 the Sponsor.
- 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 the Sponsors' Quality Assurance auditors 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 the Sponsors' Quality Assurance auditors and by all applicable regulatory authorities. The period of time these documents must be maintained is governed by county-specific regulations. The Sponsor or its designee will inform the Investigator when these documents may be destroyed. The Sponsor 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 the Sponsor 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 the Sponsor.

10.11 Publication Policy

The Sponsor 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 Sponsor-sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study. In addition, the Sponsor 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 Sponsor 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, the Sponsor 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. The Sponsor (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.
2. **Authorship and Publication Committee:** The Sponsor, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE and ISMPP. It is anticipated that a publication committee will be formed to assume oversight of these activities. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
3. **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted at least 30 days prior to submission for publication or presentation to the Sponsor for review, approval, and to ensure consistency with the policy in this protocol. The Sponsor 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 the Sponsor 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 the Sponsor to publish the study in a fair and accurate manner, the Sponsor 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 the Sponsor 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, the Sponsor reports clinical findings based on the guidance of The CONsolidated Standards of Reporting Trials (CONSORT) Statement [Mohler, 2012]. Additionally, 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, the Sponsor 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.

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12 APPENDICES

Appendix 1 Spirometry Assessment Criteria

Acceptable Versus Usable Tests

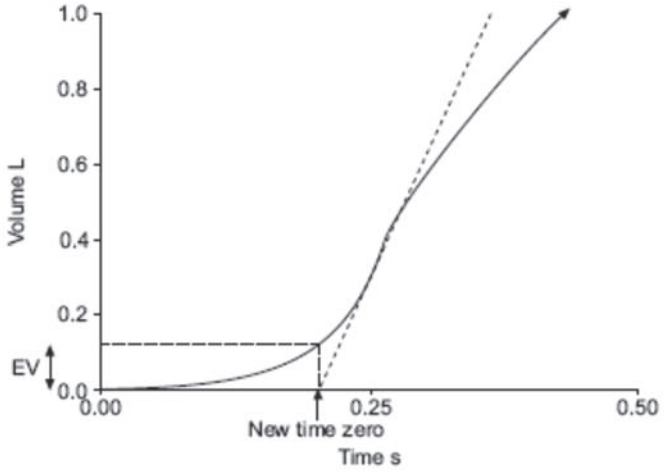
***Acceptable* Tests must meet the following Criteria:**

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

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

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

Figure A2-1 Example of a Usable Spirogram



EV=back extrapolation volume

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

Between-Maneuver Reproducibility Criteria

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

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

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

If acceptability criteria are not met, continue testing until they are met or the subject cannot/ should not continue (maximum of eight attempts).

Appendix 2 Spirometry Performance Recommendations

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

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

FEV_1 AND FVC MANEUVERS

Equipment Requirements

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

Display

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

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

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

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

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

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

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

Validation

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

Quality Control

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

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

Table A1-2 Summary of Equipment Quality Control

Test	Minimal Interval	Action
Volume	Daily	Calibration check with a 3-L syringe
Leak	Daily	2 cmH_2O (0.3 kPa) constant pressure for 1 minute
Volume Linearity	Quarterly	1-L increments with a calibrating syringe measured over the entire volume range
Flow Linearity	Weekly	Test at least three different flow ranges
Time	Quarterly	Mechanical recorder check with stop watch
Software	New versions	Log installation date and perform test using "known" subject

Calibration is the procedure for establishing the relationship between sensor-determined values of flow or volume and the actual flow or volume. A calibration check is different from calibration and is the procedure used to validate that the device is within calibration limits, eg., ±3% of true. If a device fails its calibration check, then a new calibration procedure or equipment maintenance is required. Calibration checks must be undertaken daily, or more frequently, if specified by the manufacturer. The syringe used to check the volume calibration of spirometers must have an accuracy of ±15 mL or ±0.5% of the full scale (15 mL for a 3-L syringe), and the manufacturer must provide recommendations concerning appropriate intervals between syringe calibration checks. Users should be aware that a syringe with an adjustable or variable stop may be out of calibration if the stop is reset or accidentally moved. Calibration syringes should be periodically (eg., monthly) leak tested at more than one volume up to their maximum; this can be done by attempting to empty them with the outlet corked. A dropped or damaged syringe should be considered out of calibration until it is checked.

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

Quality Control for Volume-Measuring Devices

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

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

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

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

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

Quality Control for Flow-Measuring Devices

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

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

VITAL CAPACITY MANEUVERS

Equipment

For measurements of vital capacity (VC), the spirometer or flow meter must comply with the requirements for FVC (as described previously) and be capable of accumulating volume for ≥30 s. Expiratory maneuvers or, ideally, both inspiratory and expiratory maneuvers should be included in the display of VC maneuver. Regardless of whether the inspiratory or expiratory maneuver is used for deriving measurements, a display of the entire recorded VC maneuver must be provided. The maximal expiratory volume must be assessed to determine

whether the subject has obtained a plateau in the expiratory effort. For display of the slow VC, the time scale may be reduced to 5 mm-s^{-1}.

TECHNICAL CONSIDERATIONS

Minimal recommendations for spirometry systems

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

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

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

ATS=American Thoracic Society; BTPS=body temperature and pressure saturated; FEV_1=forced expiratory volume in 1 second; FEV_t=forced expiratory volume in t seconds; FVC=forced vital capacity; VC=vital capacity

BTPS correction

All spirometry values should be reported at BTPS by any method (measuring temperature and barometric pressure) proven effective by the manufacturer. For volume-type spirometers, the temperature inside the spirometer should be measured for each breathing

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

Appendix 3 Subject Instructions for Use of BFF MDI, and FF MDI Devices

How do I store the Inhaler?

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

–

For Oral Inhalation Only

Parts of the Inhaler:

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

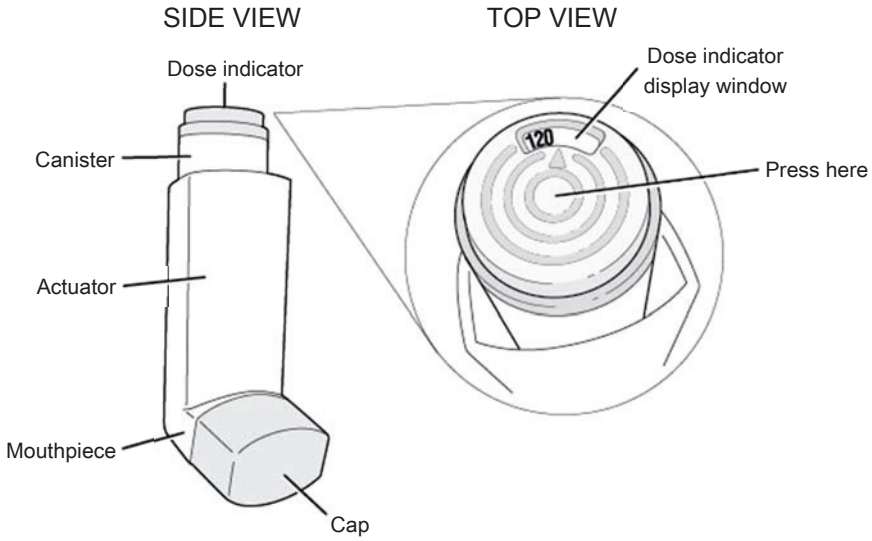


Figure 1

d. The **Dose indicator** lets you know about how many puffs are left in your inhaler and is the part of the inhaler that is pressed to dispense a puff of medication. **See Figure 1**.

e. The **Dose indicator** should be pointing just to the right of 120 when your inhaler is new. **See Figure 1**.

f. The **Dose indicator** has numbers for every 20 puffs. The **Dose indicator** display will move after every tenth puff.

g. For example, if the **Dose indicator** is pointing to 120 (**see Figure 2a**) and you take 10 puffs it will move between 120 and 100. This means that there are 110 puffs of medicine left (**see Figure 2b**). After 10 more puffs are used, the **Dose indicator** pointer will move to the number 100. This means that there are 100 puffs of medicine left (**see Figure 2c)**.

Figure 2a
120 puffs

Figure 2b
110 puffs

Figure 2c
100 puffs

h. The **Dose indicator** number will continue to change after every 20 puffs.

i. When the number in the **Dose indicator** window changes to 20 and the color behind the number changes to red, this means that there are only 20 puffs left in your inhaler. **See Figure 2d.**

Figure 2d

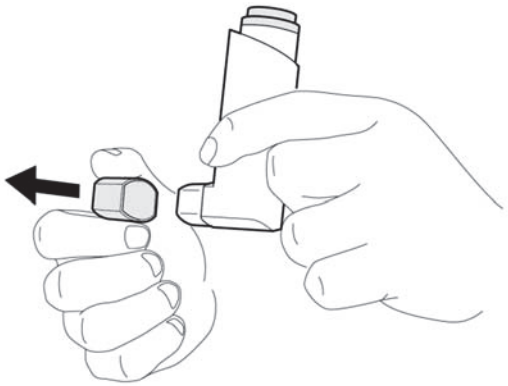
Preparing the Inhaler for Use:
The inhaler comes in a foil pouch that contains a drying packet (desiccant).

j. Take the inhaler out of the foil pouch.

k. Throw away the pouch and the drying packet. Do not eat or inhale the contents of the drying packet.

l. Remove the **Cap** from the **Mouthpiece** as shown in **Figure 3.**

Figure 3



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

Priming the Inhaler:

m. Check inside the **Mouthpiece** for objects before use.

n. Hold the **Actuator** with the **Mouthpiece** pointing away from you and others as shown in **Figure 4a**.

o. Shake the inhaler well before each puff.

p. Push down fully on the center (not 'off center') of the **Dose indicator** on top of the **Canister** (**see Figure 1**) until the **Canister** stops moving in the **Actuator** to release a puff from the **Mouthpiece as shown in Figure 4b**. Note: It is normal to hear a soft click from the dose indicator as it counts down during use.

q. Repeat this priming step 3 more times for a total of 4 times, shaking the inhaler each time before you press it.

r. After completing the 4 priming puffs, your inhaler is now primed ready to use for the first time.

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

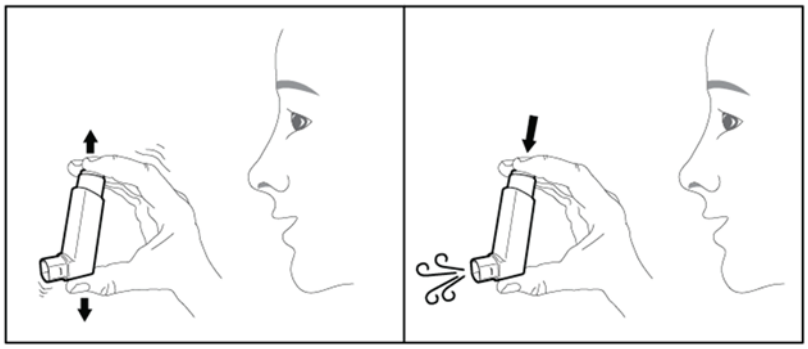


Figure 4a

Figure 4b

Using the Inhaler:
Your dose of medicine comes from **2 puffs** from the inhaler.
Refer to **Figure 5** for Step 1 through Step 8.

s. **Step 1**: Remove the **Cap** from the **Mouthpiece**.

t. **Step 2**: Shake the inhaler well before each puff.

u. **Step 3**: While holding the inhaler with the **Mouthpiece** pointing towards you breathe out through your mouth to empty as much air from your lungs as possible.

v. **Step 4**: Close your lips around the **Mouthpiece** and tilt your head back slightly to make sure your tongue is away from the **Mouthpiece**.

w. **Step 5**: Take a deep breath in (inhale) slowly through your mouth while pressing down firmly on the center (not 'off center') of the **Dose indicator** until the **Canister** stops moving in the **Actuator** and a puff has been released. Then, stop pressing the **Dose indicator**.

x. **Step 6**: When you have finished breathing in, remove the **Mouthpiece** from your mouth and hold your breath for 10 seconds or as long as comfortable.

y. **Step 7**: Then, breathe out normally.

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

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

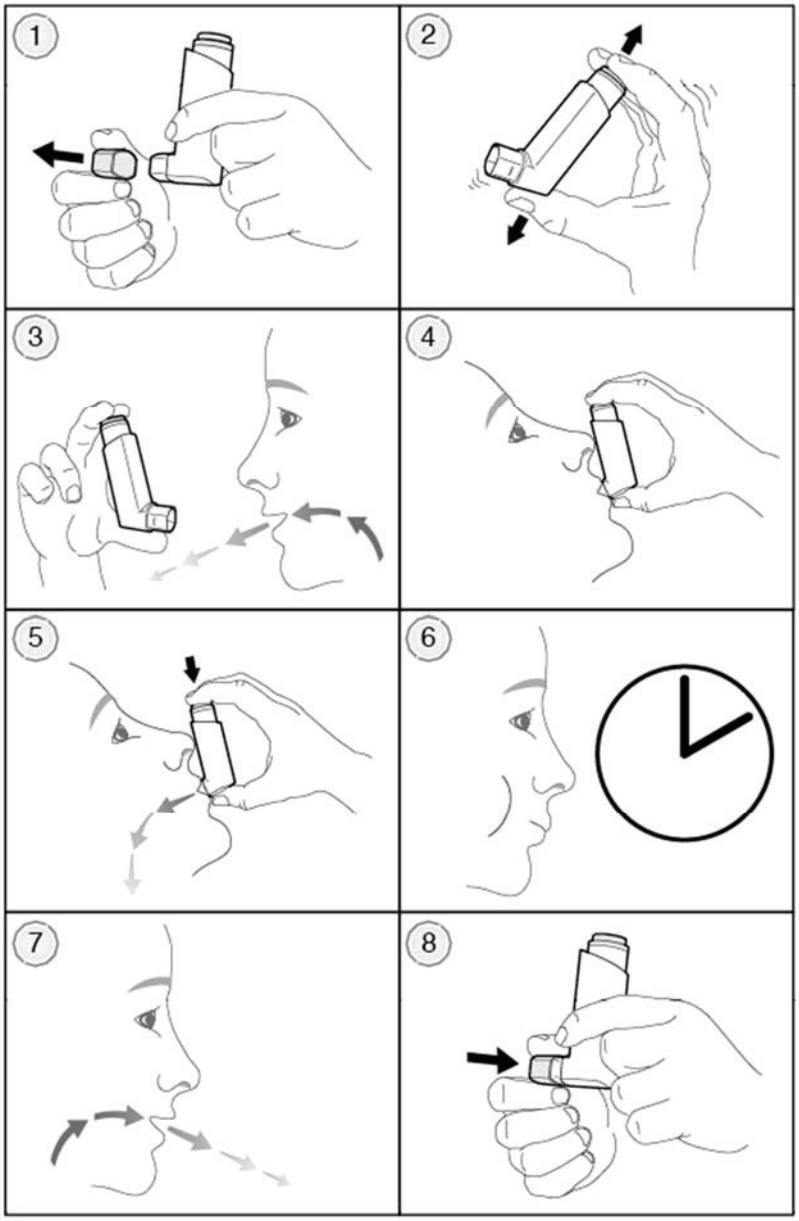


Figure 5

How to clean the Inhaler:

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

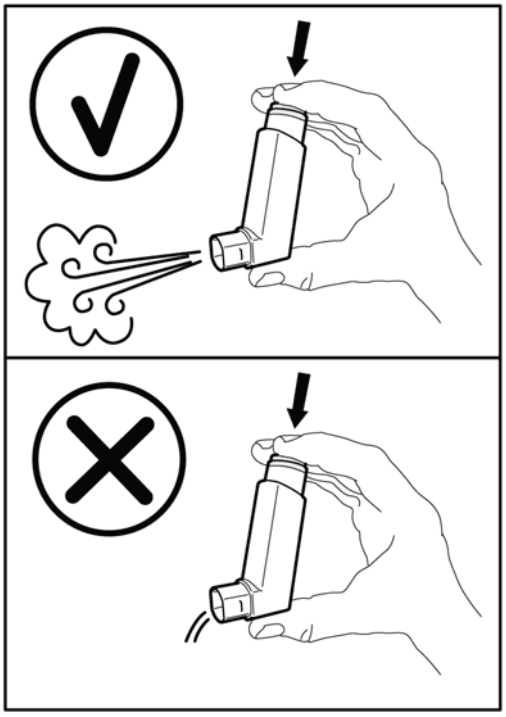
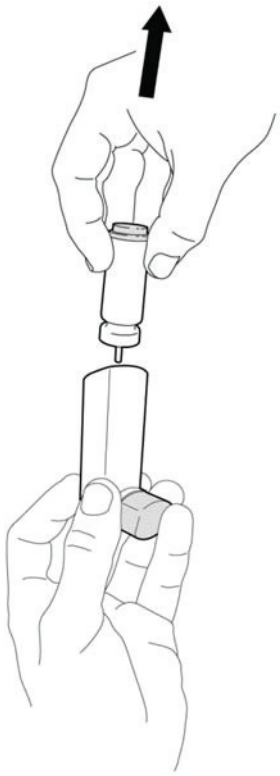


Figure 6

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

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

Figure 7



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

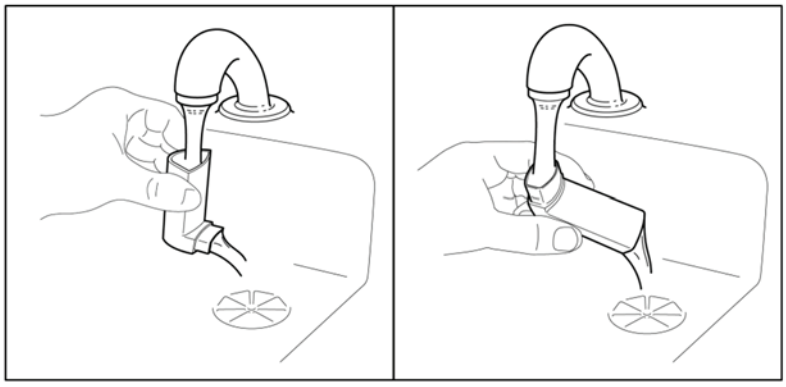


Figure 8

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

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

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

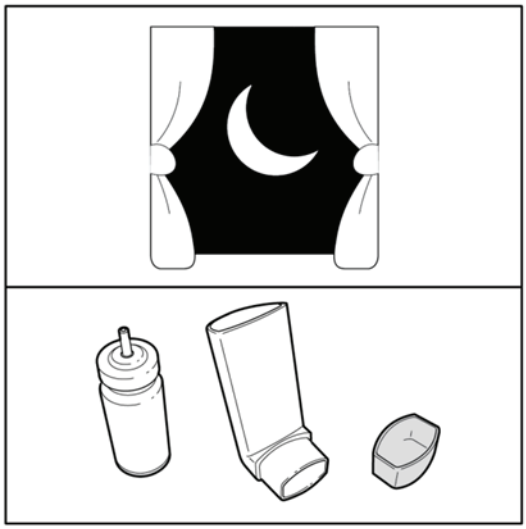


Figure 9

Reassembly of the Inhaler and Instructions for Use after Cleaning:

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

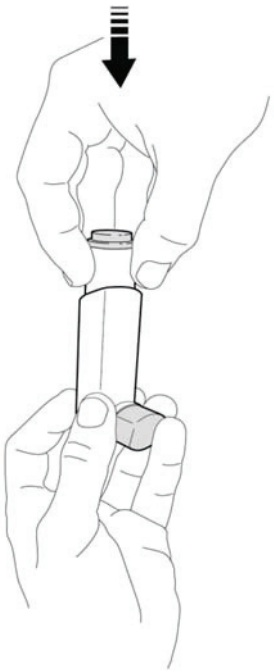


Figure 10

- Re-prime your inhaler 2 times after each cleaning.

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

Appendix 4 Instructions for Use of Ventolin HFA Inhaler

The Parts of Your VENTOLIN HFA Inhaler

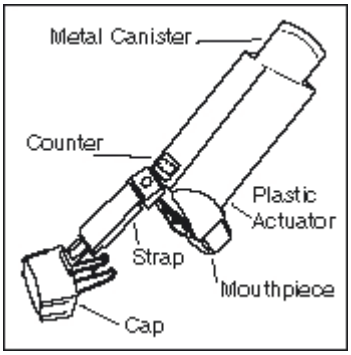


Figure 1

There are two main parts to your VENTOLIN HFA inhaler:

1. The metal canister that holds the medicine and
2. The blue plastic actuator that sprays the medicine from the canister (see Figure 1).
    a. The inhaler also has a cap that covers the mouthpiece of the actuator.
    b. The strap on the cap will stay attached to the actuator.
    c. The canister has a counter to show how many sprays of medicine you have left. The number shows through a window in the back of the actuator.

The counter starts at 204, the number will count down by 1 each time you spray the inhaler. The counter will stop counting at 000.
Never try to change the numbers or take the counter off the metal canister. The counter cannot be reset, and it is permanently attached to the canister.

Do not use the actuator with a canister of medicine from any other inhaler. In addition, do not use a VENTOLIN HFA canister with an actuator from any other inhaler.

How to Use Your VENTOLIN HFA

Before using your VENTOLIN HFA:

1. Take the inhaler out of the foil pouch. Safely throw away the pouch and the drying packet that comes inside the pouch. The counter should read 204. *The inhaler should be at room temperature before you use it.*
2. Check each time to make sure the canister fits firmly in the plastic actuator. Also, look into the mouthpiece to make sure there are no foreign objects there, especially if the strap is no longer attached to the actuator or if the cap is not being used to cover the mouthpiece.

Priming your VENTOLIN HFA:

- You must prime the inhaler to get the right amount of medicine. Prime the inhaler before you use it for the first time, if you have not used it for more than 14 days, or if it has been dropped.
    1. To prime the inhaler, take the cap off the mouthpiece of the actuator.
    2. Then shake the inhaler well, and spray it into the air away from your face.
    3. Shake and spray the inhaler like this 3 more times to finish priming it.
    4. The counter should now read 200, or 60 if you have a sample or institutional canister.

Instructions for taking a dose from your VENTOLIN HFA:

Read through the 6 steps below before using VENTOLIN HFA. If you have any questions, ask your study doctor.

1. Take the cap off the mouthpiece of the actuator. **Shake the inhaler well** before each spray.

2. Hold the inhaler with the mouthpiece down (see Figure 2). **Breathe out through your mouth** and push as much air from your lungs as you can. Put the mouthpiece in your mouth and close your lips around it.

3. **Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth** (see Figure 3). Right after the spray comes out, take your finger off the canister. After you have breathed in all the way, take the inhaler out of your mouth and close your mouth.

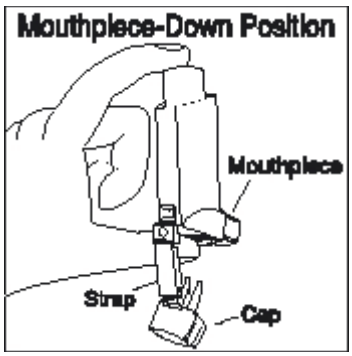


Figure 2

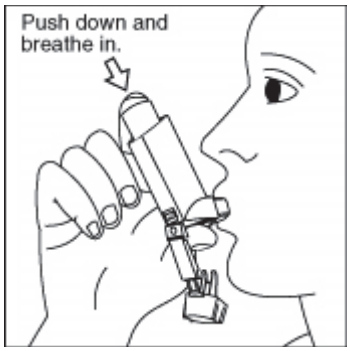


Figure 3

4. **Hold your breath as long as you can**, up to 10 seconds, then breathe normally.

5. If your doctor has prescribed more sprays, wait 1 minute and **shake** the inhaler again. Repeat steps 2 through 4.

6. Put the cap back on the mouthpiece after every time you use the inhaler, and make sure it snaps firmly into place.

When to Replace Your VENTOLIN HFA

1. **When the counter reads 020**, you should refill your prescription or ask your doctor if you need another prescription for VENTOLIN HFA.
2. **Throw the inhaler away** when the counter reads 000 or 6 months after you have taken the inhaler out of the foil pouch, whichever happens first. You should not keep using the inhaler when the counter reads 000 because you will not receive the right amount of medicine.
3. **Do not use the inhaler** after the expiration date, which is on the packaging it comes in.

How to Clean Your VENTOLIN HFA

It is very important to keep the plastic actuator clean so the medicine will not build-up and block the spray. Do not try to clean the metal canister or let it get wet. The inhaler may stop spraying if it is not cleaned correctly.

Wash the actuator at least once a week.

Cleaning instructions:

1. Take the canister out of the actuator, and take the cap off the mouthpiece. The strap on the cap will stay attached to the actuator.
2. Wash the actuator through the top with warm running water for 30 seconds (see Figure 4). Then wash the actuator again through the mouthpiece (see Figure 5).

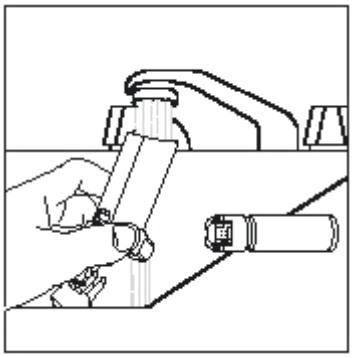


Figure 4

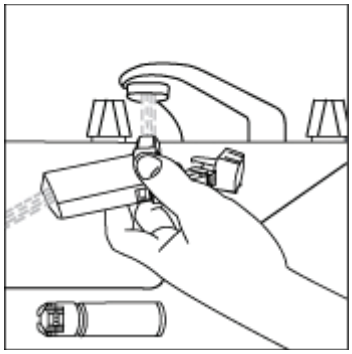


Figure 5

3. Shake off as much water from the actuator as you can. Look into the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat step 2.
4. Let the actuator air-dry completely, such as overnight (see Figure 6).

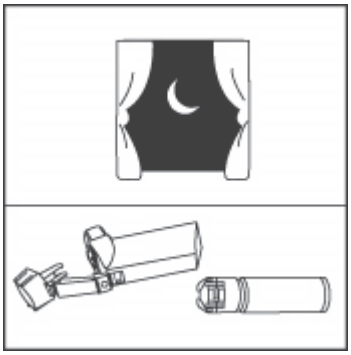


Figure 6

5. When the actuator is dry, put the canister in the actuator and make sure it fits firmly. Shake the inhaler well and spray it once into the air away from your face. (The counter will count down by 1.) Put the cap back on the mouthpiece.

If your actuator becomes blocked:

Blockage from medicine build-up is more likely to happen if you do not let the actuator air-dry completely. If the actuator gets blocked so that little or no medicine comes out of the mouthpiece (see Figure 7), wash the actuator as described in cleaning steps 1 to 5.

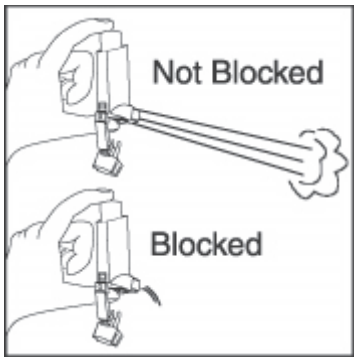


Figure 7

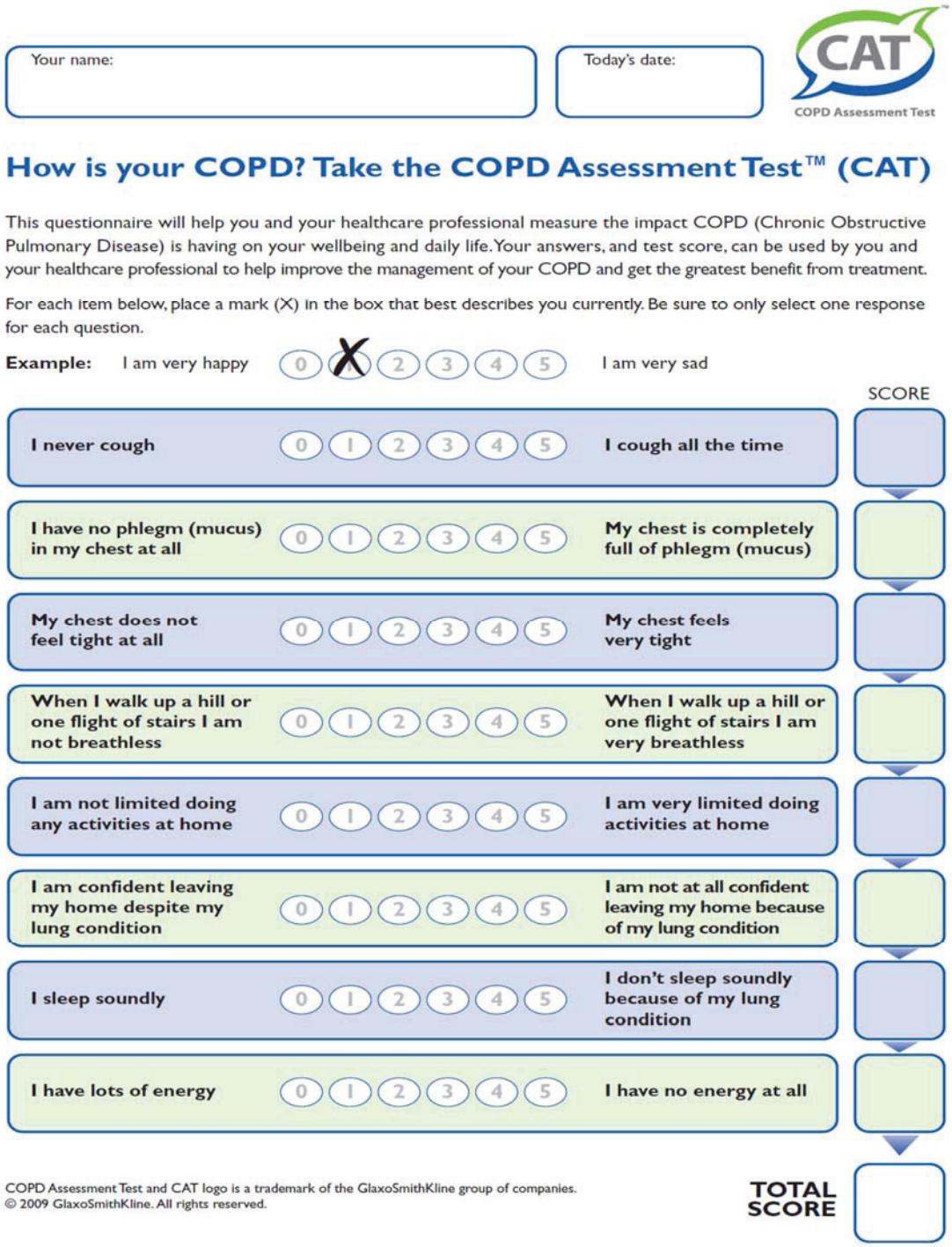
If you need to use your inhaler before the actuator is completely dry, shake as much water off the actuator as you can. Put the canister in the actuator and make sure it fits firmly. Shake the inhaler well and spray it once into the air away from your face. Then take your dose as prescribed. Then clean and air-dry it completely.

Storing Your VENTOLIN HFA

Store at room temperature with the mouthpiece down. Keep out of reach of children.
Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw into fire or incinerator.

Appendix 5 COPD Assessment Test (CAT)

(The sample provided here is for illustrative purposes only)



Your name:

Today's date:

CAT
COPD Assessment Test

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

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

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

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

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

Appendix 6 BDI/TDI Questionnaire

(The sample provided here is for illustrative purposes only)

Baseline/Transition Dyspnea Index (BDI/TDI)

BASELINE DYSPNEA INDEX

Baseline Functional Impairment

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

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

Baseline Magnitude of Task

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

Baseline Magnitude of Effort

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

TRANSITION DYSPNEA INDEX

Change in Functional Impairment

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

Change in Magnitude of Task

_____-3	*Major Deterioration*	Has deteriorated two grades or greater from baseline status.
_____-2	*Moderate Deterioration*	Has deteriorated at least one grade but fewer than two grades from baseline status.
_____-1	*Minor Deterioration*	Has deteriorated less than one grade from baseline. Subject with distinct deterioration within grade, but has not changed grades.
_____ 0	*No Change*	No change from baseline.
_____+1	*Minor Improvement*	Has improved less than one grade from baseline. Subject with distinct improvement within grade, but has not changed grades.
_____+2	*Moderate Improvement*	Has improved at least one grade but fewer than two grades from baseline.
_____+3	*Major Improvement*	Has improved two grades or greater from baseline.
_____ Z	*Further Impairment for Reasons Other than Shortness of Breath*	Subject has reduced exertion capacity, **but** not related to shortness of breath. For example, musculoskeletal problem or chest pain.

Change in Magnitude of Effort

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

Appendix 7 St. George Respiratory Questionnaire (SGRQ)

(The sample provided here is for illustrative purposes only)

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

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

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

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

Before completing the rest of the questionnaire:

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

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

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USA / US English version 1

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St. George's Respiratory Questionnaire
PART 1

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

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

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

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

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

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

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

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

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

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

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your respiratory condition?

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

If you have ever held a job:

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

Section 2

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

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

USA / US English version 3

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St. George's Respiratory Questionnaire
PART 2

Section 3

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

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

Section 4

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

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

Section 5

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

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

USA / US English version 4

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St. George's Respiratory Questionnaire
PART 2

Section 6

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

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

Section 7

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

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

USA / US English version 5

continued...

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St. George's Respiratory Questionnaire

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

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

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

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

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

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

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

USA / US English version 6

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Appendix 8 EuroQoL 5 Dimensions (EQ-5D) Questionnaire

Health Questionnaire

English version for the UK

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

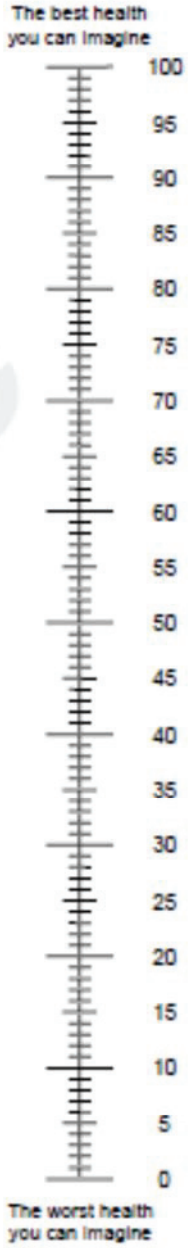
ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

2

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

YOUR HEALTH TODAY = ☐



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Appendix 9 Exacerbations of Chronic Obstructive Pulmonary Disease (EXACT)

EXACT version 1.1– *English (Universal)*
9/9/2009

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

EXACT version 1.1– *English (Universal)*
9/9/2009

Description	Required Text	Translation
4		
	How difficult was it to bring up mucus (phlegm) today?	How difficult was it to bring up mucus (phlegm) today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Quite a bit	Quite a bit
	Extremely	Extremely
5		
	Did you have chest discomfort today?	Did you have chest discomfort today?
	Not at all	Not at all
	Slight	Slight
	Moderate	Moderate
	Severe	Severe
	Extreme	Extreme
6		
	Did your chest feel tight today?	Did your chest feel tight today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
7		
	Were you breathless today?	Were you breathless today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely

EXACT version 1.1– *English (Universal)*
9/9/2009

Description	Required Text	Translation
8		
	Describe how breathless you were today:	Describe how breathless you were today:
	Unaware of breathlessness	Unaware of breathlessness
	Breathless during strenuous activity	Breathless during strenuous activity
	Breathless during light activity	Breathless during light activity
	Breathless when washing or dressing	Breathless when washing or dressing
	Present when resting	Present when resting
9		
	Were you short of breath today when performing your usual personal care activities like washing or dressing?	Were you short of breath today when performing your usual personal care activities like washing or dressing?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these
10		
	Were you short of breath today when performing your usual indoor activities like cleaning or household work?	Were you short of breath today when performing your usual indoor activities like cleaning or household work?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these

EXACT version 1.1– *English (Universal)*
9/9/2009

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

EXACT version 1.1– *English (Universal)*
9/9/2009

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

Appendix 10 Rules for Evaluation of Abnormal Liver Laboratory Values

INTRODUCTION

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

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

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

DEFINITIONS

Potential Hy's Law

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

Hy's Law

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

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

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

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

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

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

- Determine whether the subject meets PHL criteria by reviewing all laboratory reports including previous visits.
- Notify the Sponsor representative.

FOLLOW-UP

Potential Hy's Law Criteria not met

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

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

Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

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

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

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

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

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

No later than 2 weeks after the biochemistry abnormality was initially detected, the Sponsor Medical Monitor contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the study drug. The Sponsor Medical Monitor and other subject matter experts (as appropriate) will collaborate in the review and assessment of these cases.

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

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

- If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF according to the Sponsor's standard reporting procedures.
- If the alternative explanation is not an AE, record the alternative explanation on the comment form within the eCRF.

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

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

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

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

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

Appendix 11 Dose Indicator Reading

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

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

Appendix 12 Sponsor Signatory

Study Title: A Randomized, Double-Blind, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT009 compared to PT005 in Subjects With Moderate to Very Severe COPD

Study Number: PT009003-03

Final Date: 08 January 2018

[redacted]

Signature:

Name:
Title:

Appendix 13 Investigator's Agreement and Signature Page

Study Title:	A Randomized, Double-Blind, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT009 compared to PT005 in Subjects With Moderate to Very Severe COPD
Study Number:	PT009003-03
Final Date:	08 January 2018

I agree:

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

Signature:_____ Date:_____

Name:_____

Affiliation: _____