Revised Clinical Study Protocol

Study Code	PT010005
NCT #	NCT02465567
Date:	21 JUNE 2019

A Randomized, Double-Blind, Multi-Center, Parallel Group Study to Assess the Efficacy and Safety of PT010 Relative to PT003 and PT009 on COPD Exacerbations over a 52-Week Treatment Period in Subjects With Moderate to Very Severe COPD

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

Amendment No.	Date of Amendment
Version 1	18 MAY 2015
Version 2, Amendment 1	04 JULY 2015
Version 1.1	17 AUGUST 2015
Version 3, Amendment 4	08 JANUARY 2016
Version 4, Amendment 3	25 AUGUST 2016
Version 4.1	19 SEPTEMBER 2016
Version 5, Amendment 4	03 NOVEMBER 2017
Version 6, Amendment 5	27 MARCH 2018
Version 6.1	21 JUNE 2019

CLINICAL STUDY PROTOCOL: PT010005-05

Study Title:	A Randomized, Double-Blind, Multi-Center, Parallel Group Study to Assess the Efficacy and Safety of PT010 Relative to PT003 and PT009 on COPD Exacerbations over a 52-Week Treatment Period in Subjects With Moderate to Very Severe COPD
Study Number:	PT010005-05
Study Phase:	Phase III
Product Name:	Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (PT010, BGF metered dose inhaler [MDI]) Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (PT003, GFF MDI) Budesonide and Formoterol Fumarate Inhalation Aerosol (PT009, BFF MDI)
IND Number:	118313
EudraCT Number:	2014-005671-92
Indication:	COPD
Investigators:	Multicenter
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]

	Version Number	Date
Original Protocol	Version 1.0	18 May 2015
Amended Protocol	Version 2.0	04 July 2015
Amended Protocol	Version 1.1	17 August 2015
Amended Protocol	Version 3.0	08 January 2016
Amended Protocol	Version 4.0	25 August 2016
Amended Protocol	Version 4.1	19 September 2016
Amended Protocol	Version 5.0	03 November 2017
Amended Protocol	Version 6.0	27 March 2018
Amended Protocol	Version 6.1	21 June 2019

SUMMARY OF CHANGES FROM VERSION 6.0 INCLUDED IN THIS PROTOCOL AMENDMENT VERSION 6.1

Sections(s)/Description of Change	Rationale
Synopsis, Section 2.2 Added secondary objective: to assess the effect of BGF MDI relative to GFF MDI and BFF MDI on COPD exacerbations.	This is to cover additional COPD-exacerbation-related endpoints not covered by the primary objective.
Synopsis, Sections 3.1.2, 3.1.3, and 9.4.3.7 Rate of severe COPD exacerbations is now a secondary efficacy endpoint instead of an "other" efficacy endpoint.	Severe exacerbations are highly clinically relevant and are a predictor of mortality
Synopsis, Sections 3.1.3, 3.3.1, 9.4.3.3, 9.4.3.5, 9.4.3.6, 9.4.4.1, 9.4.4.2, and 9.4.4.5 Removed analysis of the following other endpoints out of Protocol: • ~~Compliance for EQ-5D~~ • ~~Change from baseline in morning pre-dose trough, AUC_{0-4}, and peak change from baseline in forced vital capacity (FVC), peak expiratory flow rate (PEFR), and forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}).~~ • ~~Individual components of the TDI: functional impairment, magnitude of task, and magnitude of effort over 24 weeks, over 52 weeks, and at each post-randomization visit~~ • ~~Individual domains of the SGRQ: Symptoms, Activity, and Impacts over 24 weeks, over 52 weeks, and at each post-randomization visit~~ • ~~EXACT symptom domain scores for breathlessness, cough and sputum, and chest symptoms over 24 weeks, over 52 weeks and over each 4-week~~	In our previous studies, these endpoints did not provide further insights into the primary and secondary endpoints and were consequently not discussed in the CSR. Furthermore, removal of these endpoints will reduce the volume of output for the CSR and facilitate focused review.

Sections(s)/Description of Change	Rationale
~~interval of the 52-week treatment period~~ • ~~Rate and time to first COPD exacerbation treated with systemic steroids~~ • ~~Rate and time to first COPD exacerbation treated with antibiotics~~	
Synopsis, Section 3.3.2.2 For 24-hour Holter monitoring sub-study endpoints, added the following endpoints: • Change from baseline in the frequency of supraventricular ectopic beats • Incidence of withdrawal criteria being met during 24-hour Holter monitoring Added the "isolated" for the following endpoints: • Change from baseline in the frequency of isolated ventricular ectopic events (including a single premature ventricular contraction [PVC]) • Change from baseline in the frequency of isolated supraventricular ectopic events Removed the following endpoint: • ~~Incidence of sustained ventricular tachycardia (SVT) [defined as PVCs lasting>30 seconds]~~	This is to reflect previous Holter study endpoints from similar studies.
Section 3.4	The addition of "due to COPD" is for clarification purpose. The reason for addition of "Calls to any health-care provider" is to cover all types of visits for the analysis.

Sections(s)/Description of Change	Rationale
For health care resource utilization endpoints, added "due to COPD" for the endpoint "The number of days missed work". Added "Calls to any health-care provider" for the following endpoints: • The percentage of subjects with telephone calls to health care providers • The mean number of telephone calls to health care providers • The percentage of subjects with visits to health care providers • The mean number of visits to health care providers	
Section 9.4.2.1 Updated the definition for the duration of moderate or severe COPD exacerbations. A CRF-recorded COPD exacerbation resulting in a hospitalization or death will be considered as a countable moderate to severe (and also severe) COPD exacerbation regardless of whether systemic corticosteroids or systemic antibiotics were used to treat the exacerbation.	Avoid the exclusion of meaningful COPD exacerbation records from the analysis
Section 9.4.2.1 Clarified that the start day of a COPD exacerbation will not be excluded from the time-at-risk of a COPD exacerbation.	Provide a clarification for the calculation
Synopsis, Sections 9.4.2.1, 9.4.3.1, 9.4.3.3, 9.4.3.4, 9.4.3.5, 9.4.4.4, 9.4.5.1, and 9.4.5.2 Updated analyses to include the log baseline blood eosinophil count as a covariate instead of baseline blood eosinophil count.	Eosinophil counts are skewed to the right and transformation reduces the influence of a few outlying high values.
Sections 9.4.5.2, and 9.4.5.3 For FEV1 AUC 0-4, it is clarified that this is a linear mixed repeated measures (RM) ANCOVA analysis (which is the analysis type also being used for pre-dose trough FEV1) instead of ANCOVA.	This analysis model was incompletely stated before as an ANCOVA without reference to RM.

Sections(s)/Description of Change	Rationale
Section 9.4.5.4 For rate of decline in pre-dose FEV1 and FEV1 AUC0-4, added treatment and smoking status at screening as categorical covariates, and added the interaction between screening smoking status and time and the interaction between baseline FEV1 and time in the model.	These terms were inadvertently omitted in the previous version of protocol.
Section 9.4.6 The non-inferiority (NI) margin was updated from 0.1 to 1.1 for the comparisons of BGF MDI 160/14.4/9.6 µg to BFF MDI 320/9.6 µg on COPD exacerbations.	This NI margin was incorrect in the prior version of the protocol
Section 9.4.8 Criteria for upper limit for Glucose were changed for potentially clinically significant laboratory values.	This was done to align with revised safety thresholds based on medical history.
Other administrative changes to correct and/or clarify protocol language were also addressed. These changes included edits for consistency, grammar, and typographical errors, which are not summarized in this table.	

SYNOPSIS

Sponsor:

Pearl Therapeutics, Inc. ("Pearl")

[redacted]

Name of Finished Product:

Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (PT010, BGF metered dose inhaler [MDI])

Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (PT003, GFF MDI)

Budesonide and Formoterol fumarate Inhalation Aerosol (PT009, BFF MDI)

Name of Active Ingredients:

Budesonide, Glycopyrronium, and Formoterol Fumarate

Glycopyrronium and Formoterol Fumarate

Budesonide and Formoterol Fumarate

Study Title:

A Randomized, Double-Blind, Multi-Center, Parallel-Group Study to Assess the Efficacy and Safety of PT010 Relative to PT003 and PT009 on COPD Exacerbations over a 52-Week Treatment Period in Subjects with Moderate to Very Severe COPD

Study Number: PT010005-05

Study Phase: Phase III

Primary Objective:

- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on the rate of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbations

Secondary Objectives:

- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on symptoms of COPD
- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on quality of life
- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on all-cause mortality
- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on COPD exacerbations

Safety Objective:

- To assess the safety of BGF MDI relative to GFF MDI and BFF MDI

4-Hour Pulmonary Function Test (PFT) Sub-study Objective:

- To assess the effects of BGF MDI relative to GFF MDI and BFF MDI on lung function

24-Hour Holter Monitoring Sub-study Objective:

- To evaluate the cardiovascular safety of BGF MDI relative to GFF MDI and BFF MDI as evaluated by 24-hour Holter monitoring

Health Care Resource Utilization (HCRU) Objective:

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

Study Design:

This is a randomized, double-blind, multi-center, parallel group study to assess the efficacy and safety of BGF MDI 320/14.4/9.6 µg and BGF MDI 160/14.4/9.6 µg relative to GFF MDI 14.4/9.6 µg and BFF MDI 320/9.6 µg over a 52-week treatment period in approximately 8,400 subjects with moderate to very severe COPD with an increased risk of experiencing a COPD exacerbation and that remain symptomatic on the COPD Assessment Test (CAT ≥ 10) on two or more inhaled maintenance treatments.

To be considered eligible for the study, subjects must have documented history of COPD exacerbations. Subjects with a post-bronchodilator FEV_1 < 50% of predicted normal must have ≥ 1 moderate or severe COPD exacerbation in the previous 12 months. Subjects with a post-bronchodilator FEV_1 ≥ 50% of predicted normal must have ≥ 2 moderate exacerbations or ≥ 1 severe COPD exacerbation in the previous 12 months. In addition, post-bronchodilator FEV_1 for these subjects during screening should be ≥ 25% and < 65% of the predicted normal value calculated using appropriate reference equations.

Subjects will undergo a Screening Period of 1 to 4 weeks in duration. During the screening period subjects that are receiving an ICS/LABA will discontinue the ICS/LABA, but will continue the ICS component for the remainder of the screening period. Similarly, subjects treated with an ICS as part of their inhaled maintenance therapy will also be permitted to continue their ICS for the remainder of the screening period. All subjects will receive open-label Atrovent® hydrofluoroalkane (HFA; ipratropium bromide inhalation aerosol) administered QID for maintenance during Screening. 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 oral corticosteroids of up to 2 weeks in duration and a 4-week period after treatment of the exacerbation).

Subjects who successfully complete the Screening Period will then be randomized in a 1:1:1:1 scheme to BGF MDI 320/14.4/9.6 µg BID, BGF MDI 160/14.4/9.6 µg BID, BFF MDI 320/9.6 µg BID, or GFF MDI 14.4/9.6 µg BID, respectively. Approximately 2,100 subjects will be randomized to each treatment arm. 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 65% predicted), blood eosinophil count <150 cells per mm^3 or ≥150 cells per mm^3), and country. Up to a 1:2 ratio for the blood eosinophil strata was targeted with twice as many randomized subjects in the ≥ 150 cells per mm^3 category. Following randomization, subjects will enter the Treatment Period and undergo 10 additional treatment visits over 52 weeks.

Subjects who discontinue study treatment prior to Week 52 (Visit 14) will be encouraged to remain in the study to complete all remaining study visits during the 52-week treatment period. Subjects who agree to continue to be followed post treatment discontinuation will sign an ICF addendum. All subjects who agree to continue study participation beyond treatment discontinuation will complete a Treatment Discontinuation/Withdrawal Visit (refer to Table 8, and Sections 8.9 and 8.10) prior to transitioning back to regularly scheduled study visits. Subjects participating in the Holter Monitoring sub-study who discontinue from treatment will only complete regularly scheduled visits and not complete any remaining Holter sub-study assessments, however subjects participating in the PFT sub-study will continue with serial PFTs only. Treatment discontinuation subjects will return to appropriate maintenance COPD medications, per the investigator's discretion. For subjects recorded as Treatment Discontinuations that do not complete at least one post-treatment data collection, a telephone follow-up call is required at least 14 days after last study drug dose. These subjects will be followed for vital status at 52 weeks post randomization in accordance with the informed consent.

If a subject chooses not to continue with study assessments, at a minimum the subject will complete the Treatment Discontinuation/Withdrawal Visit (refer to Sections 8.9 and 8.10). These subjects will return to appropriate maintenance COPD medications, per the investigator's discretion. A follow-up telephone call will be performed at least 14 days after the last study drug dose. In the event the Treatment Discontinuation/Withdrawal Visit is performed >14 days post last study drug dosing, a follow-up TC will not be required. These subjects will be followed for vital status at 52 weeks post randomization in accordance with the informed consent.

4-Hour Pulmonary Function Test Sub-study: Serial PFTs will be conducted over 4 hours in a subset of approximately 3,060 subjects (765 subjects per treatment group) at selected visits throughout the 52-week Treatment Period. Those subjects who do not meet FEV1 Baseline Stability criteria will not be permitted to participate in the PFT Sub-study, but will be permitted to participate in the main study providing they satisfy all other eligibility criteria. Sub-study was previously open to all eosinophil levels, now only subjects who have a blood eosinophil level of ≥ 150 cells per mm3 at Visit 1 will be permitted to participate in the PFT Sub-study.

24-Hour Holter Monitoring Sub-study: Holter Monitoring will be conducted over 24 hours in a subset of approximately 800 randomized (200 subjects from each treatment group) at Visit 3 (Holter Monitoring Baseline) and Visit 8 (Week 16).

Study Population: Approximately 8,400 subjects with moderate to very severe COPD will be randomized in this study.

Product, Dose, and Mode of Administration:

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

Product Name & Dose	Product Strength	Dosage Form/ Fill Count	Administration
Study Medications			
BGF MDI 320/14.4/9.6 µg ex-actuator	160/7.2/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
BGF MDI 160/14.4/9.6 µg ex-actuator	80/7.2/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
GFF MDI 14.4/9.6 µg ex-actuator	7.2/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
BFF MDI 320/9.6 µg ex-actuator	160/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
Open-Label Products			
Ipratropium bromide HFA inhalation aerosol 34 µg ex-actuator[a]	Atrovent (ipratropium bromide) HFA will be the US-supplied product. Each inhalation contains 17 µg ex-actuator per actuation.	MDI 200 actuations	Taken as 2 inhalations QID during Screening; Supplies are open-label
Albuterol sulfate inhalation aerosol 90 µg ex-actuator[b]	Ventolin (albuterol sulfate) HFA inhalation aerosol will be the US-supplied product. Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation.	MDI 60 or 200 actuations	Taken as directed; Supplies are open-label

BFF=Budesonide and Formoterol Fumarate; BGF=Budesonide, Glycopyrronium, and Formoterol Fumarate; BID=twice daily; DPI=dry powder inhaler; GFF=Glycopyrronium and Formoterol Fumarate; HFA=hydrofluoroalkane; MDI=metered dose inhaler; QID=4 times daily; EU=Europe; US=United States

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

[b] Reversibility testing at Visit 2 and rescue medication during the study. Albuterol sulfate is also known as salbutamol sulfate in some countries.

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

Note: 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.

Duration of Treatment: It is planned that each subject will receive study treatment for 52 weeks.

Duration of Study: The entire study period is scheduled to take approximately 60 weeks (expected range between 56 to 64 weeks) for each individual subject. The study is anticipated to run for approximately 30 months and is not expected to exceed 50 months.

Efficacy Assessments:

Primary Efficacy Endpoint:

- Rate of moderate or severe COPD exacerbations

Secondary Efficacy Endpoints: Secondary **e**ndpoints that differ between approaches (US vs. ex-US) are indicated in parentheses. Endpoints which are not considered secondary for either regulatory approach have been included under other efficacy endpoints.

- Time to first moderate or severe COPD exacerbation
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Transition Dyspnea Index (TDI) focal score over 24 weeks (ex-United States [US] [ex-US])
- Change from baseline in the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) total score over 52 weeks (ex-US)
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score over 24 weeks (ex-US)
- Percentage of subjects achieving a minimal clinically important difference (MCID) of 4 units or more in SGRQ total score at Week 24 (US)
- Time to death (all cause)
- Rate of severe COPD exacerbations

Safety Endpoints:

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

PFT Sub-study Endpoints:

The primary PFT endpoints are:

- Change from baseline in morning pre-dose trough FEV_1 at Week 24 (US) and over 24 weeks (ex-US) for the comparison of BGF MDI to GFF MDI
- FEV_1 area under the curve from 0 to 4 hours (AUC_{0-4}) at Week 24 (US) and over 24 weeks (ex-US) for the comparison of BGF MDI to BFF MDI

Other PFT endpoints include:

- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks, over Weeks 12 to 24, over 52 weeks and at each post-randomization visit
- FEV_1 AUC_{0-4} over 24 weeks, over Weeks 12 to 24, over 52 weeks and at each post-randomization visit where measured
- Peak change from baseline in FEV_1 over 24 weeks, over Weeks 12 to 24, over 52 weeks and at each post-randomization visit where measured
- Rate of decline in pre-dose FEV_1 over 52 weeks
- Rate of decline in FEV_1 AUC_{0-4} over 52 weeks
- Time to onset of action on Day 1

24-Hour Holter Monitoring Sub-study Endpoints (Assessed at Week 16)

Primary Endpoint:

- Change from baseline in mean heart rate averaged over 24 hours

Secondary Endpoints:

- Change from baseline in mean night-time (22:00 to 06:00) and day-time (06:00 to 22:00) heart rate
- Change from baseline in the maximum 24-hour heart rate
- Change from baseline in the minimum 24-hour heart rate
- Change from baseline in the frequency of isolated ventricular ectopic events (including a single premature ventricular contraction [PVC])
- Change from baseline in the frequency of ventricular couplets (defined as two PVCs preceded or followed by regular beats)
- Change from baseline in the frequency of ventricular runs (defined as three or more PVCs preceded or followed by regular beats)
- Change from baseline in the frequency of supraventricular ectopic beats
- Change from baseline in the frequency of isolated supraventricular ectopic events
- Change from baseline in the frequency of supraventricular couplets
- Change from baseline in the frequency of supraventricular runs
- Incidence of withdrawal criteria being met during 24-hour Holter monitoring
- Incidence of atrial fibrillation with rapid ventricular response (>100 beats per minute [bpm])

Statistical Methods:

Primary Efficacy Analysis: The rate of moderate or severe COPD exacerbations will be analyzed using negative binomial regression. COPD exacerbations will be considered separate events provided that 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, log baseline blood eosinophil count, region, and inhaled corticosteroid (ICS) use at Screening.

Sample Size: [redacted]

Interim Efficacy Analyses: There will be an interim efficacy analysis at which an independent Data Monitoring Committee (DMC) will review unblinded efficacy data and determine if the study can be stopped early for unequivocal efficacy. [redacted] Should the study continue until all subjects complete, the one-sided alpha criteria for the final analysis will be adjusted based on the percent of information available at the prior interim analyses using an appropriate spending function such that the overall Type I error is controlled at one-sided 0.025. [redacted]

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

Data Monitoring Committee: An independent, external 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 Pearl at predetermined intervals. If significant safety issues arise in between scheduled meetings, ad-hoc meetings will be scheduled to review the data. Based on the safety implications of the data, the DMC may recommend modification or termination of the study. An interim efficacy analysis will be performed at which an independent Data Monitoring Committee will review unblinded efficacy data and determine if the study can be stopped early for unequivocal efficacy.

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

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

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine aminotransferase
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR(1)	autoregressive order 1
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC_{0-4}	area under the curve from 0 to 4 hours
BD MDI	Budesonide Metered Dose Inhaler
BDI	Baseline Dyspnea Index
BFF MDI	Budesonide and Formoterol Fumarate Metered Dose Inhaler
BGF MDI	Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler
BID	bis in die, twice daily
bpm	beats per minute
BMP	Basic Metabolic Panel
BTPS	body temperature and pressure saturated
CAT	Chronic Obstructive Pulmonary Disease Assessment Test
CCU	Coronary Care Unit
CCV	cardio- and cerebrovascular
CFR	Code of Federal Regulations
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
cm	centimeter
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure

DMC	Data Monitoring Committee
DPI	dry powder inhaler
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDiary	electronic Diary
eg	exempli gratia; for example,
EQ-5D-5L	EuroQol 5 Dimensions Questionnaire 5-level
ER	Emergency Room
ERS	European Respiratory Society
EU	European Union
ex-actuator	dose delivered from the actuator (i.e., mouthpiece) of the MDI
ex-US	outside the United States
EXACT	Exacerbations of Chronic Pulmonary Disease Tool – Patient Reported Outcomes
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FEF_{25-75}	forced expiratory flow between 25% and 75% of FVC
FF MDI	Formoterol Fumarate Metered Dose Inhaler
FVC	forced vital capacity
GCP	Good Clinical Practice
GFF MDI	Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP MDI	Glycopyrronium Metered Dose Inhaler
hCG	human chorionic gonadotropin
HCRU	Health Care Resource Utilization
HFA	hydrofluoroalkane
HR	heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

ICMJE	International Committee of Medical Journal Editors
ICS	inhaled corticosteroid
ICU	Intensive Care Unit
ie	id est; that is
IEC	Independent Ethics Committee
IM	intramuscular
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	intravenous
IWRS	Interactive Web Response System
JRS	Japanese Respiratory Society
L	liter
LABA	long-acting β_2 agonist
LAMA	long-acting muscarinic antagonist
LPLV	last patient last visit
MACE	major adverse cardiovascular event
MCID	minimal clinically important difference
MDI	metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
µg	microgram
mITT	Modified Intent-to-Treat
mL	milliliter
mm	millimeter
mmHg	millimeter of mercury
msec (ms)	millisecond
NSVT	Non-sustained ventricular tachycardia
NYHA	New Your Heart Association
OCS	oral corticosteroid
OTC	over-the-counter

PCS	potentially clinically significant
PEFR	peak expiratory flow rate
PFT	pulmonary function test
PIN	personal identification number
PP	Per-Protocol
PT003	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol
PT009	Budesonide and Formoterol Fumarate Inhalation Aerosol
PT010	Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol
PVC	Premature ventricular contraction
QID	quater in die; four times daily
QoL	Quality of Life
QTcF	QT corrected using Fridericia's formula
RM	repeated measures
SABA	short-acting β_2-agonist
SAE	serious adverse event
SAMA	short-acting muscarinic antagonist
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SGRQ	St. George's Respiratory Questionnaire
SNRI	selective norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVT	Sustained ventricular tachycardia
TC	telephone call
TDI	Transition Dyspnea Index
TEAE	treatment-emergent adverse event
US	United States
VAS	visual analog scale

VC	vital capacity
VPB	Ventricular premature beats

TRADEMARK INFORMATION

Trademarks Not Owned By Pearl Therapeutics, Inc.

Atrovent

Oxis

SAS

Spiriva

Symbicort

Turbuhaler

Ventolin

1 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients. Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality worldwide and results in significant economic and social burden that is both substantial and increasing. Pharmacologic therapy in COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance [Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2014); Japanese Respiratory Society (JRS, 2013).

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

Regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function, and quality of life and reduces the frequency of exacerbations in subjects with COPD with a forced expiratory volume in 1 second (FEV_1) value of <60% of predicted. Withdrawal from treatment of ICS may lead to exacerbations in some patients. When combined with a long-acting β_2-agonist (LABA), an ICS is more effective than the individual components in improving lung function, quality of life, and reducing exacerbations in subjects with moderate to very severe COPD [GOLD, 2014].

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

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

Glycopyrronium is a LAMA which exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. Glycopyrronium is approved in many countries in multiple formulations for different indications, including for the treatment of COPD. In addition, tiotropium bromide (Spiriva®) is approved worldwide as a

powder for inhalation. It has been shown to reduce the rate of COPD exacerbations and to improve the effectiveness of pulmonary rehabilitation (Niewoehner, 2005; Casaburi, 2005).

Formoterol fumarate is a selective LABA approved worldwide for use in asthma and COPD. Formoterol fumarate is also approved worldwide in combination with budesonide (e.g., Symbicort® MDI, Symbicort® Turbuhaler® (TBH [AstraZeneca, LP]) for use in patients with asthma and COPD. When inhaled, formoterol fumarate acts locally in the lung as a bronchodilator. Formoterol fumarate stimulates β_2-adrenoreceptors in the airways, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction.

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

The GOLD guidelines suggest a stepwise approach to the management of COPD. For patients, with few symptoms and a low risk of exacerbations (Group A), a short-acting bronchodilator is recommended. Long-acting bronchodilators, such as long acting β_2 agonists (LABAs) and long acting muscarinic antagonists (LAMAs) are recommended for patients with more significant symptoms, but a low risk of exacerbation (Group B). For patients with severe breathlessness, the alternative choice is a combination of long-acting bronchodilators. In patients that have few symptoms, but a high risk of exacerbations (Group C), the first choice of therapy is a fixed combination of an inhaled corticosteroid (ICS)/LABA or a LAMA. In patients with many symptoms, and a high risk of exacerbations (Group D), the first choice is an ICS/LABA or LAMA; with some evidence for a further reduction in exacerbations with triple therapy (i.e., ICS/LABA/LAMA); however, further studies of triple therapy are needed [GOLD, 2014]. Note that administration of triple therapy requires the use of at least two separate inhalers, and that all three products are not available in a single metered dose inhaler (MDI) or dry powder inhaler (DPI).

1.1 Study Rationale

BGF MDI is a novel, fixed-dose, triple combination MDI product formulated with budesonide, glycopyrronium, and formoterol fumarate for use in subjects with COPD. As described in the GOLD COPD guidelines, in some patients, the addition of a LABA/ICS to a LAMA improves lung function, quality of life, and may further reduce exacerbations. For patients categorized in Group D (those with severe or very severe disease, many symptoms, and high risk of exacerbations), the first choice of treatment is an ICS/LABA or LAMA, with some evidence for a further reduction in exacerbations with triple therapy; however, further studies of triple therapy are needed [GOLD, 2014]. Pearl is conducting this study to evaluate the treatment effect of BGF MDI (LABA/ICS/LAMA therapy) relative to GFF MDI (LAMA/LABA therapy) and BFF MDI (ICS/LABA therapy) on the rate of moderate or severe COPD exacerbations over a 52-week treatment period in subjects with moderate to very severe COPD who have a history of COPD exacerbations.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on the rate of moderate or severe COPD exacerbations

2.2 Secondary Objectives

- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on symptoms of COPD
- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on quality of life
- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on all-cause mortality
- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on COPD exacerbations

2.3 Safety Objective

- To assess the safety of BGF MDI relative to GFF MDI and BFF MDI

2.4 4-Hour Pulmonary Function Test Sub-Study Objective

- To assess the effect of BGF MDI relative to GFF MDI and BFF MDI on lung function

2.5 24-Hour Holter Monitoring Sub-study Objective

- To evaluate the cardiovascular safety of BGF MDI, GFF MDI, and BFF MDI as evaluated by 24-hour Holter monitoring

2.6 Health Care Resource Utilization Objective

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

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

3.1.1 Primary Endpoint

- Rate of moderate or severe COPD exacerbations

3.1.2 Secondary Endpoints

Secondary endpoints that differ between approaches (US vs. ex-US) are indicated in parentheses. Endpoints which are not considered secondary for either regulatory approach have been included under other efficacy endpoint.

- Time to first moderate or severe COPD exacerbation
- Change from baseline in average daily rescue Ventolin HFA use over 24weeks
- Transition Dyspnea Index (TDI) focal score over 24 weeks (ex-United States [US] [ex-US])
- Change from baseline in the Exacerbations of Chronic Pulmonary Disease Tool – (EXACT) total score over 52 weeks (ex-US)
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score over 24 weeks (ex-US)
- Percentage of subjects achieving an MCID of 4 units or more in SGRQ total score at Week 24 (US)
- Time to death (all cause)
- Rate of severe COPD exacerbations

3.1.3 Other Efficacy Endpoints

Wherever stated, analyses of an endpoint at each post-randomization visit will only be performed at time points where the endpoint will be assessed per the schedule of assessments.

- Rate of COPD exacerbations of any severity
- Time to first COPD exacerbation of any severity
- Time to first severe COPD exacerbation
- Change from baseline in average daily rescue Ventolin HFA use over 52 weeks
- Time to death (respiratory)
- Time to treatment failure (treatment discontinuation for any cause, moderate or severe exacerbation, or death)

- Change from baseline in: the EXACT total score, the EXACT Respiratory Symptoms (E-RS) total score over 24 weeks, over 52 weeks, and over each 4-week interval of the 52-week treatment period
- Percentage of days with "no rescue Ventolin HFA use"
- TDI focal score over 24 weeks (US), over 52 weeks, and at each post-randomization visit
- Percentage of subjects achieving an MCID threshold of 1 unit or more on average over 24 weeks in TDI focal score
- Percentage of subjects achieving an MCID threshold of 1 unit or more on average over 52 weeks in TDI focal score
- Change from baseline in SGRQ total score over 52 weeks, and at each post-randomization visit
- Percentage of subjects achieving an MCID of 4 units or more in SGRQ total score over 52 weeks, at Week 52, and over 24 weeks
- EuroQol 5 Dimensions Questionnaire (EQ-5D-5L) variables including the EQ-5D index score, the EQ-5D Visual Analog Score (VAS), and each of the five-dimension single item 5-level responses at each post-randomization visit.

3.2 Safety Endpoints

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

3.3 Sub-Study Endpoints

3.3.1 4-Hour Pulmonary Function Test Sub-Study Endpoints

The primary PFT endpoints are:

- Change from baseline in morning pre-dose trough FEV_1 at Week 24 (US) and over 24 weeks (ex-US) for the comparison of BGF MDI to GFF MDI
- FEV_1 area under the curve from 0 to 4 hours (AUC_{0-4}) at Week 24 (US) and over 24 weeks (ex-US) for the comparison of BGF MDI to BFF MDI

Other PFT Sub-Study Endpoints:

- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks, over Weeks 12 to 24, over 52 weeks and at each post-randomization visit

- FEV_1 AUC_{0-4} over 24 weeks, over Weeks 12 to 24, over 52 weeks and at each post-randomization visit where measured
- Peak change from baseline in FEV_1 over 24 weeks, over Weeks 12 to 24, over 52 weeks and at each post-randomization visit where measured
- Rate of decline in pre-dose FEV_1 over 52 weeks
- Rate of decline in FEV_1 AUC_{0-4} over 52 weeks
- Time to onset of action on Day 1

3.3.2 24-Hour Holter Monitoring Sub-Study Endpoints Assessed at Visit 8 (Week 16)

3.3.2.1 Primary 24-Hour Holter Monitoring Sub-Study Endpoints Endpoint

- Change from baseline in mean heart rate averaged over 24 hours

3.3.2.2 Secondary 24-Hour Holter Monitoring Sub-Study Endpoints

- Change from baseline in mean nighttime (22:00 to 06:00) and daytime (06:00 to 22:00) heart rate
- Change from baseline in the maximum 24-hour heart rate
- Change from baseline in the minimum 24-hour heart rate
- Change from baseline in the frequency of isolated ventricular ectopic events (including a single premature ventricular contraction [PVC])
- Change from baseline in the frequency of ventricular couplets (defined as two PVCs preceded or followed by regular beats)
- Change from baseline in the frequency of ventricular runs (defined as three or more PVCs preceded or followed by regular beats)
- Change from baseline in the frequency of supraventricular ectopic beats
- Change from baseline in the frequency of isolated supraventricular ectopic events
- Change from baseline in the frequency of supraventricular couplets
- Change from baseline in the frequency of supraventricular runs
- Incidence of withdrawal criteria being met during 24-hour Holter monitoring
- Incidence of atrial fibrillation with rapid ventricular response (>100 beats per minute [bpm])

3.3.3 Other Endpoints:

- Proportion of subjects with maximum heart rate >180, >160-180, >140-160, >120-140, >100-120, and 100 bpm or less
- Proportion of subjects with minimum heart rate >60, >50-60, >40-50, and ≤40 bpm
- Proportion of subjects in each category of change from baseline in the number of PVCs per hour (no change, increase of >0-<60, 60-<120, and ≥120, and decrease of >0-<60, 60-<120, and ≥120)

3.4 Health Care Resource Utilization Endpoints

- The number of days missed work due to COPD
- The number of days that primary caregivers of subjects missed from work as a result of the subject's COPD
- The percentage of subjects with telephone calls to health care providers
  - Calls to any health-care provider (physician or other)
  - Calls to physician
  - Calls to other healthcare provider
- The mean number of telephone calls to health care providers
  - Calls to any health-care provider (physician or other)
  - Calls to physician
  - Calls to other healthcare provider
- The percentage of subjects with visits to health care providers
  - Visits to any health-care provider (general practitioner [GP], specialist, or other)
  - Visits to GP
  - Visits to specialist
  - Visits to other healthcare 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 healthcare 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 subject 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 subject spent no time in the ICU or the CCU
- The percentage of subjects hospitalized with no time 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 Intensive Care Units (ICU)
- The percentage of subjects in the Intensive Care Unit (ICU)
- The mean number of days in Coronary Care Units (CCU)
- The percentage of subjects in the Coronary Care Units (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 randomized, double-blind, multi-center, parallel group study to assess the efficacy and safety of BGF MDI 320/14.4/9.6 µg and BGF MDI 160/14.4/9.6 µg relative to GFF MDI 14.4/9.6 µg and BFF MDI 320/9.6 µg over a 52-week treatment period in 8,400 subjects with moderate to very severe COPD with an increased risk of experiencing a COPD exacerbation and that remain symptomatic (CAT ≥ 10) on two or more inhaled maintenance treatments. [redacted]

To be considered eligible for the study, subjects must have documented history of COPD exacerbation(s). Subjects with a post-bronchodilator FEV_1 < 50% of predicted normal are required to have ≥ 1 moderate or severe COPD exacerbation in the 12 months prior to Screening (Visit 1). Subjects with a post-bronchodilator FEV_1 ≥ 50% of predicted normal are required to have ≥ 2 moderate exacerbations or ≥ 1 severe COPD exacerbation (hospitalized) in the 12 months prior to Screening (Visit 1). In addition, post-bronchodilator FEV_1 obtained at Visit 2 must be ≥ 25% and < 65% of the predicted normal value calculated using appropriate reference equations.

At Visit 1 (Screening), all subjects are to sign an Informed Consent Form (ICF) prior to the conduct of any screening assessments. The Investigator will evaluate subjects to determine eligibility for participation (i.e., inclusion/exclusion criteria). Subjects who screen fail due to spirometry criteria will not be allowed to re-screen. Providing the subject meets the eligibility criteria, the Investigator or designee will review current COPD medications and, if necessary, will make arrangements to adjust the prohibited COPD therapy to protocol-allowable COPD therapy as described in Section 5.4.

All subjects will undergo a Screening Period of 1 to 4 weeks in duration and will receive sponsor-provided open-label Atrovent® hydrofluoroalkane (HFA; ipratropium bromide inhalation aerosol) administered QID for maintenance during Screening. All subjects will receive sponsor-provided Ventolin® HFA (albuterol sulfate inhalation aerosol) for rescue use throughout the study.

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.

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

In instances where a moderate or severe 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 [OCS] of up to 2 weeks in duration and a 4-week period after treatment for exacerbation) without the need to repeat completed visits.

In order to allow for an adequate washout of previous maintenance medications, subjects will undergo a Washout Period of at least 1 week (at least 2 weeks if taking Spiriva), but not greater than 26 days in duration prior to returning to the clinic for Visit 2.

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

Reversibility to a SABA and to a SAMA will be tested on two separate test days. At Visit 2, reversibility to Ventolin HFA (SABA) will be evaluated (see Section 7.1.1.1). The spirometry data obtained at Visit 2 will be used as an inclusion criterion (Section 5.1). In addition, at Visits 1and 4, the burden of disease will be assessed through the COPD Assessment Test (CAT). Subjects will complete the CAT at Screening (Visit 1) and this assessment will be used as an entry criterion. Subjects will also complete the CAT at Randomization (Visit 4) to characterize the population on maximal therapy. Subject eDiary compliance will be reviewed, and the subject will be retrained, if appropriate (See Section 7.1.2).

At Visit 3, reversibility to Atrovent HFA (short-acting muscarinic antagonist) will be evaluated (see Section 7.1.1.1). The spirometry data obtained at this visit will not be used as an entry criterion but will be used to characterize the population. Subject eDiary compliance will be reviewed, and the subject will be retrained, if appropriate.

This study includes 2 sub-studies, a PFT sub-study, and a 24-hour Holter Monitoring sub-study. A subset of sites will be identified and designated for participation in the PFT and 24-Hour Holter monitoring sub-studies. Individual subjects will be allowed to participate in both sub-studies.

A subset of approximately 3,060 subjects (765 subjects per treatment arm) at designated study sites will be invited to participate in the PFT sub-study. In these subjects, serial PFTs will be conducted over 4 hours at selected visits throughout the 52-week Treatment Period (see Section 7.1.1 and Table 8-1 for selected visits and collection times). PFT sub-study subjects will be required to meet FEV_1 baseline stability criteria (the baseline FEV_1 at Visit 4 must be within ±20% or 200 mL of mean of the pre-dose FEV_1 values obtained at the two preceding visits; see Section 7.1.2.2) to be eligible for PFT sub-study participation. Those subjects who do not meet FEV_1 Baseline Stability criteria will not be permitted to participate in the PFT sub-study but will be permitted to participate in the main study providing they satisfy all other eligibility criteria. While the PFT sub-study was previously open to all eosinophil levels, now only subjects who have a blood eosinophil level of ≥ 150 cells per mm^3 at Visit 1 will be permitted to participate in the PFT sub-study.

Subjects who successfully complete the Screening Period will then be randomized in a 1:1:1:1 scheme to BGF MDI 320/14.4/9.6 µg BID, BGF MDI 160/14.4/9.6 µg BID, BFF MDI 320/9.6 µg BID, or GFF MDI 14.4/9.6 µg BID, respectively.

Approximately 2,100 subjects will be randomized to each treatment arm. Randomization will be stratified by exacerbation history (1 or ≥ 2 moderate or severe exacerbations), post-bronchodilator FEV_1 (25% to <50% or 50% to 65% predicted), blood eosinophil count (<150 cells per mm^3 or ≥150 cells per mm^3), and country. Up to a 1:2 ratio for the blood eosinophil strata was targeted with twice as many randomized subjects in the ≥ 150 cells per mm^3 category. [redacted]

Following randomization, subjects will enter the Treatment Period and undergo 5 additional in-clinic treatment visits and 6 telephone call visits over 52 weeks.

At Visit 4 (Randomization Visit; Treatment Day 1), subjects eDiary compliance will be reviewed. Subjects who are unable to meet the compliance requirement (>70% subject completion of eDiary assessments) in the last 7 days preceding the Randomization Visit will be screen failed (refer to Section 7.1.2). All Sponsor-provided medications provided during

the Screening Period will be discontinued and collected by site personnel for accountability. See Section 8 for details of the assessments to be performed at each of these visits.

A subset of approximately 800 subjects (200 subjects from each treatment group) at designated study sites will be invited to participate in the 24-Hour Holter Monitor sub-study. In these subjects, a 24-hour Holter monitor will be collected between Visit 3 and Visit 4 (Holter Monitor Baseline) and Visit 8 (Week 16). Those subjects who do not satisfy the baseline 24-hour Holter Monitor Sub-study eligibility criteria will be screen failed and will not be eligible to re-screen (See Section 7.2.5).

Throughout the course of the study the subjects will be required to complete the following questionnaires; Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) , St. George's Respiratory Questionnaire (SGRQ), EuroQol 5 Dimensions Questionnaire (EQ-5D-5L), Chronic Obstructive Pulmonary Disease Assessment Test (CAT) and Exacerbations of Chronic Pulmonary Disease Tool – Patient Reported Outcomes (EXACT) (see Section 8 for details and timing of the assessments). Site will be requested to complete HCRU questionnaire throughout the study (see Section 8 for details and timing of the assessments).

Subjects who discontinue study treatment prior to Week 52 (Visit 14) will be encouraged to remain in the study to complete all remaining study visits during the 52-week treatment period. Subjects who agree to continue to be followed post treatment discontinuation will sign an ICF addendum. All subjects who agree to continue study participation beyond treatment discontinuation will complete a Treatment Discontinuation Visit (refer to Sections 8.9 and 8.10) prior to transitioning back to regularly scheduled study visits. Subjects participating in the Holter Monitoring sub-study who discontinue from treatment will only complete regularly scheduled visits and not complete any remaining Holter sub-study assessments, however subjects participating in the PFT sub-study will continue with serial PFTs. Treatment discontinuation subjects will return to appropriate maintenance COPD medications, per the investigator's discretion. For subjects recorded as Treatment Discontinuations that do not complete at least one post-treatment data collection a telephone follow-up call is required at least 14 days after last study drug dose and vital status must be captured at 52 weeks post randomization.

If a subject chooses not to continue with study assessments, at a minimum the subject will complete the Treatment Discontinuation/Withdrawal Visit (refer to Table 8). These subjects will return to appropriate maintenance COPD medications, per the investigator's discretion. A follow-up telephone call will be performed at least 14 days after the last study drug dose. In the event the Treatment Discontinuation/Withdrawal Visit is performed >14 days post last study drug dosing; a follow-up phone call will not be required. These subjects will be followed for vital status at 52 weeks post randomization in accordance with the informed consent.

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

General Considerations for Treatment Visits 4 through 14

- Subjects that are randomized will be instructed to discontinue Atrovent HFA and ICS used during the screening period, and only use sponsor-provided inhaled study medications for the remainder of the study.
- At the start of each study visit, prior to any study procedures being performed, site personnel must confirm the subject withheld all COPD medications, including study medication, rescue Ventolin HFA or locally available product (where necessary), for at least 6 hours, by confirming the last time of dosing for all COPD medication(s).
- **Note:** Subjects who inadvertently took COPD medication(s) within 6 hours of the start of study procedures must be rescheduled as soon as is practical but within the specified visit window. In addition, before the in-clinic dose is administered, the site must confirm the subject met all other protocol specified requirements (e.g., FEV_1 baseline stability and eDiary compliance).
- Subjects not participating in the PFT sub-study will be required to return to the clinic approximately the same time as Visit 4 for all treatment visits (± 2 hours) but not to exceed 12:00 PM and will be required to remain at the clinic until completion of all protocol-defined assessments.
- The in-clinic dosing time for study drug (BGF MDI, GFF MDI, and BFF MDI) will be recorded as the time of administration of the second puff.
- All post-randomization visits will be scheduled relative to Visit 4 (Day 1). Thus Visit 5, will be scheduled 4 weeks ±2 days of Visit 4, and Visits 6, 7, 8, 9, 10, 11, 12, 13, and 14 will be scheduled 8, 12, 16, 20, 24, 28, 36, 44 and 52 weeks ±5 days of Visit 4, respectively. Sites should make every effort to maintain subjects within the scheduled visit window. If a visit falls outside the expected visit window the subsequent visit should still be scheduled as planned relative to Visit 4.

4-Hour PFT Sub-study Subjects only

- At the start of each study visit, prior to any study procedures being performed, site personnel must confirm the subject withheld all COPD medications, including study medication, rescue Ventolin HFA or locally available product (where necessary), for at least 6 hours, by confirming the last time of dosing for all COPD medication(s).

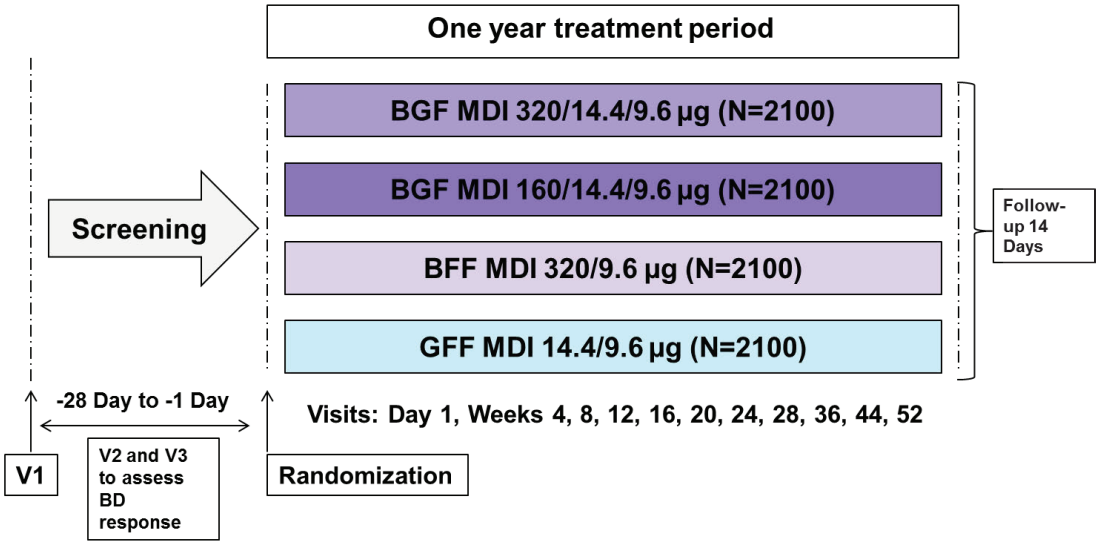
Note: Subjects who inadvertently took COPD medication(s) within 6 hours of the start of study procedures must be delayed (but not to exceed dosing by 10am) or rescheduled within the specified visit window.

- Subjects enrolled in the PFT sub-study must not ingest xanthine and/or xanthine analogue (caffeine)-containing foods, beverages or caffeine containing medications for at least 6 hours prior to each study visit and for the duration of each study visit. Examples of such products include coffee, tea, chocolate, and cola. Decaffeinated beverages are acceptable. Subjects will be required to refrain from smoking (nicotine gums or patches are allowed) for at least 4 hours prior to each study visit and throughout the duration of each study visit.

- In order to minimize diurnal variance, sites should make every effort to assess subjects at the same time throughout the study and to discuss the importance of dosing in a timely manner every 12 hours.
- Subjects participating in the PFT sub-study will be required to return to the clinic at approximately the same time as Visit 4 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 and to withhold all COPD medications (locally available products, if applicable) for at least 6 hours prior to PFTs;
  - To refrain from ingesting xanthine (caffeine)-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit;
  - To refrain from smoking for at least 4 hours prior to the study visit and throughout the duration of each study visit.
- Site personnel will instruct subjects not to take any COPD medications, without site personnel permission, during a visit until all study procedures have been completed, and the subject is discharged. Site personnel should take every precaution to prevent subject use of COPD medications during the test day. Site personnel may request the subject to surrender all COPD medications prior to the start of the visit before performing any study procedures and return the COPD medications to the subject at the end of the visit when all study procedures are completed. Subjects will be asked to abstain wherever possible from using rescue Ventolin HFA during study visits. If a subject is experiencing severe symptoms and requires Ventolin® HFA for relief of COPD symptoms at any time during a test day, site personnel must note the time and justification of use in the subject's chart and all subsequent spirometry assessments should be stopped. However, safety assessments should be continued at the discretion of the Investigator.

The overall study design is summarized and illustrated in Figure 1.

Figure 1. Study Design



Abbreviations: BFF=Budesonide and Formoterol Fumarate; BGF=Budesonide, Glycopyrronium, and Formoterol Fumarate; GFF=Glycopyrronium and Formoterol Fumarate; BD=Bronchodilator, MDI=metered dose inhaler

4.2 Rationale of Study Design

BGF MDI is a novel, fixed-dose triple combination MDI product formulated with budesonide, glycopyrronium, and formoterol fumarate for treatment of subjects with COPD. As described in the GOLD COPD guidelines, in some patients, the addition of a LABA/ICS to a LAMA improves lung function, quality of life, and may further reduce exacerbations. For patients categorized in Group D (those with severe or very severe disease, many symptoms, and high risk of exacerbations), the first choice of treatment is an ICS/LABA or LAMA, with some evidence for a further reduction in exacerbations with triple therapy; however, further studies of triple therapy are needed [GOLD, 2014].

This study is designed to evaluate the treatment effect of BGF MDI (LABA/ICS/LAMA therapy) relative to GFF MDI (LAMA/LABA therapy) and BFF MDI (ICS/LABA therapy) on the rate of moderate or severe COPD exacerbations over a 1-year treatment period in subjects with moderate to very severe COPD, who have a history of COPD exacerbations. To that end, this study will assess the long-term (52 weeks) efficacy and safety of BGF MDI at doses of 320/14.4/9.6 µg and 160/14.4/9.6 µg relative to GFF MDI 14.4/9.6 µg and BFF MDI 320/9.6 µg, all administered BID, on the rate of moderate or severe COPD exacerbations in subjects with a history of previous COPD exacerbations.

Consistent with this objective, this study will evaluate a patient population that remains symptomatic despite treatment with 2 or more inhaled maintenance medications. Subjects with a post-bronchodilator FEV_1 <50% of predicted normal must have a documented history of ≥ 1 moderate or severe COPD exacerbation in the previous 12 months. Subjects with a post-bronchodilator FEV_1 ≥ 50% of predicted normal must have a documented history of ≥ 2 moderate exacerbations or a documented history of ≥1 severe COPD exacerbation in the 12 months prior to Screening (Visit 1).

A randomized, double-blind, parallel group design was adopted in order to minimize bias in treatment allocation and to allow unbiased comparisons of treatment groups.

4.3 Rationale of Dose/Regimen and Duration of Treatment

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

The doses of the glycopyrronium and formoterol fumarate components of BGF MDI and BFF MDI match the doses utilized in the GFF MDI development program. [redacted]

[redacted]

Note: The End of Study is defined as the date on which data are collected for the last subject's Follow-up Telephone Call.

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

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

1. Give their signed written informed consent to participate.
2. Are at least 40 years of age and no older than 80 years at Visit 1.
3. A female is eligible to enter and participate in the study if she is of:
   a. Non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal)
   b. Childbearing potential has a negative serum pregnancy test at Visit 1, and agrees to one of the following acceptable contraceptive methods used consistently and correctly as outlined below (i.e., in accordance with the approved product label and the instructions of the physician for the duration of the study – from Visit 1 (Screening) until 14 days after the Final Visit):
      - Complete abstinence from intercourse (when it is preferred and usual lifestyle of the patient); or
      - Implants of levonorgestrel inserted for at least 1 month prior to the study drug administration but not beyond the third successive year following insertion; or

- Injectable progestogen administered for at least 1 month prior to study drug administration; or
- Oral contraceptive (combined or progestogen only) administered for at least one monthly cycle prior to study drug administration; or
- Double barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository); or
- An intrauterine device, inserted by a qualified physician, with published data showing that the highest expected failure rate is less than 1% per year; or
- Estrogenic vaginal ring; or
- Percutaneous contraceptive patches.
- **Note:** The acceptable contraceptive methods listed above are subject to locally approved contraceptive methods.

4. COPD Diagnosis: Subjects with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) [Celli, 2004] or by locally applicable guidelines, e.g., JRS Guidelines [JRS, 2013] characterized by:
   - Progressive airflow limitation associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.
5. Tobacco Use: Current or former smokers with a history of at least 10 pack-years of cigarette smoking. [Number of pack-years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years represent 10 pack-years)].
6. COPD Severity: Subjects with an established clinical history of COPD and severity defined as:
   - At Visit 1, FEV_1/FVC ratio must be <0.70 and FEV_1 must be <65% predicted normal value calculated using NHANES III reference equations (*Or reference norms applicable to other regions, e.g., for Japan, use JRS reference equations; [JRS, 2013])*.
   - At Visit 2, post-bronchodilator FEV_1/FVC ratio of <0.70 and post-bronchodilator FEV_1 must be ≥25% to <65% predicted normal value, calculated using NHANES III reference equations *(Or reference norms applicable to other regions, e.g., for Japan, use JRS reference equations [JRS, 2013])*
   - At Visit 4, the average of the -60 min and -30 min pre-dose FEV_1 assessments must be <65% predicted normal value, calculated using NHANES III reference equations *(Or reference norms applicable to other regions, e.g., for Japan, use JRS reference equations [JRS, 2013])*. Note: This criterion applies to subjects in the PFT sub-study only

     Symptomatic (CAT ≥10) at Screening (Visit 1).
7. Required COPD Maintenance Therapy:
   - All Subjects must have been on two or more inhaled maintenance therapies for the management of their COPD for at least 6 weeks prior to Screening. Scheduled SABA and/or scheduled SAMA are considered inhaled maintenance therapies.

8. History of Exacerbations:
   - Subjects with a post-bronchodilator FEV_1 <50% of predicted normal must have a documented history of ≥ 1 moderate or severe COPD exacerbation in the 12 months prior to Screening (Visit 1).
   - Subjects with a post-bronchodilator FEV_1 ≥ 50% of predicted normal must have a documented history of ≥ 2 moderate exacerbations or a documented history of ≥1 severe COPD exacerbation in the 12 months prior to Screening (Visit 1).

   Note:

   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 symptoms of COPD (e.g. increased dyspnea, increased sputum volume, or a change in sputum purulence (color)). Subject verbal reports are not acceptable.

   - Antibiotics or corticosteroids used for the treatment of URI with no lower respiratory symptoms do not qualify for the treatment of COPD exacerbation.
9. Subject is willing and, in the opinion of the investigator, able to adjust current COPD therapy, as required by the protocol.
10. Screening clinical laboratory 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 within 6 months prior to Visit 1 must be acceptable to the Investigator. Subjects who have a chest x-ray that reveals clinically significant abnormalities not believed to be due to the presence of COPD should not be included. A chest x-ray must be conducted if the most recent chest x-ray or CT scan are more than 6 months old at the time of Visit 1 except in countries with restrictive radiology assessment practice where only subjects who have had a chest x-ray or CT scan (thorax) performed outside of the study in the last 6 months are allowed to be enrolled. Alternatively, in these countries, an MRI may be used instead of a CT scan or chest x-ray as per local practice assessment.
13. Compliance: Subjects must be willing to remain at the study center as required per protocol to complete all visit assessments.

5.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

1. Significant diseases or conditions other than COPD, which, in the opinion of the Investigator, may put the subject at risk because of participation in the study or may influence either the results of the study or the subject's ability to participate in the study.
2. Women who are pregnant or lactating or are planning to become pregnant during the course of the study, or women of childbearing potential who are not using an acceptable method of contraception.
3. Respiratory:
   a. Asthma: Subjects, who in the opinion of the Investigator, have a current diagnosis of asthma.

b. Alpha-1 Antitrypsin Deficiency: Subjects who have alpha-1 antitrypsin deficiency as the cause of COPD.

c. Other Respiratory Disorders: Subjects who have other active pulmonary disease such as active tuberculosis, lung cancer, significant bronchiectasis (high resolution CT evidence of bronchiectasis that causes repeated acute exacerbations), sarcoidosis, idiopathic interstitial pulmonary fibrosis, primary pulmonary hypertension, or uncontrolled sleep apnea (i.e., in the opinion of the Investigator severity of the disorder would impact the conduct of the study). Note: Allergic rhinitis is not exclusionary.

d. Lung Volume Reduction: Subjects who have undergone lung volume reduction surgery, lobectomy or bronchoscopic lung volume reduction (endobronchial blockers, airway bypass, endobronchial valves, thermal vapor ablation, biological sealants, and airway implants) within 6 months of Visit 1.

e. Hospitalization: Subjects who have been hospitalized due to poorly controlled COPD within 6 weeks prior to Visit 1 (Screening) with less than a 4-week washout of corticosteroids and/or antibiotics prior to Visit 1 (Screening).

f. Poorly Controlled COPD: Subjects who have poorly controlled COPD, defined as acute worsening of COPD that requires treatment with oral corticosteroids or antibiotics within 6 weeks prior to Visit 1 (Screening) with less than a 4-week washout of corticosteroids and/or antibiotics prior to Visit 1 (Screening).

g. Lower Respiratory Tract Infection: Subjects who had lower respiratory tract infections that required antibiotics within 6 weeks prior to Visit 1 (Screening) with less than a 4-week washout of antibiotics prior to Visit 1 (Screening).

h. Other Respiratory tract infections (e.g., upper respiratory tract infection) that have not resolved at least 7 days prior to Screening.

i. Chest x-ray (frontal and lateral) with suspicion of pneumonia or other condition/abnormality that will require additional investigation/treatment or put the subject at risk because of participation in the study.

j. Risk factors for pneumonia: immune suppression (HIV) severe neurological disorders affecting control of the upper airway or other risk factors that in the opinion of the Investigator would put the subject at substantial risk of pneumonia.

k. Pneumonia not clinically resolved within 14 days of Visit 1.

l. Spirometry Performance:

- Acceptability: Subjects who cannot perform acceptable spirometry (i.e., meet ATS/ERS acceptability criteria)
- Repeatability: Subjects who cannot perform technically acceptable spirometry with at least 3 acceptable flow-volume curves with 2 or more meeting ATS repeatability criteria for FEV_1 during at least 1 of the pre-bronchodilator assessments at Visit 2 (-60 minute or -30 minute) and at the post-bronchodilator assessment at Visit 2.

  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 for inclusion in

the main study, but they are excluded from participating in the PFT sub-study. Subjects who fail to meet acceptability and repeatability criteria at Visit 2 must be screen failed.

- FEV_1 Baseline Stability (for PFT sub-study only): Subjects who cannot meet protocol-specified baseline stability criteria. FEV_1 baseline stability is defined as the average of the -60 minute and -30-minute pre-dose FEV_1 assessments at Visit 4 being within ±20% or 200 mL of the mean of the pre-bronchodilator FEV_1 assessments obtained at the 2 preceding visits (average of pre-dose FEV_1 assessments obtained at Visit 2 and Visit 3).

m. Oxygen: Subjects receiving long-term-oxygen therapy (LTOT) or nocturnal oxygen therapy required for greater than 15 hours a day. Note: As needed oxygen use is not exclusionary.

n. Subject use of any non-invasive positive pressure ventilation device. Note: Subjects using continuous positive airway pressure or bi-level positive airway pressure for Sleep Apnea Syndrome are allowed in the study if not used for ventilatory support.

o. Change in smoking status (i.e., start or stop smoking) or initiation of a smoking cessation program within 6 weeks of Visit 1 and throughout the Screening Period (Visit 1 to Visit 4).

p. Pulmonary Rehabilitation: Subjects who have participated in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1 (Screening) or who are scheduled to enter the 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. Subjects who are in the maintenance phase of a pulmonary rehabilitation program are not to be excluded.

q. Subjects who have initiated or altered the dose regimen of intranasal corticosteroids, intranasal antihistamines, or a combination thereof within 7 days prior to Visit 1 or during the Screening Period (Visit 1 to Visit 4).

4. Cardiac disease:

a. Subjects who have unstable ischemic heart disease, left ventricular failure, or documented myocardial infarction within 6 months of enrollment. Subjects with a recent history of acute coronary syndrome, or who have undergone percutaneous coronary intervention or coronary artery bypass graft within the past 3 months are to be excluded.

b. Subjects with congestive heart failure (CHF NYHA Class III/IV).

c. Clinically significant abnormal ECG: A clinically significant abnormal ECG is defined as (but not limited to) any of the following:

- Clinically significant conduction abnormalities [e.g., left bundle branch block, Wolff-Parkinson-White syndrome or evidence of second degree (Mobitz Type II) or third-degree atrioventricular block (unless pacemaker or defibrillator has been inserted)].

- Clinically significant arrhythmias (e.g., atrial fibrillation with irregular ventricular response, atrial flutter, ventricular tachycardia). Note: atrial fibrillation that has been clinically stable for at least 6 months and that has been

appropriately treated with anticoagulation and controlled with a rate control strategy (i.e., selective beta blocker, calcium channel blocker, digoxin or ablation therapy) for at least 6 months is allowed for inclusion. In such subjects, if atrial fibrillation is present at Visit 1, resting ventricular rate must be <100 beats per minute (bpm).

- QT interval corrected for heart rate (using Fridericia's formula; QTcF) ≥500 milliseconds (msec) in subjects with QRS <120 msec and QTcF ≥530 msec in subjects with QRS ≥120 msec
- Ventricular rate <45 bpm.
- ST-T wave abnormalities deemed to be clinically significant by the Investigator. Note: Subjects with non-specific ST-T wave abnormalities that are not deemed clinically significant (per Investigator) are allowed.
- Any other ECG abnormalities not listed above that in the opinion of the Investigator are clinically significant.

d. Clinically Uncontrolled Hypertension: Subjects who have clinically significant uncontrolled hypertension.

5. Neurological:
   a. Subjects with seizures requiring anticonvulsants within 12 months prior to Visit 1 (Screening). Note: Subjects treated with anticonvulsant medication for 12 months or more with no seizure events are eligible.
   b. Subjects taking selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) whose dose has not been stable for at least four weeks prior to Visit 1 or is altered at any point during the Screening Period (Visit 1 to Visit 4) or exceeds the maximum recommended dose.
   c. Subjects who have experienced a cerebrovascular accident within 6 months prior to Visit 1.
6. Renal:
   a. Subjects with symptomatic prostatic hypertrophy that is clinically significant and not adequately controlled with appropriate therapy in the opinion of the Investigator. Subjects with a trans-urethral resection of prostate or full resection of the prostate within 6 months prior to Visit 1 are excluded from the study.
   b. Subjects with bladder neck obstruction or urinary retention that is clinically significant in the opinion of the Investigator.
   c. Subjects with a calculated creatinine clearance ≤30 mL/minute using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [Levey, 2009] at Visit 1 and on repeat testing prior to Visit 2.

      Note: Subjects with overactive bladder syndrome treated with oral anticholinergics who have been on treatment for at least 1 month are allowed in the study.

7. Endocrine:
   a. Subjects, who in the opinion of the Investigator, have uncontrolled hypo- or hyperthyroidism, hypokalemia, or hyperadrenergic state.
   b. Subjects, who in the opinion of the Investigator, have uncontrolled Type I or II diabetes.
8. Liver: Subjects with abnormal liver function tests defined as AST, ALT, or total bilirubin ≥1.5 times upper limit of normal at Visit 1 and on repeat testing prior to Visit 2.

   Note: Chronic stable hepatitis B and C is acceptable if the subject otherwise meets study entry criteria.
9. Cancer: Subjects who have cancer that has not been in complete remission for at least five years. Note: Subjects with squamous cell carcinoma of the skin, basal cell carcinoma of the skin, or localized prostate cancer are eligible, if in the opinion of the Investigator, the condition has been adequately worked up, is clinically controlled and the subject's participation in the study would not represent a safety concern.
10. Glaucoma: Subjects with a diagnosis of narrow angle glaucoma, which, in the opinion of the Investigator, have not been adequately treated. All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective beta-blockers (such as betaxolol, carteolol, levobunolol, metipranolol, and timolol), and prostaglandin analogues.
11. Drug Allergy: Subjects who have a history of hypersensitivity to β_2-agonists, budesonide or any other corticosteroid components, glycopyrronium or other muscarinic anticholinergics, or any component of the MDI or dry powder inhaler (DPI).
12. Substance Abuse: Subjects, who in the opinion of the Investigator, significantly abuse alcohol or drugs.
13. Medication prior to spirometry: Subjects who are medically unable to withhold their short-acting bronchodilators for the 6-hour period required prior to spirometry testing at each study visit will be ineligible to participate in the PFT sub-study.
14. Prohibited Medications: Subjects who, in the opinion of the Investigator, would be unable to abstain from protocol-defined prohibited medications during the screening period and treatment phases of this study (refer to Section 5.4).
15. Subjects using any herbal inhalation and nebulizer products within 2 weeks prior to Visit 1 (Screening) and do not agree to stop using them during the study drug treatment.

    Note: Nebulized products (e.g. albuterol/salbutamol, ipratropium) are acceptable, but requires a minimum of a 6-hour washout prior to Visit 1 and must be discontinued at Visit 1 and throughout the study.
16. Vaccinations Subjects who received a live attenuated vaccination within 7 days prior to Visit 1 (Screening).
17. Non-compliance: Subjects unable to comply with study procedures including non-compliance with diary completion (i.e., <70% subject completion of diary assessments in the last 7 days preceding Visit 4).
18. Affiliations with Investigator site: Study Investigators, sub-Investigators, study coordinators, employees of a participating Investigator or immediate family members of the aforementioned are excluded from participation in this study.

19. Questionable Validity of Consent: Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol), or other conditions that will limit the validity of informed consent to participate in the study.
20. Subjects using prohibited medications (refer to Table 5-1).
21. Investigational Drugs or Devices: Treatment with investigational study drug or device in another clinical study within the last 30 days or five half-lives prior to Visit 1 (Screening), whichever is longer.

    Note: Subject participation in observational studies (i.e., studies that do not require change to medication or an additional intervention) is not exclusionary.
22. Hand-to-Breath Coordination: Subjects who require the use of a spacer device to compensate for poor hand-to-breath coordination with a MDI. Note: Use of a nebulizer to deliver maintenance COPD medications is prohibited throughout the study.
23. Previous Participation: Subjects who were previously enrolled in any PT009 or PT010 study conducted or sponsored by Pearl Therapeutics, Inc.

5.2.1 24-Hour Holter Monitoring Sub-study Exclusion Criteria

Subjects with a pacemaker or implantable cardioverter-defibrillator (ICD)/cardiac resynchronization therapy (CRT)/cardiac resynchronization therapy-defibrillator (CRT_D) devices will not be allowed into the Holter monitor sub-study.

Clinically significant abnormal findings during the baseline Holter monitor recording defined as (but not limited to) any of the following:

1. Average HR ≤40 bpm for any 1 hour.
2. Second-degree AV block (Type 2) or third-degree AV block.
3. Sinus pause of:
   - 2.5 seconds duration during daytime
   - 3.0 seconds duration during nighttime
4. Any episode of ventricular flutter and/or ventricular fibrillation.
5. Any episode of non-sustained ventricular tachycardia (NSVT) with symptoms of hypotension or syncope or asymptomatic non-sustained VT >15 ventricular premature beats (VPB's) in a row.
6. Sustained ventricular tachycardia (SVT) (>30 seconds in duration)
7. Five or more episodes of NSVT/ 24 hours
8. Greater than 500 VPB/hr

5.3 Subject Identification

All subjects who undergo screening procedures will be assigned a unique screening identification number at Screening (Visit 1). Only subjects continuing to meet entry

inclusion/exclusion criteria at Visit 4 will be assigned a unique subject randomization number. Randomization will be centralized through the use of an IWRS.

5.4 Prior, Concomitant, and Prohibited Medications

All prescription and over-the-counter (OTC) medications taken by the subject during 30 days before Visit 1 (Screening) will be recorded on the prior/concomitant medications electronic Case Report Form (eCRF). Any additions, deletions, or changes in the dose of these medications while in the study should be entered on the eCRF. Any current ongoing medications, including OTC drugs and herbal supplements, will be allowed provided they are not prohibited by the protocol (see Section 5.4.3) and are approved by the Investigator. Subjects should also be instructed to contact the Investigator if they develop any illnesses.

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

5.4.1 Allowed Medications to Treat a COPD Exacerbation

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

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

5.4.2 Pneumococcal and Annual Influenza Vaccination

All subjects should be vaccinated with pneumococcal vaccine per local guidelines policies, availability, and affordability as described in current global recommendations (GOLD, 2016). For subjects that have been previously vaccinated with pneumococcal vaccine, the investigator should assess whether a booster vaccination is required. Annual influenza vaccine should also be administered per local guidelines. Pneumococcal and/or annual influenza vaccine can be given at Visit 1 or at any other visit throughout the study at the discretion of the investigator; however, administration should occur after obtaining all

requisite PFT assessments for that specific test day. There should be at least 7 days between vaccination and subsequent PFT assessments.

5.4.3 Prohibited COPD Medications and Required Washout Prior to Visit 2

Subjects that meet the screening criteria at Visit 1 that are being treated with any of the medications listed in Table 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 the study, and should a subject require use of any of the listed medications, they should be discontinued.

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

Class of Medication	Minimum Washout Period Prior to Visit 2
LAMAs	Tiotropium: 14 days Aclidinium: 7 days Glycopyrronium: 7 days Umeclidinium: 7 days
Short-acting muscarinic antagonists (SAMA)[a]	6 hours
LABAs (inhaled)	7 days (14 days for indacaterol and olodaterol)
Fixed-combinations of LABA/LAMA	7 days (14 days for indacaterol/glycopyrronium and olodaterol/tiotropium)
Fixed-combinations of LABA/ICS	7 days
Fixed-combinations of SABAs and SAMAs	6 hours
SABAs[b]	6 hours
Oral β-agonists	2 days
Theophylline (total daily dose >400 mg/day)[c]	7 days

Abbreviations: COPD=chronic obstructive pulmonary disease; HFA=hydrofluoroalkane; ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist; LAMA=long-acting muscarinic antagonist; SABA=short-acting β_2-agonist

[a] Discontinue and use only sponsor-provided Atrovent HFA during screening

[b] Discontinue and use only sponsor-provided rescue Ventolin HFA throughout the study

[c] Theophylline (≤400 mg/day) is permitted provided the subject has been on a stable dose of therapy for at least 4 weeks prior to Randomization.

Note: Roflumilast (or any PDE4 inhibitor) is allowed provided the subject has been on a stable dose of therapy for at least 2 months prior to Randomization.

Subjects who have received depot corticosteroids including intra-articular or intraocular corticosteroids require a 6 weeks washout prior to Screening (Visit 1). Subjects that have received oral, intravenous or intramuscular corticosteroids for any reason require a minimum of a 4-week washout prior to Screening (Visit 1).

Note:

- Subjects who are steroid dependent and maintained on an equivalent of up to 5 mg prednisone per day or up to 10 mg every other day for at least 3 months prior to Visit 1 are eligible for enrollment, provided the dose of oral steroids remains consistent and does not exceed this threshold for the last two weeks prior to randomization (Visit 4).
- During the Treatment Period (Visit 4 to Visit 14), subjects may be treated with systemic corticosteroids if required.

Subjects who meet all entry criteria but are using 1 or more of the prohibited COPD medications (previously listed) will have their maintenance therapy for COPD adjusted as follows:

- Subjects taking COPD medications (listed previously) at Visit 1 (Screening) will discontinue these medications for the duration of the Study and be switched to Sponsor-provided Atrovent HFA administered 4 times daily (QID) and Sponsor-provided Ventolin HFA to be administered up to 4 times per day, as needed, for control of symptoms during the Screening Period.
- Subjects receiving a maintenance dose of an ICS as part of a fixed-dose combination therapy containing fluticasone and salmeterol, mometasone and formoterol, budesonide and formoterol or fluticasone and formoterol or other approved fixed dose ICS/LABA combinations must have been on the ICS component for at least 4 weeks prior to Visit 1 (Screening) and maintained on a stable dose for at least 4 weeks prior to Visit 1 (Screening). These subjects will be switched to the corresponding dose of fluticasone, mometasone, or budesonide administered as a single agent BID, with Sponsor-provided Atrovent HFA administered QID, and Sponsor-provided Ventolin HFA to be administered up to QID, as needed, to control symptoms during the Screening Period.
- Subjects receiving a maintenance dose of an ICS that is not administered as a fixed-dose combination together with a LABA will continue the ICS provided they have been maintained on a stable dose for at least 4 weeks prior to Visit 1 (Screening).
- All subjects treated with either a LABA (salmeterol, formoterol, indacaterol, vilanterol, olodaterol), or currently-marketed LAMA (tiotropium, aclidinium, glycopyrronium, umeclidinium) administered alone, as a loose combination, or as a fixed combination (e.g., umeclidinium/vilanterol, glycopyrronium/indacaterol, aclidinium bromide/formoterol fumarate) will have these medications discontinued and replaced with Sponsor-provided Atrovent HFA administered QID, and Sponsor-provided Ventolin HFA to be administered up to QID, as needed for control of symptoms during the Screening Period.

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

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

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

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

Class of Medication	Minimum Washout Period Prior to Visit 2
Leukotriene antagonists (eg, zafirlukast, montelukast, and zilueton)	7 days
Cromoglycate	7 days
Nedocromil	7 days
Ketotifen [a]	7 days

[a] Ketotifen eye drops and inhalation solution (where available) are allowed.

5.4.4 Other Prohibited Medications

Table 3 lists certain non-COPD medications that can be used under the stated conditions during this study. Each concomitant drug must be individually assessed against all exclusion criteria.

Table 3. Non-COPD Medications Allowed Under Certain Conditions

Medications Allowed Under Certain Conditions	Condition
SSRIs or SNRIs	Treatment regimen has been stable for at least 4 weeks prior to Visit 1 and not altered during the Screening Period, and does not exceed the maximum recommended dose
Intranasal corticosteroids, intranasal antihistamines, or combination thereof	Administered at constant dose and dosing regimen for at least 7 days prior to Screening (Visit 1) and during the Screening Period

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

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

Subjects requiring medications presented in Table 4 are prohibited from participating in this study. Subjects who recently discontinued use of these medications may be considered for study enrollment provided they have met the minimum Washout Period prior to Visit 1 (Screening). These medications are prohibited throughout the course of the study, and, should a subject require use of any of the listed medications, the subject should be

discontinued from randomized treatment but encouraged to continue in the study and complete all remaining study visits.

Table 4. Prohibited Medications

Prohibited Medications	Minimum Cessation Period Prior to Screening (Visit 1)
Any drug with potential to significantly prolong the QT interval[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)	7 days
Cardiac antiarrhythmics Class Ia, III	7 days (amiodarone 3 months)
Anticonvulsants for seizure disorder	Allowed if stable dose for 12 months and free of seizures for 1 year
Anticonvulsants for other indications	Allowed if stable dose for at least 3 months and free of seizures for 1 year
Tricyclic antidepressants[b]	14 days
Monoamine oxidase inhibitors	14 days
Anti-tumor necrosis factor α antibodies (eg, infliximab and any other members of this class of drugs)	30 days or 5 half-lives, whichever is longer
Monoclonal antibodies	30 days or 5 half-lives, whichever is longer
Antipsychotic drugs [b]	30 days
Systemic calcineurin inhibitors, protease inhibitors	30 days
Systemic anticholinergics [c]	7 days
Chinese complementary and alternative bronchodilatory medicines (CAM), ie, herbal therapies (eg, *Astragalus membranaceus [*huáng qí*], Panax ginseng [ginseng products]* and *Cordyceps sinensis. A. membranaceus [ghost moth caterpillar fungus])*[d]	10 days

Note: Benzodiazepines are not exclusionary.

[a] Subjects who are on medications that have the potential to prolong the QTc interval may be enrolled provided the dose has remained stable for at least 3 months prior to Screening, 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. Note: Short courses (≤ 4 weeks) of antibiotics with the potential to prolong the QT interval (e.g. azithromycin, clarithromycin) are permitted.

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

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

Table 4. Prohibited Medications

Prohibited Medications	Minimum Cessation Period Prior to Screening (Visit 1)

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

5.5 Other Restrictions, Illicit Drugs, or Drugs of Abuse

5.5.1 Illicit Drugs

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

5.5.2 Dietary Restrictions

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

5.6 Smoking Status

Changes in a subject's smoking status (i.e., stopping or restarting smoking) may have an impact on the efficacy outcome measures. At Visits 1, 2, 3, 4, 5, 7, 10, 12, and 14, the subject will be asked about any recent change in their smoking status (i.e., whether a subject's status has changed from smoker to nonsmoker or vice versa). Any change in smoking status during the Screening Period (Visit 1 to Visit 4) will result in a screen failure. Smoking status changes during the 52-week Treatment Period will be captured in the eCRF, but the subject will be permitted to continue in the study. Subjects enrolled in the PFT sub-study will be required to refrain from smoking (including medical marijuana and electronic cigarettes) for at least 4 hours prior to each study visit and throughout the duration of each study visit. Study participants may utilize various nicotine replacement treatments such as chewing gum and patches as needed, in accordance with recommendations from the Investigator during the entire study visit.

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

5.7 Reasons for Treatment Discontinuation or Study Withdrawal

Subjects may be withdrawn from the study at any time at their own request, upon request of the Investigator, or by Pearl at any time or for any reason. A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). For all subjects who withdraw from the study for any reason they, their family or healthcare

providers, will be contacted 52 weeks post randomization to determine vital status, and if appropriate, cause of death (Section 8.13). The subject may voluntarily discontinue treatment at any time without prejudice to further treatment.

If a subject experiences any of the changes of concern listed below, a repeat assessment should be obtained, and if confirmed, the subject should be discontinued from randomized treatment but encouraged to continue in the study and complete all remaining study visits (See Section 8.9). The changes of concern include:

- Calculated QTcF intervals >500 msec and have increased by 60 msec or more over test day baseline value.

  Note: *Applicable to EU-specific regions only* - Calculated QTcF intervals ≥500 msec OR ≥ 60 msec over test day baseline.

- Hepatic impairment defined as abnormal liver function test of AST, ALT or total bilirubin ≥3 times upper limit of normal on repeat testing.
- Subjects participating in the 24-hour Holter Monitoring sub-study who experience any clinically significant abnormal findings during the Holter Monitoring recording as described in Section 5.2.1

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

- Following dosing, a heart rate increase of >40 bpm from the pre-dose value obtained on that specific test day and the measured value is also >120 bpm.

  Note: *Applicable to EU-specific regions only* - Following dosing, a heart rate increase of > 25 bpm from the pre-dose value obtained on that specific test day, without any threshold.

- Following dosing, a systolic blood pressure increase of >40 mmHg from the pre-dose value obtained on that specific test day and the measured value is also >160 mmHg.

  Note: *Applicable to EU-specific regions only* - Following dosing, a systolic BP (SBP) increase of > 30 mmHg from the pre-dose value obtained on that specific test day, without any threshold, or a clinically relevant change from baseline as determined by the Investigator.

- Decrease in creatinine clearance to a value ≤30 mL/minute using CKD-EPI formula or a clinically relevant change from baseline as determined by the Investigator.

  Note: *Applicable to EU-specific regions only* - A decrease of 33% in calculated creatinine clearance from baseline using CKD-EPI without any threshold.

If a subject requires any of the following prohibited medications (other than study-provided medication or COPD medications used during the treatment of a severe COPD exacerbation as described in Section 5.4.1), they should be discontinued from randomized treatment but encouraged to continue in the study and complete all remaining study visits (See Section 8.9):

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

NOTE: Subjects who suffer an exacerbation (regardless of severity) will remain in the study and continue to take their assigned study drug unless the Investigator decides that it is in the best interest of the subject to discontinue randomized treatment and/or withdraw from the study (See Section 8.9).

If a female subject becomes pregnant during the course of the study, the subject will be withdrawn from the study and the pregnancy will be followed through delivery or final outcome (see Section 7.3.12).

Subjects who prematurely discontinue treatment from the study drug should return to the study center and complete procedures described in Section 8.9. The reason for premature discontinuation of study drug should be documented in the source documentation and recorded in the eCRF.

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

6.1 Subject Information

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

6.2 Product Descriptions

Investigational materials will be provided by Pearl as summarized in Table 5 Atrovent HFA and Ventolin HFA will be supplied as open-label MDIs.

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

Table 5. Product Descriptions

Product Name & Dose	Product Strength	Dosage Form/ Fill Count	Administration
Study Drug			
BGF MDI 320/14.4/9.6 µg ex-actuator	160/7.2/4.8 µg per actuation	MDI 120 inhalations	Taken as 2 inhalations BID
BGF MDI 160/14.4/9.6 µg ex-actuator	80/7.2/4.8 µg per actuation	MDI 120 inhalations	Taken as 2 inhalations BID
GFF MDI 14.4/9.6 µg ex-actuator	7.2/4.8 µg per actuation	MDI 120 inhalations	Taken as 2 inhalations BID
BFF MDI 320/9.6 µg ex-actuator	160/4.8 µg per actuation	MDI 120 inhalations	Taken as 2 inhalations BID
Open-Label Products			
Ipratropium bromide HFA inhalation aerosol 34 µg ex-actuator[a]	Atrovent (ipratropium bromide) HFA will be the US-supplied product. Each inhalation contains 17 µg ex-actuator per actuation.	MDI 200 actuations	Taken as 2 inhalations QID during Screening; Supplies are open-label
Albuterol sulfate HFA inhalation aerosol 90 µg ex-actuator[b]	Ventolin (albuterol sulfate) HFA inhalation aerosol will be the US-supplied product. Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation.	MDI 60 or 200 actuations	Taken as directed; Supplies are open-label

Abbreviations: BFF=Budesonide and Formoterol Fumarate; BGF=Budesonide, Glycopyrronium, and Formoterol Fumarate; BID=twice daily; ex-actuator=dose delivered from the actuator (ie, mouthpiece) of the MDI; GFF=Glycopyrronium and Formoterol Fumarate; HFA=hydrofluoroalkane; MDI=metered dose inhaler; QID=four times daily; US=United States

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

[b] Reversibility testing at Visit 2 and rescue medication during the study. Albuterol sulfate is also known as salbutamol sulfate in some countries.

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

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

Open-label Atrovent HFA MDIs will be provided from commercial supplies. Manufacturer's instructions for study drug administration are provided in Appendix 5.

Open-label Ventolin HFA with dose counters will be provided from commercial supplies. Manufacturer's instructions for study drug administration are provided in Appendix 6

6.3 Primary Packaging and Labeling Information

Investigational materials will be packaged by the Sponsor. Atrovent HFA, and Ventolin HFA will be supplied as open-label MDIs.

Blinded Supplies: Each MDI will be labeled with a single label. The MDI actuator will be labeled with a single label. The foil pouch will be labeled with a single label.

Open-label Supplies: Open-label Atrovent HFA and Ventolin HFA will be provided as individually-labeled MDIs. Each MDI will contain a single label. The MDI actuator will be

labeled with a single label. Labels will be printed with black ink and may include the following text: Labels will be printed with black ink and may include the following text:

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

ID = identification; # = number

6.4 Secondary Packaging and Labeling Information (Box)

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

Table 6. Description of Boxes

Drug Supplies	Individual Box Contents
Blinded	1 MDI
Atrovent(ipratropium bromide) HFA[a]	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 #	Dosing Instructions (if applicable)
Space for entry of screening #	Storage Conditions
Component ID #	Compound ID - Protocol #
Space for entry of randomization #	Country regulatory requirements
Kit Contents (1 MDI)	Sponsor address (if applicable)
Space for entry of Interval ID	Translation Key (if applicable)
Re-evaluation/Expiration date (if applicable)	

6.5 Emergency Unblinding of Treatment Assignment

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

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

Whenever possible, the Investigator must first discuss options with the Medical Monitor or appropriate study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the Investigator must notify Pearl as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

6.6 Storage Requirements

Blinded supplies: BGF MDI, BFF MDI, and GFF 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 per Package Insert. Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use. Do not use or store near heat or open flame. Exposure to temperatures above 120°F (49°C) may cause bursting. Never throw into a fire or incinerator.

Atrovent® HFA supplies: Store per Package Insert. For optimal results, the canister should be at room temperature before use. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F (49°C) may cause bursting. Never throw the inhaler into a fire or incinerator.

The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in accordance with the product label. Documentation of temperature monitoring should be maintained.

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

6.7.1 BGF MDI, GFF MDI, and BFF MDI

Individual BGF MDI, GFF MDI, and BFF 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. Open label MDIs and DPIs will be packaged in a visit treatment box. The visit treatment box will have a label with a component ID number. Confirm that the identifier given by IWRS and the component ID

number written on the label are the same. The visit treatment box is labeled with a 2-part label. Write the subject number and treatment visit number on each of the 2-part labels. The 'tear-off' part of the label is to be placed onto the IWRS confirmation report.

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

The MDI must be primed in a separate room from the subject treatment area. Each dose will consist of 2 puffs from the MDI. Subjects will be dispensed the MDI and instructed to continue taking study drug BID, two puffs in the morning and two puffs in the evening approximately 12 hours apart, until subject returns to the clinic. Refer to Appendix 4 for instructions on the administration and cleaning of BGF MDI, GFF MDI, and BFF MDI.

6.7.2 Atrovent® HFA (Ipratropium Bromide)

Refer to Appendix 5 for instructions on the administration of Atrovent® HFA.

6.7.3 Ventolin HFA® (Albuterol Sulfate)

Refer to Appendix 6 for instructions on the administration of Ventolin® HFA (Albuterol Sulfate).

6.8 Drug Accountability/Return of Clinical Supplies

Under no circumstances will the Investigator(s) allow the study drug to be used other than as directed by this protocol.

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secure location to which only the Investigator and designated study personnel have access. Storage conditions for the clinical supplies should be observed, monitored, and documented. Clinical supplies are to be dispensed only in accordance with the protocol. The Investigator or designee is responsible for keeping accurate records of the clinical supplies received from Pearl, the amount dispensed to and returned by the subject, and the amount remaining at the conclusion of the study. Study 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 Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned as directed by Pearl.

Sites should check with the 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 Clinical Monitor.

For each subject, all used study drug materials will be collected. Used subject supplies will be kept at room temperature in a secure and locked cabinet until returned to Pearl or designee.

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

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

7 STUDY PROCEDURES

A schedule of events is provided in Table 8. Other detailed schedules are provided for timed assessments for all post-randomization in-clinic visits for subjects participating in the PFT sub-study (Visits 4, 5, 7, 10, 12, and 14; Day 1, Weeks 4, 12, 24, 36, and 52) Table 8-1; timed assessments for all post-randomization in-clinic visits for subjects NOT participating in the PFT sub-study (Visits 4, 5, 7, 10, 12, and 14; Day 1, Weeks 4, 12, 24, 36, and 52) Table 8-2; assessments to be collected at telephone visits (Visits 6, 8, 9, 11, and 13; Weeks 8, 16, 20, 28, and 44) Table 8-3; timed assessment at Visit 3 (Screening Period) and Visit 8 (Week 16) for 24-hour Holter Monitoring Sub-study, Table 8-4.

7.1 Efficacy Assessments

7.1.1 Pulmonary Function Tests

Forced expiratory spirometry maneuvers for derivation of FEV_1, FVC, and PEFR will be assessed using a spirometer that meets or exceeds minimum performance recommendations of the ATS (see Appendix 2).

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

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

To standardize spirometry, all sites will be provided with identical spirometry systems (KoKo Spirometer, nSpire Health, Inc., Longmont, CO, US) with customized, study-specific software. Every effort will be made to provide all sites with standardized spirometry equipment. 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 characterization purposes. These patients will not be eligible for participation in the PFT sub-study. Local equipment needs to be reviewed by the study monitor and must meet or exceed minimum performance recommendations of the ATS (see Appendix 2). The volume accuracy of the spirometer is to be checked daily with appropriate documentation in a calibration log prior to the conduct of PFT's on each test day.

All study staff responsible for performing pulmonary function testing will receive standardized training at the Investigator Meetings. All technicians are required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable PFTs (ATS criteria), prior to performing testing 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 efforts will be stored electronically. After completion of testing, the

study staff will electronically transmit the spirometric measurements for centralized quality assurance review [redacted] Feedback on the quality of the measurements will be provided to the investigational site and to Pearl or designee for central data management.

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

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

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

For Subjects participating in the 4-Hour PFT sub-study, additional spirometry assessments will be conducted at Visits 4, 5, 7, 10, 12, and 14 (Day 1 and Weeks 4, 12, 24, 36, and 52). At these visits, spirometry will be conducted at 60 minutes and 30 minutes prior to study drug administration and at 15 and 30 minutes, and 1, 2, and 4 hours after study drug administration. An additional spirometry assessment will be conducted at 5 minutes after study drug administration at Visit 4 (Day 1) only. The mean of the -60 minute and -30 minute pre-dose spirometry assessments conducted at Visit 4 will be used to establish baseline $FEV_{1,}$ FVC, PEFR, and FEF_{25-75}.

Note: While the PFT sub-study was previously open to all eosinophil levels, subjects must now have a blood eosinophil count of ≥ 150 cells per mm^3 at Visit 1 to participate in the PFT sub-study.

Subjects not participating in the 4-Hour PFT sub-study will be required to return to the clinic approximately the same time as Visit 4 for all treatment visits (± 2 hours) but not to exceed 12:00 PM and will be required to remain at the clinic until completion of all protocol-defined assessments.

7.1.1.1 Characterization of Reversibility

Reversibility to Ventolin HFA (SABA) will be evaluated at Visit 2 and to Atrovent HFA (SAMA) will be evaluated at Visit 3. The procedures will be as follows:

- Reversibility testing to Ventolin HFA (Visit 2 only):
  - Perform pre-bronchodilator PFTs (-60 minute and -30 minute) prior to administration of Ventolin HFA.
  - Administer 4 puffs of Ventolin HFA.
  - Perform post-bronchodilator PFTs 30 minutes after the administration of Ventolin HFA.
- Reversibility testing to Atrovent HFA (Visit 3 Only):
  - Perform pre-bronchodilator PFTs (-60 minute and -30 minute) prior to administration of Atrovent HFA.

- Administer 4 puffs of Atrovent HFA.
- Perform post-bronchodilator PFTs 30 minutes after the administration of Atrovent HFA.

Reversibility will be a comparison of the average best FEV_1 effort obtained at -60 minute and -30 minute pre-bronchodilator to the best FEV_1 effort obtained at 30 minutes post-bronchodilator following administration of Ventolin HFA or Atrovent HFA. A subject is determined to be responsive to Ventolin HFA if the improvement in FEV_1 approximately 30 minutes following administration of 4 puffs of Ventolin HFA is ≥12% and ≥200 mL. Reversibility to Atrovent HFA is used for characterization purposes only.

7.1.1.2 FEV_1 Baseline Stability Criteria

For Subjects participating in the 4-Hour PFT sub-study, all FEV_1 comparisons will be made to the baseline (mean of 60 and 30 minutes prior to dosing) values obtained at Visit 4, thus 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. The baseline FEV_1 at Visit 4 must be within ±20% or 200 mL of the mean of the pre-dose FEV_1 obtained at the two preceding visits (average of pre-dose FEV_1 obtained at Visit 2 and Visit 3).

Subjects who are unable to meet FEV_1 Baseline Stability, will not be included in the PFT sub-study, but will be allowed to be randomized and continue into the study.

At Visit 4 (Randomization), if the pre-dose FEV_1 average is outside of the ±20% or 200 mL range, but the -30 minute assessment is within ±22% or 220 mL, then another assessment may be conducted 30 minutes later. If the last two assessments meet the FEV_1 baseline stability criteria (i.e., within ±20% or 200 mL), the initial 60-minute pre-dose assessment will not be used and the last two assessments will be used to establish the eligibility criteria. If the test day FEV_1 is not within ± 20% or 200 mL, the subject will no longer be eligible to participate in the PFT sub-study but may be randomized into the main study providing all other eligibility criteria are met.

Note: For Subjects not participating in the 4-Hour PFT sub-study, spirometry will only be conducted during screening and therefore, the FEV_1 baseline stability criteria requirement does not apply

7.1.2 Subject Electronic Diary Data Collection

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

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

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

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

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

7.1.2.1 Rescue Medication Use

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

7.1.2.2 Medication Compliance

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

7.1.2.3 Major/minor Symptom Worsening Assessment and Alert System

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

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

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

7.1.3 COPD Exacerbation

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

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

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

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

7.1.3.1 Severity of COPD Exacerbation

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

Exacerbations will be considered moderate if they result in:

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

Exacerbations will be considered severe if they result in:

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

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

7.1.3.2 Duration of COPD Exacerbation

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

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

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

7.1.3.3 Approach for Capturing COPD Exacerbations

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

7.1.3.4 Other Information

An electronic diary (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 hospitalization).

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

7.1.3.5 Investigator-Judged COPD Exacerbations

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

7.1.4 Subject Questionnaires

The following subject questionnaires will be completed by subjects using the study-supplied electronic questionnaire devices at specified visits throughout the study: CAT, SGRQ, BDI/TDI, EQ-5D-5L. The EXACT questionnaire will be captured via the subject eDiary (see Section 7.1.2). 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 then the EQ-5D-5L.

7.1.4.1 Chronic Obstructive Pulmonary Disease Assessment Test (CAT)

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

Subjects will complete the CAT (see Appendix 7 at Screening (Visit 1) and this assessment will be used as an entry criterion. Subjects will also complete the CAT at Randomization (Visit 4) to characterize the population on maximal therapy. The CAT score will describe the burden and symptomatic impact of COPD in subjects enrolled in the study and will be used to determine subject eligibility to participate in the study.

7.1.4.2 Baseline and Transition Dyspnea Indices

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

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

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

7.1.4.3 St. George's Respiratory Questionnaire

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

The SGRQ contains 50 items divided into 3 domains: "Symptoms" concerned with respiratory symptoms, their frequency and severity; "Activity" concerned with activities that cause or are limited by breathlessness; and "Impacts" which covers a range of aspects concerned with social functioning and psychological disturbances resulting from airway

disease. A "Total" score combining each domain will be calculated. In each case the lowest possible value is zero and the highest is 100. Higher values correspond to greater impairment of quality of life. Completed questionnaires will be reviewed and examined by the Investigator or designee, before the clinical examination, for responses which may indicate potential AEs or SAEs. The Investigator should review not only the responses to the questions in the questionnaire but also for any unsolicited comments written by the subject. Investigators should not encourage the subjects to change the responses reported in the questionnaire.

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

7.1.4.4 European Quality-of-Life-5 Dimensions Questionnaire

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

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

The EQ-5D-5L (see Appendix 10) will be completed by the subject prior to study drug administration at Visit 4 (Day 1, Randomization) and at each post-randomization visit including the Treatment Discontinuation/Withdrawal Visit. The EQ-5D-5L will be captured on the Sponsor-provided tablet, and not in the eDiary.

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). The instrument was developed for daily, at home, administration using a handheld electronic device. Respondents are instructed to complete the diary each evening just prior to bedtime and to answer the questions while considering their experiences "today". The instrument includes assessments of breathlessness (5 items), cough and sputum (2 items), chest symptoms (3 items), and 4 additional items (difficulty with sputum, tired or weak, sleep disturbance, and psychological state).

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

and recovery, the EXACT can provide information on event frequency and duration as well as event severity.

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

The EXACT (see Appendix 11) will be completed daily by the subject as part of the eDiary assessments.

7.2 Safety Assessments

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

7.2.1 Medical/Surgical History and Physical Examination

Medical history, including specific cardiovascular history details, will be collected at Screening (Visit 1) and updated during the Screening Period (Visit 1 to Visit 4). The number of COPD exacerbations requiring oral steroids and/or oral antibiotics, or hospitalization within 12 months of Screening (Visit 1) will be collected. A complete physical examination will be performed at Visit 1 (Screening) and at Visit 14 (Final Visit) or the Treatment Discontinuation/Withdrawal Visit. A complete physical examination will include evaluation of the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. Weight, assessed in ordinary indoor clothing with shoes removed, will be recorded at Visit 1 (Screening) and Visit 14 (Final Visit) only. Height will be recorded at Visit 1 (Screening) only.

7.2.2 Vital Sign Measurements

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

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

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

At Visit 4 (Randomization) only, pre-dose vital signs will be obtained twice at least 5 minutes apart within 1 hour prior to dosing. Post-dose vital signs will be obtained at 30 minutes. **For 4- Hour PFT sub-study subjects only** vital signs will be obtained at 2 hours post study drug dosing.

- At post-randomization Visits 5, 7, 10, 12, and 14 (Weeks 4, 12, 24, 36, and 52):
  - Pre-dose vital signs will be obtained once within 1 hour prior to dosing
  - Post-dose vital signs will be obtained at 30 minutes.
  - **For PFT sub-study subjects only** vital signs will be obtained at 2 hours post study drug dosing

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

7.2.3 12-Lead Electrocardiogram

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

Timed ECGs will be obtained as follows:

- At Visit 4 (Randomization Visit) only, Pre-dose ECGs will be obtained twice at least 5 minutes apart within 1 hour prior to dosing.
- At post randomization in-clinic visits [Visits 5, 10, and 14 (Weeks 4, 24, and 52)]:
  - Pre-dose ECGs will be obtained once within 1 hour prior to dosing
- **For 4-Hour PFT sub-study subjects only**, post-dose ECGs will be obtained at 30 minutes and 2 hours post-dosing at [Visit 4 (Randomization), and Visits 5, 10, and 14 (Weeks 4, 24, and 52)].

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

The ECG parameters that will be assessed include 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 test day baseline value, the Investigator will make a determination on the suitability of continuing the subject in the study. If QTcF interval prolongation exceeding these limits is verified during treatment, the subject's medical history should be examined closely for risk factors that may have contributed to the event, including evidence of prior genotyping for hereditary long QT syndromes, if appropriate.

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

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

7.2.4 Clinical Laboratory Tests

Clinical safety laboratory tests will be analyzed by a central laboratory according to standardized, validated assays (see Section 10.4). The laboratory will supply detailed instructions and all containers for blood and urine investigations. Blood sample volumes will meet the laboratory's specification. The central laboratory will supply procedures for the preparation and collection of these samples.

All clinical laboratory tests (hematology, clinical chemistry, and urinalysis) will be obtained at Visit 1 (Screening) and prior to dosing at Visit 4 (Day 1), Visit 5 (Week 4), Visit 10 (Week 24), and Visit 14 (Week 52) and the Treatment Discontinuation/Withdrawal Visit.

For subjects participating in the PFT sub-study, a Basic Metabolic Panel (BMP) will be obtained at 2 hours post-dosing at Visit 4 (Day 1), Visit 5 (Week 4), Visit 10 (Week 24), and Visit 14 (Week 52) or the Treatment Discontinuation/Withdrawal Visit.

7.2.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, eosinophils and platelet count will be measured at Visit 1 (Screening) and prior to dosing at Visit 4 (Day 1), Visit 5 (Week 4), Visit 10 (Week 24), and Visit 14 (Week 52) and the Treatment Discontinuation/Withdrawal Visit.

7.2.4.2 Clinical Chemistry

Albumin, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, total cholesterol, magnesium, phosphate, sodium, potassium, chloride, creatinine, gamma-glutamyl transferase, blood glucose, total protein, triglycerides, bicarbonate, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) will be measured at Visit 1 (Screening) and prior to dosing at Visit 4 (Day 1), Visit 5 (Week 4), Visit 10 (Week 24), and Visit 14 (Week 52) and the Treatment Discontinuation/Withdrawal Visit.

For subject participating in the PFT sub-study, a Basic Metabolic Panel (BMP) will be obtained at 2 hours post-dosing at Visit 4 (Day 1), Visit 5 (Week 4), Visit 10 (Week 24), and Visit 14 (Week 52) or the Treatment Discontinuation/Withdrawal Visit.

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

Table 7. Clinical Laboratory Tests

Hematology	
Hemoglobin	Mean corpuscular hemoglobin
Hematocrit	Mean corpuscular hemoglobin concentration
White blood cell count with differential	Mean corpuscular volume
Red blood cell count	Eosinophils
Platelet count	
Clinical Blood Chemistry	
Liver Enzyme and Other Liver Function Tests	**Other Clinical Blood Chemistry**
Alanine aminotransferase	Albumin
Aspartate aminotransferase	Blood Urea Nitrogen (BUN)
Alkaline phosphatase	Calcium[a]
Bilirubin, total	Chloride[a]
Gamma-glutamyl transferase	Cholesterol
	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 (Screening) and Visit 14 or Treatment Discontinuation	
Creatinine clearance will be estimated by the CKD-EPI formula [Levey, 2009].	

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

[a] Parameters included in the Basic Metabolic Panel.

7.2.4.3 Urinalysis

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

7.2.4.4 Pregnancy Test

A serum pregnancy test will be performed at the central laboratory in pre-menopausal women who are not surgically sterile at Visit 1 (Screening) and Visit 14 (Week 52) or the Treatment Discontinuation/Withdrawal Visit. A urine hCG pregnancy test will be performed on-site at in-clinic visits (Visits 4, 5, 7, 10, and 12 [Day 1, Weeks 4, 12, 24, and 36]) (Table 8).

7.2.5 Holter Monitoring 24-Hour Continuous Electrocardiography

The following information applies only to subjects participating in the 24-Hour Holter Monitoring Sub-study.

The designated service provider for Holter monitoring will be iCardiac Technologies, Inc, 150 Allens Creek Road, Rochester, NY 14618. All Holter monitor recordings will be assessed for cardiac arrhythmias by an independent cardiologist appointed by iCardiac.

Continuous 12-lead ECGs (Holter monitor assessment) will be obtained at Visit 3 (baseline) and Visit 8 (Week 16). The Visit 3 and Visit 8 Holter monitor recordings are to be initiated in the morning at approximately the same time (+/- 2 hours).

Continuous Holter monitor recording will be collected for a minimum of 24 hours. Holter monitor recordings should contain a minimum of 18 hours of acceptable quality recording in a 24-hour period to be deemed an acceptable Holter monitor assessment.

The Visit 3 (Screening) Holter monitoring will be initiated subsequent to the post-dose spirometry assessments. The Holter recording obtained at Visit 3 will be used to determine the subject's eligibility for participation in the 24-Hour Holter Monitor sub-study and will serve as the baseline for all comparisons. If the initial Holter monitor assessment at Visit 3 is unacceptable, the Holter monitor will be reconnected for another 24 hours using a new Holter monitor hook-up kit. The subject will be instructed to continue his/her medications as per study protocol. The subject will return the following day for removal of the Holter monitor.

If the Holter monitoring quality remains unacceptable on the second attempt, no further attempts will be made and the subject will be permitted to enroll in the study but will be excluded from the Holter monitor sub-study. If clinically significant findings are noted on any of the Holter monitor recordings as defined in Section 5.2.1, the subject will be considered a screen failure and will not be eligible to enroll in the study.

At Visit 8 (Week 16) Holter monitoring will be initiated 15-30 minutes prior to the administration of the morning dose of study medication. Subjects will take their morning

dose of study medication at the clinic. Subjects will be instructed to return to the clinic the following day for removal of the Holter monitor.

When the subject returns to the clinic the following day, the quality of the Holter monitor recordings will be assessed at the site. If the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours) on the first attempt, a second attempt will be made for another 24 hours using a new Holter monitor hook-up kit. The subject will be instructed to continue his/her medications as per study protocol. The subject will return the following day for removal of the second Holter Monitor. No further attempts are allowed if the second attempt is unacceptable.

Following Holter monitoring at Visit 8 (Week 16), subjects continue on treatment provided no clinically significant findings (as defined in Section 5.2.1) are reported by iCardiac following review of the Holter monitor recordings.

Data for analysis will include:

- General trends including heart rate
- Hourly rhythm comments
- Ventricular ectopy summary
- Ventricular run summary
- Supraventricular ectopy summary
- Supraventricular run summary
- Any other clinically relevant arrhythmias, including atrial fibrillation and pronounced bradycardia.

Manual summary interpretation of the data is sent as a report to the site and to Pearl Therapeutics.

7.3 Adverse Events

7.3.1 Performing Adverse Event 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 must report the AE immediately to Pearl. In addition, certain AEs (as described in Section 7.3.10) are classified as "serious" and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as an SAE to Pearl or its designee.

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

7.3.2 Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the US Code of Federal Regulations (21 CFR 312.32) and EU Directive 2001/83/EC and are included herein.

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Adverse events include, but are not limited to:

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

An AE does **not** include:

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

7.3.3 Pre-Randomization Adverse Events

Adverse events that occur between the time subject signs the informed consent form for the study and the time when that subject is randomized will be summarized as medical history and not as an adverse event 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

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

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

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

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

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

7.3.6 Chronic Obstructive Pulmonary Disease Exacerbations

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

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

7.3.7 Adverse Events of Special Interest

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

7.3.7.1 LABA and LAMA Effects

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

7.3.7.2 Local Steroid Effects

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

7.3.7.3 Pneumonia

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

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

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

- Elevated white blood cell counts
- Hypoxemia

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

Radiographs will be evaluated locally and the results (infiltrate compatible with pneumonia) will be documented within the source document 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) up to 10 to 14 days after the date of pneumonia diagnosis.

7.3.7.4 Paradoxical Bronchospasm

Monitoring for paradoxical bronchospasm will occur at each in-clinic visit during the Treatment Period (Visits 4 through 14) at 15 and 30 minutes post-dose. In this study, paradoxical bronchospasm is defined as a reduction in FEV_1 of >20% from baseline (i.e., the mean FEV_1 values obtained 60 and 30 minutes prior to study drug administration) that occurs within 30 minutes post-dosing with associated symptoms of wheezing, shortness of breath, or cough.

7.3.8 Major Adverse Cardiovascular Events

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

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

The Clinical Endpoint Adjudication Charters will be established to govern these processes as described in Section 7.3.16.

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 (eg, an abnormality that results in study drug dose reduction, suspension, or treatment discontinuation)
- A laboratory abnormality that results in any therapeutic intervention (ie, 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

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

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

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

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

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

An adverse reaction 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 he/she receives that information. This follow-up information will be a detailed written report that may include copies of hospital records, case reports, autopsy reports, and other pertinent documents.

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

The Investigator is responsible for continuing to report any new or relevant follow-up information that he/she 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 Medical Monitor or designee any need for supplemental investigations of SAEs. The results of these additional assessments conducted must be reported to Pearl. If a subject dies during participation in the study and a post-mortem examination is performed, a copy of the autopsy report must be submitted to Pearl.

7.3.10.3 Post-Study Follow Up of Adverse Events

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

7.3.10.4 Notification of Post-Study Serious Adverse Events

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

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

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

7.3.10.6 Health Authority Safety Reports

Pearl or its representatives will submit a safety report to the appropriate regulatory agencies for any suspected adverse reaction that is both serious and unexpected within the appropriate time frame.

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

7.3.11 Overdose

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

7.3.12 Pregnancy

To ensure subject safety, each pregnancy in a female subject from Visit 1 (Screening) until study completion must be reported to Pearl within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be recorded on a Paper Pregnancy Report Form and reported by the Investigator to Pearl Pharmacovigilance or designee. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Pearl study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.3.13 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 13 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, intramuscular, or intravenous corticosteroids for the management of COPD exacerbations or other conditions is not a reason for early treatment discontinuation or study withdrawal. Use of corticosteroids, however, should be documented. 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 other indications will follow their visit schedule. If a subject requires intraocular corticosteroids, this use should be fully documented and the Investigator should make a determination as to the suitability of the subject continuing on randomized treatment.

7.3.16 Clinical Endpoint Committee

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

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

Further details are provided in the Adjudication Committee Charters.

7.3.16.1 Cardiovascular and Cerebrovascular Clinical Endpoint Adjudication Charter

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

7.3.16.2 Cause-Specific Mortality Clinical Endpoint Adjudication Charter

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

7.3.16.3 Pneumonia Clinical Endpoint Adjudication Charter

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

7.3.17 Data Monitoring Committee

An external Data Monitoring Committee (DMC) will be set up to provide systematic and unbiased assessment of safety for Study PT010005. Members of the DMC will review data at predetermined intervals. If significant safety issues arise in between scheduled meetings, ad hoc meetings will be scheduled to review the data. Based on the safety implications of the data, the DMC may recommend modification or termination of the study.

7.4 Health Care Resource Utilization

The number of days missed from work, days that primary caregivers of subjects missed work as a result of the subjects COPD, telephone calls to health care providers, visits to health care providers, Emergency Room (ER) visits, days in the hospital, days in Intensive Care Units (ICU), days in Coronary Care Units (CCU), , use of ambulance transport, will be captured at Visit 5 (Week 4), Visit 6 (Week 8), Visit 7 (Week 12), Visit 8 (Week 16), Visit 9 (Week 20), Visit 10 (Week 24), Visit 11 (Week 28), Visit 12 (Week 36), Visit 13 (Week 44), Visit 14 (Week 52), and telephone follow up call or Treatment Discontinuation/Withdrawal Visit.

7.5 Termination of the Study

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

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

8 STUDY ACTIVITIES

A time and events schedule is provided in Table 8. Other detailed schedules are provided for timed assessments for all post-randomization in-clinic visits for subjects participating in the PFT sub-study (Visits 4, 5, 7, 10, 12, and 14; Day 1, Weeks 4, 12, 24, 36, and 52) Table 8-1; timed assessments for all post-randomization in-clinic visits for subjects NOT participating in the PFT sub-study (Visits 4, 5, 7, 10, 12, and 14; Day 1, Weeks 4, 12, 24, 36, and 52) Table 8-2; assessments to be collected at telephone visits (Visits 6, 8, 9, 11, and 13; Weeks 8, 16, 20, 28, and 44) Table 8-3; timed assessment at Visit 3 (Screening Period) and Visit 8 (Week 16) for 24-hour Holter Monitoring Sub-study, Table 8-4.

Table 8. Schedule of Events

Procedures	Screening			52-Week Treatment Period											Follow-up TC
	Visit 1	Visit 2	Visit 3	Visit 4 (Rand)	Visit 5 Week 4	Visit 6 Week 8	Visit 7 Week 12	Visit 8 Week 16	Visit 9 Week 20	Visit 10 Week 24	Visit 11 Week 28	Visit 12 Week 36	Visit 13 Week 44	Visit 14 Week 52	
Study Day[a]	Day -28 to -12	Day -16 to -2	Day -15 to -1	Day 1	Day 29±2	Day 57±5	Day 85±5	Day 113±5	Day 141±5	Day 169±5	Day 197±5	Day 253±5	Day 309±5	Day 366±5	Day 380
IN-CLINIC	X	X	X	X	X		X			X		X		X	
TELEPHONE CONTACT						X		X	X		X		X		X
Informed Consent	X														
Eligibility Criteria	X	X	X	X											
Verify Continued Eligibility					X		X			X		X		X	
Reversibility Testing[b]		X	X												
Demographics and Medical/Surgical History	X														
Smoking Status	X	X	X	X	X		X			X		X		X	
Chest Imaging	X[q]														
CAT[c]	X			X											
Prior/Concomitant Medications[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[p]	X
Spirometry (All subjects)[e]	X	X	X												
Spirometry (PFT Sub-study)[e]				X	X		X			X		X		X	
Physical Examination[f]	X													X[p]	
Vital Signs	X	X	X	X	X		X			X		X		X[p]	
12-Lead ECG[g]	X			X	X					X				X[p]	
Pregnancy Test[h]	X			X	X		X			X		X		X[p]	
Clinical Laboratory Testing[i]	X			X	X					X				X[p]	
Adjust COPD Medications[j]	X													X[p]	
Adverse Events/COPD Exacerbations.	X	X	X	X	X	X	X	X	X	X	X	X	X	X[p]	X

Procedures	Screening			52-Week Treatment Period											Follow-up TC
	Visit 1	Visit 2	Visit 3	Visit 4 (Rand)	Visit 5 Week 4	Visit 6 Week 8	Visit 7 Week 12	Visit 8 Week 16	Visit 9 Week 20	Visit 10 Week 24	Visit 11 Week 28	Visit 12 Week 36	Visit 13 Week 44	Visit 14 Week 52	
Study Day[a]	Day -28 to -12	Day -16 to -2	Day -15 to -1	Day 1	Day 29±2	Day 57±5	Day 85±5	Day 113±5	Day 141±5	Day 169±5	Day 197±5	Day 253±5	Day 309±5	Day 366±5	Day 380
IN-CLINIC	X	X	X	X	X		X			X		X		X	
TELEPHONE CONTACT						X		X	X		X		X		X
Inhalation Device and Dose Indicator Training	X	X	X	X											
Study Drug Dispensing[j]	X[J]			X	X		X			X		X		X	
24-hour Holter Monitoring[k]			X					X							
Study Drug Collection				X	X		X			X		X		X[p]	
Study Drug Administration[l]				X	X		X			X		X		X	
BDI/TDI[m]				X	X		X			X		X		X[p]	
SGRQ[m]				X	X		X			X		X		X[p]	
EQ-5D-5L[m]				X	X		X			X		X		X[p]	
HCRU					X	X	X	X	X	X	X	X	X	X[p]	X
eDiary Dispensing/Collection	X													X[p]	
eDiary Training[n]	X														
eDiary Review[o]		X	X	X	X		X			X		X		X	
Vital Status Check														X	

Abbreviations: BDI/TDI=Baseline Dyspnea Index/Transition Dyspnea Index; CAT=COPD Assessment Test; COPD=chronic obstructive pulmonary disease; eDiary=electronic diary; ECG=electrocardiogram; EQ-5D=EuroQol 5 Dimensions Questionnaire; Exac.=exacerbations; EXACT =Exacerbations of Chronic Pulmonary Disease Tool; hCG=human chorionic gonadotropin; HCRU=health care resource utilization; MDI=metered dose inhaler; PFT=pulmonary function test; Rand=randomization; SGRQ=St. George's Respiratory Questionnaire; TC=Telephone Call

[a] Scheduling Visits: The minimum Screening Period is between 1 to 4 weeks in duration (can be extended to a maximum of 10 weeks in case of an exacerbation during the Screening Period). Sites 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 (Visit 2) and ipratropium bromide (Visit 3).

[c] Subjects will complete the CAT at Screening (Visit 1) as an entry criterion. Subjects will also complete the CAT at Randomization (Visit 4) to characterize the population on maximal therapy.

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

[e] Refer to Section 7.1.1 for spirometry assessments and specific time points required for Screening, and for the PFT sub-study. Table 8-1 also provides the timed assessments for the PFT sub-study. While the PFT sub-study was previously open to all eosinophil levels, subjects must now have a blood eosinophil count of ≥ 150 cells per mm^3 at Visit 1 to participate in the PFT sub-study. 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 for inclusion in the main study but they are excluded from participating in the PFT sub-study. Subjects who fail to meet acceptability and repeatability criteria at Visit 2 must be screen failed.

[f] Physical examination includes evaluation of weight at Visit 1 (Screening) and Visit 14 (Final Visit) and height at Visit 1 (Screening) only.

[g] Refer to Section 7.2.3 for ECG assessments and specific time points.

[h] Females of childbearing potential: A serum pregnancy test will be performed at the central laboratory in pre-menopausal women who are not surgically sterile at Visit 1 (Screening) and Visit 14 (Week 52) or at the Treatment Discontinuation/Withdrawal Visit. A urine hCG pregnancy test will be performed on-site at in-clinic visits (Visits 4, 5, 7, 10, and 12 [Day 1, Weeks 4, 12, 24, and 36]) If any of these tests are positive, the subject must be discontinued from the study.

[i] Refer to Section 7.2.4 for clinical laboratory assessments and specific time points.

[j] At Visit 1 (Screening), stop prohibited COPD medications and change COPD medications as specified in Section 5.4.3 (i.e., ipratropium bromide for use between Visits 1 to 4, and albuterol for rescue use throughout the study). Sponsor-provided run-in medication will be dispensed only after a subject is determined to be eligible to proceed to Visit 2 (i.e., only if a subject meets COPD definition following spirometry assessments at Screening) and will be collected prior to Randomization at Visit 4. At the end of Visit 14, return subject to pre-study or other appropriate inhaled maintenance COPD medications.

[k] Refer to Section 7.2.5 for further information on 24-Hour Holter Monitoring. Table 8-4 also provides the timed assessments for the 24-Hour Holter Monitoring sub-study. Visit 8 (Week 16) is an in-clinic visit for subjects participating in the 24-Hour Holter Monitoring Sub-study

[l] In-clinic dosing time is recorded as time of the 2nd puff/inhalation. The in-clinic dosing time should occur within 12±2 hours of the prior evening dosing time.

[m] When BDI/TDI, SGRQ, and/or EQ-5D-5L are obtained at the same visit, BDI/TDI will be collected first followed immediately by SGRQ, then EQ-5D-5L. These questionnaires must be completed by the subject prior to any other visit procedures.

[n] Subjects will be issued and trained on eDiary use only after they are determined to qualify to proceed to Visit 2.

[o] 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 subject diary review. Refer to Section 7.1.2 for details on subject diary review.

[p] These are the minimum procedures that should be completed at a Treatment Discontinuation/Withdrawal Visit, refer to Section 8.9.

[q] Obtain a new chest x-ray if image was not obtained within the 6 months prior to Visit 1 (Screening). In countries with restrictive radiology assessment practices, 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.

Table 8-1. Timed Assessments for all Post-randomization In-clinic Visits for Subjects Participating in the PFT Sub-study (Visits 4, 5, 7, 10, 12, and 14; Day 1, Weeks 4, 12, 24, 36, and 52)

Clinical Variable	Pre-dose		Post-dose					
	-1 hour	-30 minutes	5 minutes	15 minutes	30 minutes	1 hour	2 hours	4 hours
Review of Electronic Diary[a]	X							
Vital Signs[b,c]	X				X		X	
Spirometry (FEV_1, FVC, PEFR, FEF_{25-75})[f]	X	X	X[f]	X	X	X	X	X
Study Drug Collection/Dispensing[g,h]	X[†]							
TDI[i]	X[†]							
SGRQ[i]	X[†]							
EQ-5D-5L[i]	X[†]							
Assessments to be performed at Visits 4, 5, 10, and 14 (Day 1, Weeks 4, 24, and 52)								
12-Lead ECG[b,d]	X				X		X	
Clinical Laboratory Testing[b,e]	X[†]						X	

Abbreviations: BDI/TDI=Baseline Dyspnea Index/Transition Dyspnea Index; COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5 Dimensions Questionnaire; EXACT =Exacerbations of Chronic Pulmonary Disease Tool; FEF_{25-75}=forced expiratory flow between 25% to 75% of FVC; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; hCG=human chorionic gonadotropin; PEFR=peak expiratory flow rate; PFT=pulmonary function test; SGRQ=St. George's Respiratory Questionnaire

Note: While the PFT sub-study was previously open to all eosinophil levels, subjects must now have a blood eosinophil count of ≥ 150 cells per mm^3 at Visit 1 to participate in the PFT sub-study.

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

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

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 Safety assessments (vital signs, clinical laboratory assessments, ECGs) should be started approximately 5 to 10 minutes ahead of the specified time point to ensure that spirometry for FEV_1, FVC, PEFR, and FEF_{25-75} determination will be conducted as close to the specified time points as possible (i.e., FEV_1, FVC, PEFR, and FEF_{25-75} assessments need to be conducted within ±15 minutes of specified time prior to study drug administration; ±5 minutes of specified time for the first 60 minutes after study drug administration; and ±15 minutes of specified time point for assessments obtained thereafter).

[c] At Visit 4 only, pre-dose vital signs (heart rate, blood pressure) will be collected twice, at least 5 minutes apart. 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.

[d] At Visit 4 only, pre-dose ECG will be collected at least twice, 5 minutes apart. Refer to Section 7.2.3 for ECG assessments and specific time points

[e] All clinical laboratory tests (hematology, chemistry, and urinalysis) will be assessed within 60 minutes prior to dosing at these visits. The 2-hour post-dose collection will be a basic metabolic panel only. Females of childbearing potential: Serum pregnancy test will be performed at Visit 1 (Screening) and Visit 14 (Final Visit) or at the Treatment Discontinuation/Withdrawal Visit; urine hCG screening will be performed at in-clinic visits (Visits 4, 5, 7, 10, and 12 [Day 1, Weeks 4, 12, 24, and 36]). Refer to Section 7.2.4 for clinical laboratory assessments and specific time points.

[f] Spirometry assessments will be obtained in those subjects participating in the PFT sub-study. Post-dose spirometry will be collected at 5 minutes on Visit 4 (Day 1) only. Refer to Section 7.1.1 for spirometry assessments and specific time points.

[g] 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.

[h] Dispense study drug to subject for at-home use following the completion of all post-dose assessments. See Section 6.7 for Instructions for Preparation of Treatments for Administration and Dispensing. Study drug will not be dispensed at Visit 14 (Week 52).

[i] When BDI/TDI, SGRQ, and/or EQ-5D-5L are obtained at the same visit, BDI/TDI will be collected first followed immediately by SGRQ, then EQ-5D-5L. These questionnaires must be completed by the subject prior to any other visit procedures. BDI/TDI will be obtained at all in clinic post randomization visits. SGRQ will be obtained at Visits 4, 5, 7, 10, 12 and 14 (Day 1 and Weeks 4, 12, 24, 36 and 52). EQ5D-5L will be obtained at Visits 4, 5, 7, 10, 12 and 14 (Day 1 and Weeks 4, 12, 24, 36 and 52). Refer to Section 7.1.4 for subject questionnaires and time points.

Table 8-2. Timed Assessments for all Post-randomization In-clinic Visits for Subjects not Participating in the PFT Sub-study (Visits 4, 5, 7, 10, 12, and 14; Day 1, Weeks 4, 12, 24, 36, and 52)

Clinical Variable	Pre-dose	Post-dose
	-1 hour	30 minutes
Review of Electronic Diary[a]	X	
Vital Signs[b]	X	X
12-Lead ECG[c]	X	
Clinical Laboratory Testing[d]	X†	
Study Drug Collection[e]	X†	
Study Drug Dispensing[f]		
BDI/TDI[g]	X†	
SGRQ[g]	X†	
EQ-5D-5L[g]	X†	

Abbreviations: BDI/TDI=Baseline Dyspnea Index/Transition Dyspnea Index; COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5 Dimensions Questionnaire; EXACT =Exacerbations of Chronic Pulmonary Disease Tool; hCG=human chorionic gonadotropin; 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 4, 5, 10, and 14 only (Day 1, and Weeks 4, 24, and 52; see Table 8. Refer to Section 7.2.3 for ECG assessments and specific time points

[d] Clinical laboratory tests will be performed at Visits 4, 5, 10, and 14 only (Day 1, and Weeks 4, 24, and 52); see Table 8. 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 (Visits 4, 5, 7, 10, and 12,[Day 1, Weeks 4, 12, 24, and 36]). 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

[f] Dispense study drug to subject for at-home use following the completion of all post-dose assessments. See Section 6.7 for Instructions for Preparation of Treatments for Administration and Dispensing.

[g] When BDI/TDI, SGRQ, and/or EQ-5D-5L are obtained at the same visit, BDI/TDI will be collected first followed immediately by SGRQ, then EQ-5D-5L. These questionnaires must be completed by the subject prior to any other visit procedures. BDI/TDI will be obtained at all in clinic post randomization visits. SGRQ will be obtained at Visits 4, 5, 7, 10, 12 and 14 (Day 1 and Weeks 4, 12, 24, 36 and 52). EQ5D-5L will be obtained at Visits 4, 5, 7, 10, 12 and 14 (Day 1 and Weeks 4, 12, 24, 36 and 52). Refer to Section 7.1.4 for subject questionnaires and time points.

Table 8-3. Assessments to be collected at Post-randomization Telephone Visits (Visits 6, 8, 9, 11, and 13; Weeks 8, 16, 20, 28, and 44)

Clinical Variable	
Review of Electronic Diary	X
AEs/Exacerbations	X
Concomitant Medications	X
HCRU	X
Abbreviations: AEs = Adverse Events; HCRU = Health Care Resource Utilization	

Table 8-4. Schedule of Events at Visit 3 (Screening Period) and Visit 8 (Week 16) for 24-Hour Holter Monitoring Sub-study

	Screening Period			Treatment Period		
Procedures	**Visit 3**	**Visit 3b**	**Visit 3c**	**Visit 8**	**Visit 8b**	**Visit 8c**
24-Hour Holter Monitoring (1st Attempt)	X[a]			X[b]		
Removal of 24-Hour Holter Monitor (1st Attempt)[c]		X			X	
24-Hour Holter Monitoring (2nd Attempt)[d]		X[d]			X[d]	
Removal of 24-Hour Holter Monitor (2nd Attempt)[e]			X[e]			X[e]

a. Attach Holter monitoring device and initiate 24-hour Holter Monitor recording following the post-dose spirometry assessments.

b. Attach Holter monitoring device and initiate 24-hour Holter Monitor recording following the pre-dose spirometry assessments but 15-30 minutes prior to the administration of the morning dose of study medication.

c. Site personnel will determine the acceptability of Holter monitor recording.

d. If the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours) on the first attempt, a second attempt will be made for another 24 hours using a new Holter monitor hook-up kit.

e. No further attempts will be allowed if the second attempt is unacceptable.

Note: Subjects can proceed to Visit 4 (Randomization) or Visit 8 (Week 16) provided no clinically significant findings (as defined in Section 5.2.1) are reported by iCardiac following review of the Holter monitor recordings.

Note: Subjects who discontinue treatment before Week 12 will NOT be eligible for Holter assessments.

8.1 Visit 1 (Screening)

- Obtain informed consent.
- Register the subject in IWRS to obtain subject screening number.
- Obtain demographic data, including age, race, smoking history/status, medical/surgical history (including cardiovascular risk factors and history), and age of onset of COPD.
- Review inclusion/exclusion criteria.
- Obtain medication history, including COPD medications.
- Conduct a serum pregnancy test for all female subjects unless it is documented in the medical history that the subject has been irreversibly surgically sterilized (hysterectomy, oophorectomy, or bilateral tubal ligation) or they are at least 2 years post-menopausal.
- Conduct a complete physical examination (general appearance, skin, head, eyes, ears, nose, throat, neck [including thyroid], lymph nodes, chest, heart, abdomen, extremities, and nervous system).
  - Record COPD exacerbations and AEs (if any).
    Note: Adverse events that occur during the Screening Period (Visit 1 to Visit 4, before study drug dosing) will be summarized as medical history and not as a study AE, unless the event meets the definition of an SAE.
- Obtain height, weight, and vital signs (HR and blood pressure after being supine or seated for 5 minutes, and 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 (e.g. Germany) where only subjects who have had a chest x-ray or CT scan (thorax) performed outside of the study in the last 6 months are allowed to be enrolled. Alternatively, in these countries, an MRI may be used instead of a CT scan or chest x-ray as per local practice assessment.
  - Stop prohibited COPD medications and change concurrent COPD medications, as specified in protocol (refer to Section 5.4).
  - Obtain subject assignment information of Atrovent HFA and Ventolin HFA from IWRS.
  - 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. All subjects will receive open-label Atrovent® hydrofluoroalkane (HFA; ipratropium bromide inhalation aerosol) administered QID for maintenance during Screening. Ventolin® HFA (albuterol sulfate inhalation aerosol) will be provided for rescue use throughout the study. All ICS use will be stopped at randomization.
  - In order to allow for adequate washout of previous maintenance medications, subjects will undergo a Washout Period of at least 1 week (at least 2 weeks if taking Spiriva), but not greater than 26 days in duration prior to returning to the clinic for Visit 2. 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).

- 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, Sponsor-provided Ventolin HFA and Atrovent HFA to the next scheduled clinic visit.

8.2 Visit 2

- 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 4, 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 Exclusion Criteria 5.2 #3l), and post-dose spirometry values.
- Obtain spirometry pre-bronchodilator 60 and 30 minutes and 30 minutes post bronchodilator.
- 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 Atrovent HF, and rescue Ventolin HFA.
- Provide subjects with study drug as assigned by IWRS.
- Subjects will be instructed to bring their eDiary, and Sponsor-provided Atrovent HFA and Ventolin HFA to the next scheduled clinic visit.

8.3 Visit 3

- Review subject diary entries and retrain subject if subject has not met diary compliance requirement of >70% subject completion of diary assessments.
- Review all prior medications and ensure adherence to COPD regimen.
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, Visit 3 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 4, 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.
- Obtain vital signs 60 minutes pre-bronchodilator and 30 minutes post-bronchodilator.
- Perform reversibility test to Sponsor-provided Atrovent HFA (see Section 7.1.1.1 for instructions).
- Obtain spirometry pre-bronchodilator 60 and 30 minutes and 30 minutes post bronchodilator.
- **If a subject is participating in the 24 –hour Holter Monitoring Sub-Study**, attach Holter monitor and initiate 24-hour Holter monitor recording following the post-dose spirometry assessments (see Section 7.2.5 and Table 8-4 for further instructions).

- Subjects will be instructed to return the following day (Visit 3b) for the removal of the Holter monitor.

- Schedule Visit 4 (Randomization Visit, Day 1).

  Note: Visit 4 (Randomization Visit, Day 1) can be scheduled at minimum 1 day after Visit 3 and no later than 28 days after Visit 1 (Screening).

  Ensure subject has adequate supply of sponsor-provided Atrovent HFA and sponsor-provided rescue Ventolin HFA.

- Provide subjects with study drug as assigned by IWRS.

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

8.4 Visit 4 (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 4.

- **If a subject is participating in the PFT sub-study**, determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, Visit 4 must be rescheduled).

  Note: While the PFT sub-study was previously open to all eosinophil levels, subjects must now have a blood eosinophil count of ≥ 150 cells per mm^3 at Visit 1 to participate in the PFT sub-study.

- Have subject complete BDI questionnaire followed by SGRQ questionnaire, and EQ-5D-5L, before any other study procedures are performed.

- Obtain CAT (only to characterize the population on maximal therapy)

- Record COPD exacerbations and AEs (if any).

- Review smoking status

- A urine pregnancy test will be performed for women of childbearing potential at each of the in-clinic visits.

- Review all concomitant medications and ensure adherence to COPD regimen.

- Subjects treated with an ICS during screening must discontinue ICS use prior to randomization and throughout the study.

- Collect Sponsor-provided Atrovent HFA and Ventolin HFA dispensed during the Screening Period.
  - Discontinue all ICS throughout the study
  - 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

- **For Subjects participating in the 4-Hour PFT sub-study**, perform spirometry assessments 60 and 30 minutes pre-dose (see Table 8-1).

  Note: To be randomized, subjects in the PFT sub-study must meet the reproducibility criteria (see Section 7.1.1.2 for additional details). If the FEV_1 Baseline Stability criteria are not met at Visit 4 (Randomization) the subject will not be eligible to be participate in the PFT sub-study but may be randomized and included in the overall study.

  Note: While the PFT sub-study was previously open to all eosinophil levels, subjects must now have a blood eosinophil count of ≥ 150 cells per mm^3 at Visit 1 to participate in the PFT sub-study.

- 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 (see Appendix 12). 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 8-3).
  - Obtain vital signs 30 minutes post-dose
- **For Subjects participating in the 4-Hour PFT sub-study**:
  - Perform spirometry assessments 5, 15, 30 minutes and 1, 2, and 4 hours post-dose (see Table 8-1).
  - Central Laboratory Test (BMP) will be collected 2 hours post-dose
  - Obtain vital signs and ECGs 30 minutes and 2 hours 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.

- Provide subjects with study drug as assigned by IWRS.
- Schedule Visit 5 and ensure subject has adequate supply of study drug including rescue Ventolin HFA.

8.5 In-Clinic Visits 5, 7, 10, and 12 (Weeks 4, 12, 24, 36)

- Review subject eDiary (including EXACT etc.) 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 each in-clinic visits.
- Confirm subject eligibility to continue.
- 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 8-3).
  - Obtain central laboratory tests at Visit 5 and Visit 10 only
  - Obtain vital signs 60 minutes pre-dose at Visit 5, 7, 10 and 12
  - Obtain ECGs 60 minutes pre-dose at Visit 5 and 10 only
- **For Subjects participating in the 4-Hour PFT sub-study**, perform spirometry assessments 60 and 30 minutes pre-dose (see Table 8-1)
- 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
- **For Subjects participating in the 4-Hour PFT sub-study**:
  - Perform spirometry assessments at 15, 30 minutes and 1, 2, and 4 hours post-dose (see Table 8-1)
  - Central Laboratory Test (BMP) will be collected 2 hours post-dose at Visit 5 and Visit 10 only
    - Obtain vital signs 30 minutes and 2 hours post-dose at Visit 5, 7, 10 and 12
    - Obtain ECGs 30 minutes and 2 hours at Visit 5 and 10 only
- 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 a Sponsor-provided rescue Ventolin HFA. Note: At Visit 7 (Week 12), if a subject is participating in the 24 –hour Holter Monitoring Sub-Study, they will be scheduled to return to the clinic at Visit 8 (Week 16)
- For the subject who discontinues 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 Section 8.9.

8.6 In-Clinic Visit 8 (Weeks 16) For 24 –Hour Holter Monitoring Sub-Study Subjects Only

- If a subject is participating in the 24 –hour Holter Monitoring Sub-Study, they will need to return to the clinic at Visit 8 (Week 16).
- Attach Holter monitor and initiate 24-hour Holter monitor 15-30 minutes prior to the administration of the morning dose of study medication. (see Section 7.2.5 and Table 8-4 for further instructions).

- Subjects will take their morning dose of study medication at the clinic following initiation of Holter monitoring.
- Subjects will be instructed to return the following day (Visit 8b) for the removal of the Holter monitor.
- Note: At Visit 8b if the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours) on the first attempt, a second attempt will be made for another 24 hours using a new Holter monitor hook-up kit (See Section 7.2.5 for further instructions).

8.7 Telephone Visits 6, 8, 9, 11, and 13 (Weeks 8, 16, 20, 28, and 44)

- Review subject eDiary for data collection compliance.
- Collect HCRU information.
- Record COPD exacerbations and AEs (if any).
- Review all concomitant medications and ensure adherence to COPD regimen.
- 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 Section 8.9.

8.8 Final Visit (Visit 14; Week 52)

- 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
- Perform all pre-dose assessments (see Table 8-1 and Table 8-2).
    - Obtain central laboratory tests and serum pregnancy test for women of childbearing potential
    - Obtain vital signs and ECGs 60 minutes pre-dose
- **For Subjects participating in the 4-Hour PFT sub-study**, perform spirometry assessments 60 and 30 minutes pre-dose (see Table 8-1)

- 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.
- Conduct a physical examination
- 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
- **For Subjects participating in the 4-Hour PFT sub-study**:
  - Perform spirometry assessments at 15, 30 minutes and 1, 2, and 4 hours post-dose (see Table 8-1)
  - Central Laboratory Test (BMP) will be collected 2 hours post-dose
  - Obtain vital signs and ECGs 30 minutes and 2 hours post- dose
- Collect subject eDiary.
- Collect all study drugs including Sponsor-provided Ventolin HFA.
- At completion of all Visit 14 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 14.

8.9 Procedures for Treatment Discontinuation and Study Withdrawal Subjects

Subjects who discontinue study treatment prior to Week 52 (Visit 14) will be encouraged to remain in the study to complete all remaining study visits during the 52 week treatment period. Subjects who agree to continue to be followed post treatment discontinuation will sign an ICF addendum. All subjects who agree to continue study participation beyond treatment discontinuation will complete a Treatment Discontinuation/Withdrawal Visit (refer to Section 8.10) prior to transitioning back to regularly scheduled study visits. Subjects participating in the Holter Monitoring sub-study who discontinue from treatment will only complete regular scheduled visits and not complete any remaining Holter sub-study assessments. Subjects participating in the PFT sub-study who discontinue from treatment will continue to complete spirometry assessments. Treatment discontinuation subjects will return to appropriate maintenance COPD medications, per the investigator's discretion.

For subjects who discontinue study treatment but continue to participate in the study to complete all remaining study visits, all AEs/SAEs will be collected through the 14-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 the 14-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/Withdrawal Visit (refer to Table 8). These subjects will return to appropriate maintenance COPD medications, per the investigators discretion. A follow-up telephone call will be performed at least 14 days after the last study drug dose. All AEs/SAEs will be collected through the 14-day follow-up telephone call. In the event the Treatment Discontinuation/Withdrawal Visit is performed >14 days post last study drug dosing; a follow-up TC will not be required. These subjects will be followed for vital status at 52 weeks post randomization in accordance with the informed consent.

8.10 Unscheduled Visit and Treatment Discontinuation/Withdrawal Visit

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

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

- Complete TDI questionnaire first; followed by SGRQ questionnaire and EQ-5D-5L before any other study procedures are performed.
- Collect HCRU information.
- Record COPD exacerbations and AEs (if any).
- Review concomitant medications.
- Conduct a physical examination, including vital signs.

- Perform ECG and collect blood samples for hematology, chemistry and urinalysis.
- Collect a blood sample for pregnancy test for women of child-bearing potential.
- Collect subject eDiary.

  Note: Subjects who have discontinued treatment but continue in the study will have their eDiary re-dispensed
- 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.
- Inform subject about reporting all SAEs up to 14 days following the last dose of study drug.
- Capture the reason for treatment discontinuation.

8.11 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.

8.12 52-Week Post-Randomization Vital Status Confirmation

All subjects who discontinue study treatment prior to 52 weeks post- randomization will have their vital status confirmed at 52 weeks post-randomization.

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

- The first and second attempts may be conducted as telephone follow-up call to the subject within 2 weeks after 52 weeks post-randomization
- The third attempt will be by certified mail to the subject's address provided at the time of informed consent within 3 weeks after 52 weeks post-randomization.
- The fourth attempt will be made as a telephone follow-up call to the next of kin/emergency contact provided at the time of informed consent within 4 weeks after 52 weeks post-randomization

- A fifth attempt will be made through a certified letter to the next of kin/emergency contact provided at the time of informed consent within 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.

8.13 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. The following categories should be used to describe these events in the eCRF:

- Subject discretion (document reason)
- Investigator considers it to be in the best interest of the subject
- AE(s)/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

The primary objective of this study is to assess the effect of BGF MDI relative to GFF MDI and BFF MDI on the rate of moderate or severe COPD exacerbations in subjects with a history of previous COPD exacerbations. In addition, as secondary and other objectives, this study will assess the effects of BGF MDI relative to GFF MDI and BFF MDI on COPD symptoms, disease-related health status, pulmonary function, and long-term safety and tolerability, as well as HCRU. This study will include a 52-week Treatment Period, preceded by a 2- to 4-week Screening Period and followed by a 2-week follow-up TC.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

All efficacy assessments are relative to pre-dose baseline obtained at or prior to Visit 4 and are stated in Section 3.

9.2.2 Safety Endpoints

- AEs
- 12-lead ECG
- Clinical laboratory testing
- Vital sign measurements

9.3 Study 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 randomized treatment group. Efficacy data obtained after discontinuation of treatment, but prior to withdrawal from the study, will be included. The ITT population will be used for sensitivity analyses.
- The **Modified Intent-to-Treat (mITT) Population** is a subset of the ITT Population defined as all subjects with post-randomization data obtained prior to discontinuation from treatment. Any data collected after completion of or discontinuation from randomized study medication will be excluded from the mITT analysis but will still be included in the ITT analysis. Subjects will be analyzed according to randomized treatment group. (Note that a subject who used a study treatment but took less than one full dose of treatment will qualify for this population). The mITT will be the primary population for all efficacy analyses except for the non-inferiority analyses. Note: The

knowledge that a subject did not have a COPD exacerbation constitutes an efficacy assessment.

- The **Per-Protocol (PP) Population** is a subset of the mITT Population defined as all subjects with post-randomization data obtained prior to any major protocol deviations. Data obtained after any major protocol deviation or discontinuation from treatment will be excluded. Since receiving the wrong treatment will be a major protocol deviation, subjects in the PP population will be analyzed as randomized (which for this population is identical to analysis by the actual treatment received). Any evaluability criteria with a potential impact on efficacy results will be identified during blinded data review prior to database lock. Major protocol deviations (protocol violations), therefore, can result in exclusion of all data from a particular subject from the PP population or require exclusion of data from a specific time point and/or subsequent time points for an endpoint.
- The **Safety Population** is similar to the mITT Population (all subjects who are randomized to treatment and receive any amount of the study treatment). However, subjects will be analyzed according to treatment received rather than randomized. If a subject received more than one 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 had no post-dose safety assessments. (Note that a subject who used a study treatment but took less than one full dose of treatment will qualify for this population). **Note:** The statement that a subject had no AEs also constitutes a safety assessment.

- The **Holter Monitoring Population** is defined as all subjects in the Safety Population who had at least 18 hours of acceptable quality Holter monitoring data at both Visit 3 (Holter Monitor Baseline) and Visit 8 (Week 16). Exclusions from this population may be identified by Pearl Therapeutics prior to database lock and unblinding.

Analyses will be performed as follows:

Demographics will be summarized for the mITT, PP, and Safety Populations as well as for subjects participating in the 4-hr PFT and Holter sub-studies. Extent of exposure will be summarized for the Safety Population. The Safety Population will be used to summarize safety. Efficacy Analyses will be performed for the ITT, mITT, and PP Populations. A discussion of the various estimands follows below.

9.4 Efficacy Analysis

9.4.1 Estimands

The primary estimand of interest is called the efficacy estimand and is the effect of the randomized treatments in all subjects assuming continuation of randomized treatments for the duration of the study regardless of actual compliance. There are three additional estimands of interest. One is called the attributable estimand and is the effect of treatment in subjects attributable to the randomized treatment. For this estimand, discontinuation of randomized medication for reasons such as tolerability or lack of efficacy is considered a bad

outcome. Another estimand of interest is called the treatment policy estimand. This estimand is the effect of randomized treatment over the study period regardless of whether randomized treatment is continued. The final estimand of interest is called the per protocol estimand. This estimand is the effect of treatment on subjects who are compliant with the protocol (i.e. no major protocol deviations), including the use of randomized medication.

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

The second estimand of interest is the attributable estimand. Analyses of the attributable estimand will be conducted in the mITT Population, but data that are missing due to treatment discontinuation will be imputed based on the 95th percentile of the reference arms' distribution if the reason is reasonably attributable to tolerability or lack of efficacy. The 95th percentile applies to an endpoint for which a higher value is a worse outcome; however, the 5th percentile applies to an endpoint for which a higher value is a better outcome. More detail about the computation of the attributable estimand will be provided in the SAP.

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

Finally, the last estimand of interest is the per protocol estimand. Analysis of this estimand will use the PP Population. This estimand will serve as primary for the non-inferiority comparison of BGF MDI 160/14.4/9.6 µg to GFF MDI. It will be supportive for other comparisons of interest.

The following efficacy comparisons will be made, in the following order:

- BGF MDI 320/14.4/9.6 µg versus GFF MDI 14.4/9.6 µg
- BGF MDI 320/14.4/9.6 µg versus BFF MDI 320/9.6 µg
- BGF MDI 160/14.4/9.6 µg versus GFF MDI 14.4/9.6 µg
- BGF MDI 160/14.4/9.6 µg versus BFF MDI 320/9.6 µg

All comparisons will be for superiority, with the exception of BGF MDI 160/14.4/9.6 µg MDI to BFF MDI 320/9.6 µg, which will be for non-inferiority first, followed by superiority. Details of multiplicity controls are found in Section 9.4.6.

9.4.2 Primary Efficacy Analysis

9.4.2.1 Rate of Moderate or Severe COPD Exacerbations

The rate of moderate or severe COPD exacerbations will be analyzed using negative binomial regression. COPD exacerbations will be considered separate events provided that 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. However, the start day of a COPD exacerbation will not be excluded from the time at risk. Treatments will be compared adjusting for baseline post-bronchodilator percent predicted FEV_1, baseline COPD exacerbation history, log baseline blood eosinophil count, region, and ICS use at Screening. Baseline blood eosinophil count will be the average of all non-missing eosinophil counts obtained on the study prior to first dose of study medication.

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

The primary analysis will be for the efficacy estimand. Secondary analyses will be produced for the attributable estimand. Sensitivity analyses will be presented on the treatment policy estimand.

Duration of COPD Exacerbation

For moderate or severe exacerbations, the duration is based on information from the eCRF COPD exacerbation page, whereas for mild exacerbations, the duration is defined by the length of symptoms as recorded in the eDiary.

For moderate or severe COPD exacerbations (using the eCRF COPD exacerbation page), the start date of a moderate or severe COPD exacerbation is the earlier of the medication start date, hospitalization start date (if the exacerbation resulted in hospitalization) and date of death (if the exacerbation resulted in death). The end date of a moderate or severe COPD exacerbation is the later of the medication end date, hospitalization (for exacerbation) end date, and date of death (from the exacerbation). In order to ensure that the same event is not counted twice, concurrent moderate or severe COPD exacerbations with start and stop dates equal to or less than 7 days apart will be considered the same event and assigned the maximum severity between the two.

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

In addition, in order to not double count exacerbations that are moderate or severe, eDiary data from dates within 7 days of a moderate or severe exacerbation will not be included as additional mild COPD exacerbations. This implies that continuing worsened symptoms that

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

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

9.4.3 Analysis of Secondary Endpoints

9.4.3.1 Time to First COPD Exacerbation: Moderate or Severe

The time to first 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, log baseline blood eosinophil count, region, 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 four 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 will be censored at Week 52 (Visit 14). Early treatment discontinuations who did not experience a COPD exacerbation will be censored at the date of discontinuation.

9.4.3.2 Time to Death: All Cause, Respiratory

Time to death due to any cause will be summarized using a Kaplan-Meier curve. Subjects will be censored at the date of last contact. The time to death will be compared between treatments using a Cox regression model, adjusted for baseline percent predicted post bronchodilator FEV_1 and baseline age as covariates. For this endpoint, the treatment policy estimand will be presented as primary. Hazard ratios with Wald 2-sided 95% CIs for these ratios will also be provided for all four treatment comparisons. Data permitting, these analyses will be repeated time to death from respiratory causes. Pearl and the CEC 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 CEC will be considered as events for this analysis.

9.4.3.3 Transition Dyspnea Index

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

At Randomization (Visit 4), the severity of dyspnea at baseline will be assessed using the BDI. At subsequent visits, change from baseline will be assessed using the TDI. Scoring and handling of missing items will be conducted in accordance with the user's guide for the TDI score. TDI will be analyzed using a RM linear model. Data from all study treatments will be included in the modeling.

The linear RM ANCOVA model will include treatment, visit, and the treatment by visit interaction, and ICS use at Screening as categorical covariates and log baseline blood eosinophil count, BDI, and 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 the entire 52 weeks, and over 24 weeks (secondary for ex-US). Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference.

As additional supportive analyses, the difference between treatments at each of the individual visits will also be evaluated and summarized. Furthermore, as supportive analyses, responder analyses will be performed where responders are defined as a response of 1.0 points or more on average over 24 weeks, and over 52 weeks. Logistic regression will be used to compare the treatment groups with BDI and log 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 of the 4 treatment comparisons.

9.4.3.4 Rescue Ventolin HFA Use

The number of puffs of rescue medication use (i.e. albuterol sulfate or locally available equivalent product) 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 (i.e. albuterol sulfate or locally available equivalent product) will be calculated overall and for each of the 4-week intervals during the Treatment Period. For every period of time for which the mean number of puffs of rescue will be calculated, missing values will be ignored in both the numerator and denominator. As such, the denominator will be adjusted based on the number of days (including half days) with non-missing values.

The difference between treatment groups in the change from baseline in average daily rescue medication use (i.e. albuterol sulfate or locally available equivalent product) use over 52 weeks will be evaluated using a similar RM approach as for TDI. Instead of visit, the number of the relevant 4-week interval (1-13) will be used as a categorical covariate in the model.

The linear repeated measures (RM) analysis of covariance (ANCOVA) model will include treatment, visit, the treatment by visit interaction, and ICS use at Screening as categorical covariates and baseline post-bronchodilator percent predicted FEV_1, baseline rescue Ventolin HFA use, log baseline blood eosinophil count, and percent reversibility to Ventolin HFA (or

locally available equivalent product) as continuous covariates. An unstructured correlation matrix will be used to model additional autocorrelation within subject. If this model fails to converge, an autoregressive order 1 [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 (secondary endpoint), and over the entire 52 weeks. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each of the 4 treatment differences.

As supportive analyses, the treatment difference for each 4-week interval will be evaluated and summarized. Additionally, as supportive analyses, daytime rescue Ventolin HFA use and nighttime rescue medication use (i.e. albuterol sulfate or locally available equivalent product) will be evaluated and summarized in a similar fashion. Two-sided p-values and point estimates with 2-sided 95% CIs will be produced for each treatment difference.

9.4.3.5 St. George's Respiratory Questionnaire

The difference between treatment groups in the change from baseline in SGRQ over 52 weeks of treatment will be evaluated using a similar RM approach as for TDI but using baseline SGRQ score instead of the BDI. Scoring and handling of missing items will be conducted in accordance with the user's guide for the SGRQ. Each response is to be given a unique empirically derived weight between 0 and 100, the weights of all responses are then summed up and divided by the maximum possible score and expressed as a percentage. Missing SGRQ total scores will not be imputed. Two-sided p-values and point estimates with 2-sided 95% CIs will be produced for each treatment difference.

Responder analyses will be performed, where responders are defined as an improvement from baseline of ≥4.0 points in the SGRQ Score. The proportion of responders at Week 24 (Secondary for US) will be compared between treatment groups using a logistic regression with baseline SGRQ Score, log baseline blood eosinophil count, and baseline post bronchodilator percent predicted FEV_1 and percent reversibility to Ventolin HFA as continuous covariates and treatment, and ICS use at Screening as categorical covariates. P-values and odds ratios with 95% CIs will be produced for each treatment comparison. The analysis will be repeated for responders at Week 24 (Secondary for ex-US), at Week 52, over 24 weeks, and over 52 weeks.

As supportive analyses, the difference between treatments at each of the individual visits will also be evaluated and summarized.

9.4.3.6 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, and the 11-item EXACT Respiratory Symptoms total score (RS-Total Score), will be calculated over 52 weeks and over each 4-week interval of the 52-week Treatment Period. The last 7 days of the 10 to 14 day Screening Period will be used to calculate the baseline. The mean change from baseline in RS-Total Score over each 4-week interval will be analyzed using a similar RM model as for TDI to estimate treatment effects over 52 weeks and over 24 weeks, but using

the corresponding 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.

9.4.3.7 Rate of Severe COPD Exacerbations

The rate of severe COPD exacerbations will be analyzed in a manner similar to the primary efficacy variable, the rate of moderate or severe COPD exacerbations.

The logarithm of time at risk of experiencing a severe (see explanation below) COPD exacerbation will be used as an offset variable in the model for the rate of severe COPD exacerbations. Time during a severe exacerbation or in the 7 days following a severe exacerbation will not be included in the calculation of exposure (i.e. time at risk). However, the start day of a severe COPD exacerbation will not be excluded from the time at risk.

Sensitivity analyses will be presented on the treatment policy estimand.

9.4.4 Analysis of Other Endpoints

9.4.4.1 Time to First COPD Exacerbation: of Any Severity

All of the above variables will be analyzed in a manner similar to the time to first moderate or severe COPD exacerbation as defined under secondary variables.

9.4.4.2 Rate of COPD Exacerbations: of Any Severity

The following efficacy variables will be analyzed in a manner similar to the primary efficacy variable, the rate of moderate or severe COPD exacerbations:

- Rate of COPD exacerbations of any severity

9.4.4.3 Time to Treatment Failure

Treatment failure is defined as a moderate or severe COPD exacerbation or discontinuation from treatment for any reason or death. Time to treatment failure will be will be analyzed in a manner similar to the time to first moderate or severe COPD exacerbation as defined under secondary variables. Subjects who do not experience a treatment failure will be censored at their Week 52 Visit or Day 365, whichever comes first.

9.4.4.4 Percentage of Days with “No Rescue Ventolin HFA Use” Over the Treatment Period

As a supportive analysis, percentage of days with “no rescue Ventolin HFA use” over 52 weeks will be analyzed. A “day with no rescue use” is defined using rescue Ventolin HFA usage data from days where rescue Ventolin HFA usage data is non-missing as any day where the subject reported no puffs of rescue Ventolin HFA. The percentage of days with “no rescue use” will be summarized by treatment and analyzed using ANCOVA with baseline average daily rescue Ventolin HFA use, log baseline blood eosinophil count ,

post-bronchodilator percent predicted FEV_1, and percent reversibility to Ventolin HFA as continuous covariates and ICS use at Screening as a categorical covariate.

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

The EQ-5D-5L data will be scored to calculate an index score based upon subjects' responses to the 5 dimensions. The visual analogue scale will be scored from 0 (worst imaginable health state) through 100 (best imaginable health state) to represent the subject's self-report concerning how bad or how good their health was during that day. The percentage of subject's categorical responses to each of the 5-dimensions will be summarized. Descriptive statistics for the index score and VAS will be presented by treatment group. VAS scores over 52 weeks may be analyzed using RM ANCOVA with age and baseline score as continuous covariates and region, gender, and treatment as categorical covariates. .

9.4.5 Analysis of PFT Sub Study

Pulmonary function testing will be conducted in a subset of subjects at the randomization visit and at Weeks 12, 24, 36, and 52.

9.4.5.1 Change from Baseline in Morning Pre-dose Trough FEV_1 at Week 24 (US) and Over 24 Weeks (ex US) for the comparison of BGF MDI to GFF MDI

The change from baseline in morning pre-dose trough FEV_1 will be analyzed using an RM linear model. The ANCOVA model will include baseline FEV_1, log baseline blood eosinophil count, and percent reversibility to Ventolin HFA as continuous covariates and visit, treatment, the treatment by visit interaction, and ICS use at Screening as categorical covariates. Baseline is defined as the average of the non-missing -60 minute and -30 minute values obtained prior to dosing at Day 1 (Visit 4). An unstructured correlation model will be used to model additional autocorrelation within subject. If this model fit fails to converge, an AR(1) structure will be used to model correlation between time points from the same subject; for this model, subject will be included as a random effect. Contrasts will be used to obtain estimates of the treatment differences at Week 24, over 24 weeks, as well as at each visit. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference.

Additional sensitivity analyses will be implemented based on a cumulative responder approach as described in Farrar 2006 for the change from baseline in morning pre-dose trough FEV_1 at Week 24. A cumulative distribution plot by treatment arm (Farrar et al., 2006) will also be produced. The cumulative responder curves for each treatment will then be compared pairwise using Kolmogorov-Smirnov tests.

9.4.5.2 FEV_1 AUC_{0-4} at Week 24 (US) and Over 24 Weeks (ex-US)

FEV_1 AUC_{0-4} will be calculated using the trapezoidal rule and transformed into a weighted average by dividing by the time in hours from dosing of the last measurement included (typically 4 hours). Only one non-missing post-dose value is required for the calculation of

AUC. Actual time from dosing will be used if available; otherwise scheduled time will be used. The differences between treatment groups in FEV_1 AUC_{0-4} at Week 24 and over 24 weeks will be evaluated using a linear mixed RM ANCOVA model with baseline FEV_1, log baseline blood eosinophil count, and percent reversibility to Ventolin HFA as continuous covariates and treatment, ICS use at Screening as a categorical covariate. Two-sided p-values and point estimates with two-sided 95% CIs will be produced for each treatment difference.

9.4.5.3 Other PFT Sub-study Analyses

In addition to the two primary PFT endpoints discussed above (Sections 9.4.5.1 and 9.4.5.2), the change from baseline in morning pre-dose trough FEV_1 over 24 weeks, over Weeks 12 to 24, and over 52 weeks, FEV_1 AUC_{0-4}, and peak change from baseline in FEV_1 over 52 weeks and at each visit will be estimated and compared between treatment groups using the same linear mixed RM model as pre-dose trough FEV_1. Similar analyses will be conducted for FVC, PEFR, and FEF_{25-75} over 52 weeks and at each post-randomization visit.

9.4.5.4 Rate of decline in pre-dose FEV_1 and FEV_1 AUC_{0-4} over 52 weeks

The rate of decline in pre-dose FEV_1 will be analyzed as follows. Pre-dose FEV_1 will be analyzed with a linear mixed model with random subject slopes of FEV_1 versus time and random subject intercepts. An unstructured covariance matrix will be employed for these two random effects. The model will fit a distinct fixed mean for each treatment and a distinct fixed slope (of FEV_1 versus time) for each treatment. The model will include the interaction between treatment (as a categorical covariate) and time (as a continuous covariate), and the interaction between screening smoking status and time and the interaction between baseline FEV_1 and time. Other covariates in the model will be percentage reversibility to Ventolin HFA, baseline FEV_1, and log baseline blood eosinophil count as continuous covariates, and treatment, smoking status at screening, and ICS use at Screening as a categorical covariate. The rate of decline (the negative of the slope) will be estimated and compared between treatments

The rate of decline in FEV_1 AUC_{0-4} over 52 weeks will be analyzed in a similar manner.

9.4.5.5 Time to Onset on Day 1

The onset of action will be determined for each treatment using the 5 minutes and 15 minutes post-dosing FEV_1 assessments from Day 1. The onset of action for each product will be defined as the median time point to 100 ml improvement in FEV_1 from baseline.

9.4.6 Control of Type I Error

All comparisons will be for superiority, with the exception of BGF MDI 160/14.4/9.6 µg MDI to BFF. The comparisons of BGF MDI 160/14.4/9.6 µg to BFF MDI 320/9.6 µg on COPD exacerbations will be for non-inferiority (NI) with an NI margin of 1.1, followed by superiority; however, attaining statistical significance in the superiority comparison is not a pre-requisite to proceeding down the testing hierarchy.

If BGF MDI 320/14.4/9.6 µg significantly reduces the rate of moderate or severe COPD exacerbations compared to both GFF MDI 14.4/9.6 µg and BFF MDI 320/9.6 µg (using first the efficacy estimand and then the attributable estimand as the first secondary), then primary endpoints from the lung function sub-study will be assessed. For the US approaches, these are first FEV_1 AUC_{0-4} at Week 24 for the comparison of BGF MDI 320/14.4/9.6 µg to BFF MDI 320/9.6 µg and then the change from baseline in morning pre-dose trough FEV_1 at Week 24 for the comparison of BGF MDI 320/14.4/9.6 µg to GFF MDI 14.4/9.6 µg. For ex-US Approaches, these are first FEV_1 AUC_{0-4} over 24 weeks for the comparison of BGF MDI 320/14.4/9.6 µg to BFF MDI 320/9.6 µg and then the change from baseline in morning pre-dose trough FEV_1 over 24 weeks for the comparison of BGF MDI 320/14.4/9.6 µg to GFF MDI 14.4/9.6 µg. If these comparisons are statistically significant, then for both the US and Ex-US approaches, the rate of moderate or severe exacerbations in the subgroup of subjects with a history of ≥ 2 exacerbations at baseline will be compared between BGF MDI 320/14.4/9.6 µg and GFF MDI 14.4/9.6 µg and between BGF MDI 320/14.4/9.6 µg and BFF MDI 320/9.6 µg, as will the other secondary endpoints. BGF MDI 160/14.4/9.6 µg will follow a similar approach, except that the comparison to BFF 320/9.6 µg will be for non-inferiority first. Non-inferiority margins for secondary endpoints are specified in the SAP. If BGF MDI 160/14.4/9.6 µg significantly reduces the rate of moderate or severe COPD exacerbations compared to GFF MDI 14.4/9.6 µg and is non-inferior to BFF MDI 320/9.6 µg, then primary endpoints from the lung function sub-study will be assessed as outlined above.

For both registration approaches, US and ex-US, and for each dose of BGF MDI, if the primary and first secondary measures are statistically significant for all comparisons, then Type I error for the remainder of the secondary measures with the exception of time to death (all cause) will be controlled by using Hochberg within each comparison [Hochberg 1988]. If all of the secondary measures are significant, then time to death (all cause) will be tested within each comparison.

The family-wise Type I error rate is maintained throughout the trial, including the interim analysis by one-sided group sequential testing. Further details about maintaining the Type I error throughout multiple tests may be found in the SAP.

9.4.7 Safety Analysis

9.4.7.1 Adverse Events

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

9.4.7.2 MACE Events Determined by Clinical Endpoint Committee

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

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

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

9.4.7.3 Pneumonia Events Determined by CEC

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

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

9.4.8 Clinical Laboratory Measurements

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

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

The number and percent of subjects with potentially clinically significant (PCS) laboratory values will be summarized. The PCS values for serum potassium are <3.0 mmol/L or >6.0 mmol/L and for blood glucose <2.2 mmol/L, or >13.9 mmol/L if no history of diabetes, >27.8 mmol/L regardless of baseline. PCS values for additional labs will be defined in the Statistical Analysis Plan (SAP). No hypothesis tests will be performed.

9.4.9 Vital Signs

Summary statistics (mean, median, SD, and range) for absolute values and change from baseline values in SBP, DBP, HR, and temperature will be tabulated for each treatment and

assessment time. Baseline values for vital signs will be defined as the average of the values prior to dosing at the Randomization Visit (Visit 4). The PCS values for vital signs will be defined in the SAP and the percentage of subjects with PCS values will be summarized. No hypothesis tests will be performed.

9.4.10 ECGs

Summary statistics (mean, median, SD, and range) for raw values and change from baseline values in HR, RR interval, PR interval, QRS axis, QRS interval, QT interval, and QTcF interval will be calculated, where baseline is defined as the average of the pre-dose measurements taken prior to the start of treatment at the Randomization Visit (Visit 4). The QTcF (Fridericia corrected QT) is defined as (QT/[RR1/3]). The RR Interval (msec) is estimated as 60000/HR. These assessments will be tabulated for each treatment and assessment time. The PCS values for ECG parameters will be defined in the SAP, and the percentage and number of subjects with PCS ECG values will be tabulated. No hypothesis tests will be performed.

9.4.11 Health Care Resource Utilization

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

9.4.12 24-Hour Holter Monitoring

Holter monitoring will be conducted over 24 hours in a subset of approximately 800 randomized subjects (200 subjects from each treatment arm) at Visit 3 (Holter Monitor Baseline) and Visit 8 (Week 16). If there is not at least 18 hours of acceptable quality monitoring for a given assessment, then the assessment is to be repeated. In these cases, the second assessment will be used whether for baseline and/or for the Visit 8 (Week 16) value. However, any incidence of AEs indicated by the incomplete Holter monitor findings at Week 4 will be captured.

Primary Holter Monitoring Endpoint:

The change from baseline in mean 24-hour heart rate (HR) obtained using Holter monitoring at Week 16 will be analyzed using an ANCOVA model to evaluate treatment differences with baseline mean 24-hour HR (obtained during 24-hour Holter monitoring at screening) as a covariate. LS means and estimated treatment differences with 95% CIs will be provided. The raw mean values and change from baseline values will also be summarized by treatment group.

Secondary Holter Monitoring Endpoints:

The change from baseline at Week 16 (Visit 8) in the mean daytime (06:00 to 22:00) HR, mean nighttime (22:00 to 06:00) HR, maximum 24-hour HR, and minimum 24-hour HR will each be summarized and analyzed in a similar manner to the primary Holter monitoring endpoint.

A frequency distribution of the following will be provided:

- Proportion of subjects with maximum heart rate during treatment of >180, >160-180, >140-160, >120-140, >100-120, and 100 bpm or less.
- Proportion of subjects with minimum heart rate during treatment of >60, >50-60, >40-50, and <40 bpm

The change from baseline in the number of Holter monitor events will be summarized descriptively. This analysis will be performed for change from baseline for the following parameters (calculated per hour): number of isolated ventricular events (PVCs), number of ventricular couplets, and number of ventricular runs, number of isolated supraventricular events, number of supraventricular couplets, and number of supraventricular runs. The ventricular variables will each be analyzed using an ANCOVA to evaluate treatment differences with baseline number of PVCs as a covariate. The supraventricular variables will each be analyzed using an ANCOVA to evaluate treatment differences with baseline number of supraventricular ectopic events as a covariate. LS means and estimated treatment differences with 95% CIs will be provided. The raw mean values and change from baseline values will also be summarized by treatment group. The distribution of the frequency of these events for baseline (Visit 3) and at Week 16 will be evaluated for each event and if necessary, a natural log transformation or ln (value +1) will be used to normalize (prior to calculating the change from baseline value which will be analyzed). If a log transformation is used, then both descriptive statistics as well as analysis results will be back-transformed to provide information about geometric means.

Additionally, the proportion of subjects in each category of change from baseline in the number of PVCs per hour (no change, increase of >0-<60, 60-<120, and ≥120, and decrease of >0-<60, 60-<120, and ≥120) will be tabulated.

9.5 Randomization

Subjects will be randomized to one of the four treatment arms using an IWRS in a 1:1:1:1 ratio. Randomization will be stratified by: exacerbation history (1 or ≥2 moderate or severe exacerbations), post-bronchodilator FEV_1 (25% to <50% or 50% to 65% predicted), blood eosinophil count (<150 cells per mm^3 or ≥150 cells per mm^3), and country. Center will not be used as a stratification factor given the impracticality of enrolling a large enough number of subjects to ensure balance in each of the eight strata formed by combining, exacerbation history, FEV_1, and eosinophil categories use within each center.

9.6 Experimental Design

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

9.7 Sample Size

[redacted]

9.8 Data Validation and Transformation

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

9.9 Interim Analysis

There will be an interim efficacy analysis at which an independent Data Monitoring Committee will review unblinded efficacy data and determine if the study can be stopped early for unequivocal efficacy. [redacted]

[redacted]

Should the study continue until all subjects complete, the one-sided alpha criteria for the final analysis will be adjusted based on the percent of information available at the prior interim analyses using an appropriate spending function such that the overall Type I error is controlled at one-sided 0.025.

Should the study be stopped for unequivocal efficacy, the data used for the analysis of moderate or severe exacerbations in that analysis will be considered the primary data set so that the primary result will not change. An additional analysis including all data collected after the interim snapshot data will be included in the CSR as supportive. Regardless of the efficacy interim analysis decision, enrolled subjects from China will continue all efficacy and safety assessments until approximately 52 weeks after Randomization.

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

9.10 Analysis Plan

All final analyses will be specified in a detailed SAP that will be accompanied by table and data listing shells with mock graphical representations. The analysis plan will be approved by signature before database lock and unblinding. A separate SAP was approved prior to the conduct of the planned [redacted] and if insufficient details are included in the DMC Charter, a separate SAP will also be used to describe the interim analysis.

9.11 Handling of Missing Data

All observed values prior to study withdrawal will be included in the treatment policy estimand. All observed values recorded prior to treatment discontinuation will be included in the efficacy estimand and the attributable estimand. The impact of missing data caused by subjects withdrawing from the study (not just the randomized treatment) will be evaluated. These robustness analyses will use data imputed under varying assumptions about what the relative treatment effects would have been in the unobserved data. Further details will be specified in the SAP.

For the subset of subjects included in the PFT spirometry assessment, the efficacy estimand will use all available data prior to treatment discontinuation. Change from baseline in morning pre-dose trough FEV_1 at each visit is defined as the average of the 60 and 30 minute pre-dose values minus baseline. In subjects missing either of these pre-dose assessments, the value will be calculated from the single measurement. In subjects missing both pre-dose values, morning pre-dose trough FEV_1 at that visit will not be calculated. Peak FEV_1 and FEV_1 AUC_{0-4} will be included in the efficacy, attributable, treatment policy, and per-protocol estimands as long as there is <u>one</u> non-missing post-dose value.

9.12 Statistical Software

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

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

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

10.2 Ethical Conduct of the Study and Institutional Review Board or Independent Ethics Committee Approval

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

- Guideline for Good Clinical Practice E6 (R1): Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).

- US CFR dealing with clinical studies (21 CFR parts 50, 54, 56, and 312).

- Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects) [http://www.wma.net/en/10home/index.html].

- Any additional regulatory requirements.

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

Pearl will provide the Investigator with relevant document(s)/data that are needed for IRB/IEC review and approval of the study. If the protocol, the ICF, or any other information that the IRB/IEC has approved for presentation to potential subjects is amended during the study, the Investigator is responsible for ensuring the IRB/IEC reviews and approves, where applicable, these amended documents. The Investigator must follow all applicable regulatory requirements pertaining to the use of an amended ICF including obtaining IRB/IEC approval of the amended form before new subjects consent to take part in the study using this version of the form. The IRB/IEC approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to Pearl promptly.

10.3 Subject Information and Consent

The study will be conducted in accordance with applicable subject privacy requirements. The proposed ICF, which must be in compliance with applicable regulations, must be reviewed and approved by the IRB and Pearl prior to initiation of the study.

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

10.4 Laboratory Accreditation

Any laboratory facility intended to be used for analysis of clinical laboratory samples required by this protocol must provide evidence of adequate licensure or accreditation according to the prevailing regulations in that state and/or country. Reference values and/or normal ranges for the test results must be provided to Pearl. Pearl must be notified promptly in writing of any changes occurring in reference values during the course of the study.

10.5 Confidentiality

10.5.1 Confidentiality of Data

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

10.5.2 Confidentiality of Subject/Patient Records

By signing this protocol, the Investigator agrees that Pearl (or representative), IRB/IEC, or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the ICF, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to Pearl. In addition, the Investigator agrees to treat all subject/patient data used and disclosed in connection with this study in accordance with all applicable privacy laws (ie, Health Insurance Portability and Accountability Act), rules, and regulations.

10.6 Quality Control and Assurance

Pearl is responsible for implementing and maintaining quality control and quality assurance systems with written Standard Operating Procedures to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

10.7 Data Management

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

10.8 Study Monitoring

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

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

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

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

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

After the final review of the study files, the files should be secured for the appropriate time period as specified in Section 10.9. The Investigator will also permit inspection of the study files by Pearl's Quality Assurance auditors, and authorized representatives of the FDA or other applicable regulatory agencies.

10.9 Retention of Data

Documents that individually and collectively permit evaluation of the conduct of the study and the quality of the data produced must be maintained for review by Pearl's quality assurance auditors and by all applicable regulatory authorities. The period of time these documents must be maintained is governed by applicable regulations. Pearl or its designee will inform the Investigator when these documents may be destroyed. Pearl or its designee must be notified in writing at least 6 months prior to the intended date of disposal of any study record related to this protocol to allow Pearl to make alternate storage arrangements

10.10 Financial Disclosure

The Principal Investigator or sub-Investigators named on the Form FDA 1572 or the locally accepted alternate Investigator Statement form will need to complete a financial disclosure form prior to study initiation, at any time during the study execution if new information needs to be disclosed, and for 1 year after study completion. Investigators should make the IRB/IEC aware of any financial interests that the Investigator has in the study drug.

10.11 Investigator's Final Report

Shortly after completion of the Investigator's participation in the study, the Investigator will submit a written report to Pearl.

10.12 Publication Policy

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

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

1. **Responsibility:** Each Principal Investigator is responsible for the accuracy and completeness of all data from their site. Pearl (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.
2. **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted at least 30 days prior to submission for publication or presentation to Pearl for review, approval, and to ensure consistency with the policy in this protocol. Pearl will have the right to request appropriate modification to correct facts and to represent its

opinions, or the opinions of the publication committee, if these differ with the proposed publication.

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

11 REFERENCE LIST

Celli B, MaNee W, Agusti A, et al. Standards for the diagnosis and treatment of subjects with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004; 23:932-946.

Centers for Disease Control (CDC guidelines 2013-2014). Summary Recommendations: Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2013-2014. Centers for Disease Control and Prevention (CDC). Available from: URL: http://www.cdc.gov/flu/professionals/acip/2013-summary-recommendations.htm

Centers for Disease Control (CDC guidelines 2010). Updated Recommendations for Prevention of Invasive Pneumococcal Disease Among Adults Using the 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23). Centers for Disease Control and Prevention (CDC). Morbidity and Mortality Weekly Report .2010 / 59(34);1102-1106. Available from: URL**:** http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html

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

Food and Drug Administration (FDA). Guidance for Industry: Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment. November, 2007.

From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016. Available from: http://www.goldcopd.org/.

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. Updated; 2014:1-102. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report2014_Feb07.pdf

Global Lung Initiative (GLI). Reference values for spirometry. 2012. http://www.lungfunction.org/files/GLI-2012_Reference_values.pdf

Hochberg Y, A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988**;** 75, 4, pp. 800-802.

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

Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Briel M, Drescher T, Duerring U, Henzen C, Leibbrandt Y, Maier S, Miedinger D, Müller B, Scherr A, Schindler C, Stoeckli R, Viatte S, von Garnier C, Tamm M, Rutishauser J. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. JAMA. 2013 Jun 5;309(21):2223-31.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.

Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest. 1984;85(6):751-758.

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

Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010; 340:c869.

New York Heart Association NYHA 2011 NYHA Classification, the Stages of Heart Failure. Accessed on 14 July 2014. Available online at Heart Failure Society of America: http://www.abouthf.org/questions_stages.htm.

Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med. 2005;143:317-326.

http://www.renal.org/information-resources/the-uk-eckd-guide/ckd-stages#sthash.u0MhYkto.dpbsRennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one HFA pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. Drugs. 2009;69(5):549-65.

Tashkin DP, Rennard SI, Martin P, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. Drugs. 2008; 68(14):1975 2000.

Witek TJ Jr, Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. Eur Respir J. 2003;21(2):267-272.

12 APPENDICES

Appendix 1 Spirometry Performance Recommendations

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

The following instructions are supported by ATS/ERS defined criteria [Miller 2005].

FEV_1 AND FVC MANEUVERS

Equipment Requirements

The spirometer must be capable of accumulating volume for ≥15 s (longer times are recommended) and measuring volumes of ≥8 L (body temperature (i.e., 37°C), ambient pressure, saturated with water vapor, 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 vs. volume provide more detail for the initial portion (first 1 s) of the FVC maneuver. Since this portion of the maneuver, particularly the peak expiratory flow rate, 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 2 units of flow per 1 unit of volume.

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

Validation

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

Quality Control

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

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

Table A1-2. Summary of Equipment Quality Control

Test	Minimal Interval	Action
Volume	Daily	Calibration check with a 3-L syringe
Leak	Daily	2 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, e.g., ±3% of true. If a device fails its calibration check, then new calibration procedure or equipment maintenance is required. Calibration checks must be undertaken daily, or more frequently, if specified by the manufacturer. The syringe used to check the volume calibration of spirometers must have an accuracy of ±15 mL or ±0.5% of the full scale (15 mL for a 3-L syringe), and the manufacturer must provide recommendations concerning appropriate intervals between syringe calibration checks. Users should be aware that a syringe with an adjustable or variable stop may be out of calibration if the stop is reset or accidentally moved. Calibration syringes should be periodically (e.g., monthly) leak tested at more than one volume up to their maximum; this can be done by attempting to empty them with the outlet corked. A dropped or damaged syringe should be considered out of calibration until it is checked.

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

Quality Control for Volume-Measuring Devices

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

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

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

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

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

Quality Control for Flow-Measuring Devices

With regards to volume accuracy, calibration checks must be undertaken at least daily, using a 3-L syringe discharged at least three times to give a range of flows varying between 0.5 and 12 $L\text{-}s^{-1}$ (with 3-L injection times of 6 s and 0.5 s). The volume at each flow should meet the accuracy requirement of ±3.5%. For devices using disposable flow sensors, a new sensor from the supply used for subject 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 AND 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 (i.e., in some research/surveillance applications). Instrumentation recommendations should be followed to provide accurate spirometric data and information that is comparable from laboratory to laboratory and from one time period to another. The accuracy of a spirometry system depends on characteristics of the entire system, from the volume or flow transducer and the use of an in-line filter, to the recorder, display or processor. Changes in any aspect of the equipment or errors at any step in the process can affect the accuracy of the results. For example, if the BTPS correction factor is wrong, an accurately measured FVC will be incorrectly reported. Spirometers are not required to measure all of the indices in Table A1-3, but must meet the recommendations for those that are measured. Accuracy and repeatability recommendations apply over the entire volume range of the instrument.

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

Test	Range/Accuracy (BTPS)	Flow Range ($L \cdot s^{-1}$)	Resistance and Back Pressure	Test Signal
VC	0.5–8 L, ±3% of reading or ±0.050 L, whichever is greater	0-14		3-L calibration syringe
FVC	0.5–8 L, ±3% of reading or ±0.050 L, whichever is greater	0-14	<1.5 cmH_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	<1.5 cmH_2O L^{-1} s^{-1} (0.15 kPa $L^{-1}s^{-1}$)	24 ATS waveforms
Time Zero	The timepoint from which all FEV_1 measurements are taken		Back extrapolation	

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 minutes), continuous temperature corrections may be necessary. Spirometer users should be aware of potential problems with testing performed at lower ambient temperatures: 17°C is the lower limit for ambient temperature, unless a manufacturer states that their spirometer will operate accurately at lower ambient temperatures. If barometric pressure is not used in calculating the BTPS correction factor, the range of barometric pressures over which the BTPS correction factor is valid must be published.

Appendix 2 Spirometry Assessment Criteria

Acceptable Versus Usable Tests

***Acceptable* tests must meet the following seven criteria:**

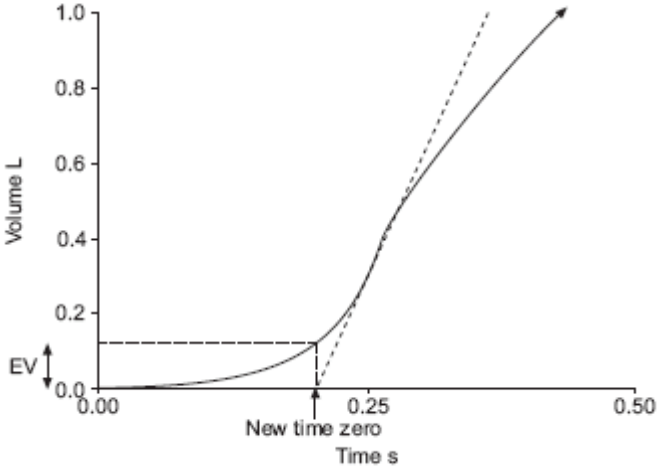
Acceptable start of exhalation with brisk upstroke, no hesitation or false start, and back EV <5% of FVC or 0.150 L, whichever is the greater. (See example in

1. Figure 2. Example of a Usable Spirogram below).
2. No cough during the first second.
3. No valsalva maneuver.
4. No leak.
5. No obstruction of mouthpiece.
6. No extra breaths.
7. Plateau achieved, 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."

Useable 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 based on the three best usable trials with observed limitations.

Figure 2. Example of a Usable Spirogram



Abbreviations: EV=back extrapolated 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 peak expiratory flow

rate, to determine the new "time zero." Forced vital capacity-4.291 L; EV-0.123 L (2.9% FVC): back extrapolation line through peak expiratory flow rate.

Between-Maneuver Reproducibility Criteria

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

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

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

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

Appendix 3 Classification of COPD Severity - GOLD Guidelines (2014)

The GOLD staging system classifies people with COPD based on their degree of airflow limitation (obstruction). The airflow limitation is measured during PFTs.

Because of lung damage, people with COPD take longer to blow air out. This impairment is called obstruction or airflow limitation. An FEV_1 less than 70% of FVC can make the diagnosis of COPD in someone with compatible symptoms and history.

In GOLD COPD, classifications are then used to describe the severity of the obstruction or airflow limitation based on post-bronchodilator FEV_1 [GOLD, 2014].

Table A3-1. Classification of Severity of Airflow Limitation in COPD (Based on Post-bronchodilator FEV_1)

Stage I	Mild COPD	$FEV_1/FVC<0.70$	$FEV_1 \geq 80\%$ normal
Stage II	Moderate COPD	$FEV_1/FVC<0.70$	FEV_1 50% to <80% normal
Stage III	Severe COPD	$FEV_1/FVC<0.70$	FEV_1 30% to <50% normal
Stage IV	Very Severe COPD	$FEV_1/FVC<0.70$	FEV_1 <30% normal

Abbreviations: COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity

Appendix 4 Subject Instructions for Use of BGF MDI, GFF MDI, and BFF MDI

How do I store the Inhaler?

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

For Oral Inhalation Only

Parts of the Inhaler:

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

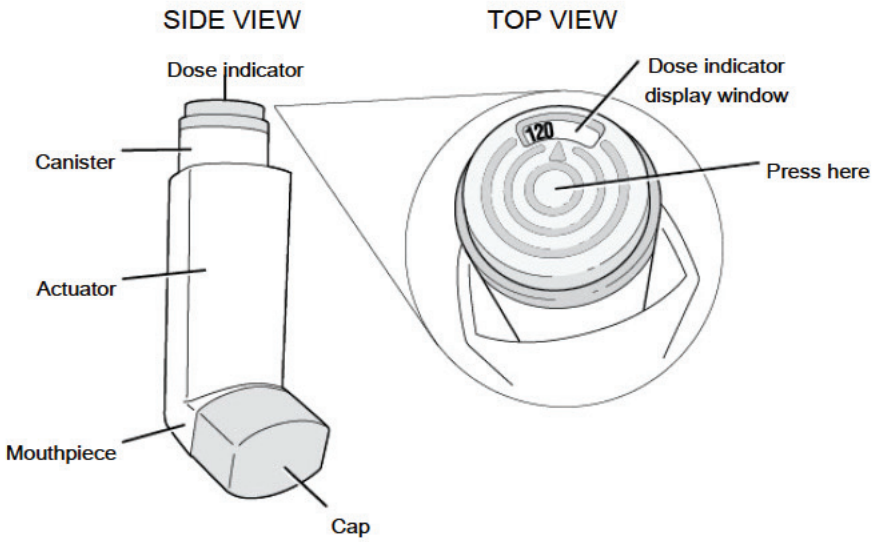


Figure 1

- The **Dose indicator** lets you know about how many puffs are left in your inhaler and is the part of the inhaler that is pressed to dispense a puff of medication. **See Figure 1**.
- The **Dose indicator** should be pointing just to the right of 120 when your inhaler is new. **See Figure 1**.
- The **Dose indicator** has numbers for every 20 puffs. The **Dose indicator** display will move after every tenth puff.
- For example, if the **Dose indicator** is pointing to 120 (**see Figure 2a**) and you take 10 puffs it will move between 120 and 100. This means that there

are 110 puffs of medicine left (**see Figure 2b**). After 10 more puffs are used, the **Dose indicator** pointer will move to the number 100. This means that there are 100 puffs of medicine left (**see Figure 2c)**.

Figure 2a
120 puffs

Figure 2b
110 puffs

Figure 2c
100 puffs

- The **Dose indicator** number will continue to change after every 20 puffs.
- When the number in the **Dose indicator** window changes to 20 and the color behind the number changes to red, this means that there are only 20 puffs left in your inhaler. **See Figure 2d.**

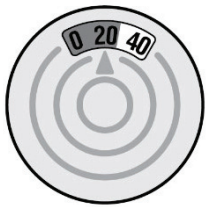


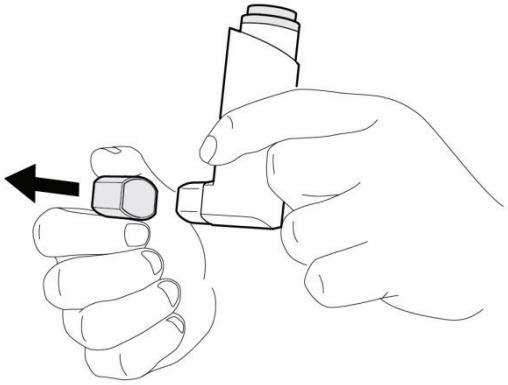
Figure 2d

Preparing the Inhaler for Use:

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

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

Figure 3



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

Priming the Inhaler:

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

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

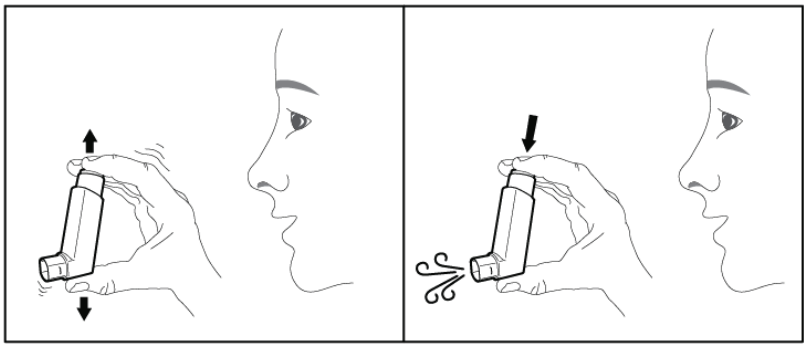


Figure 4a

Figure 4b

Using the Inhaler:

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

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

- **Step 1**: Remove the **Cap** from the **Mouthpiece**.
- **Step 2**: Shake the inhaler well before each puff.
- **Step 3**: While holding the inhaler with the **Mouthpiece** pointing towards you breathe out through your mouth to empty as much air from your lungs as possible.
- **Step 4**: Close your lips around the **Mouthpiece** and tilt your head back slightly to make sure your tongue is away from the **Mouthpiece**.
- **Step 5**: Take a deep breath in (inhale) slowly through your mouth while pressing down firmly on the center (not 'off center') of the **Dose indicator** until the **Canister** stops moving in the **Actuator** and a puff has been released. Then, stop pressing the **Dose indicator**.
- **Step 6**: When you have finished breathing in, remove the **Mouthpiece** from your mouth and hold your breath for 10 seconds or as long as comfortable.
- **Step 7**: Then, breathe out normally.

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

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

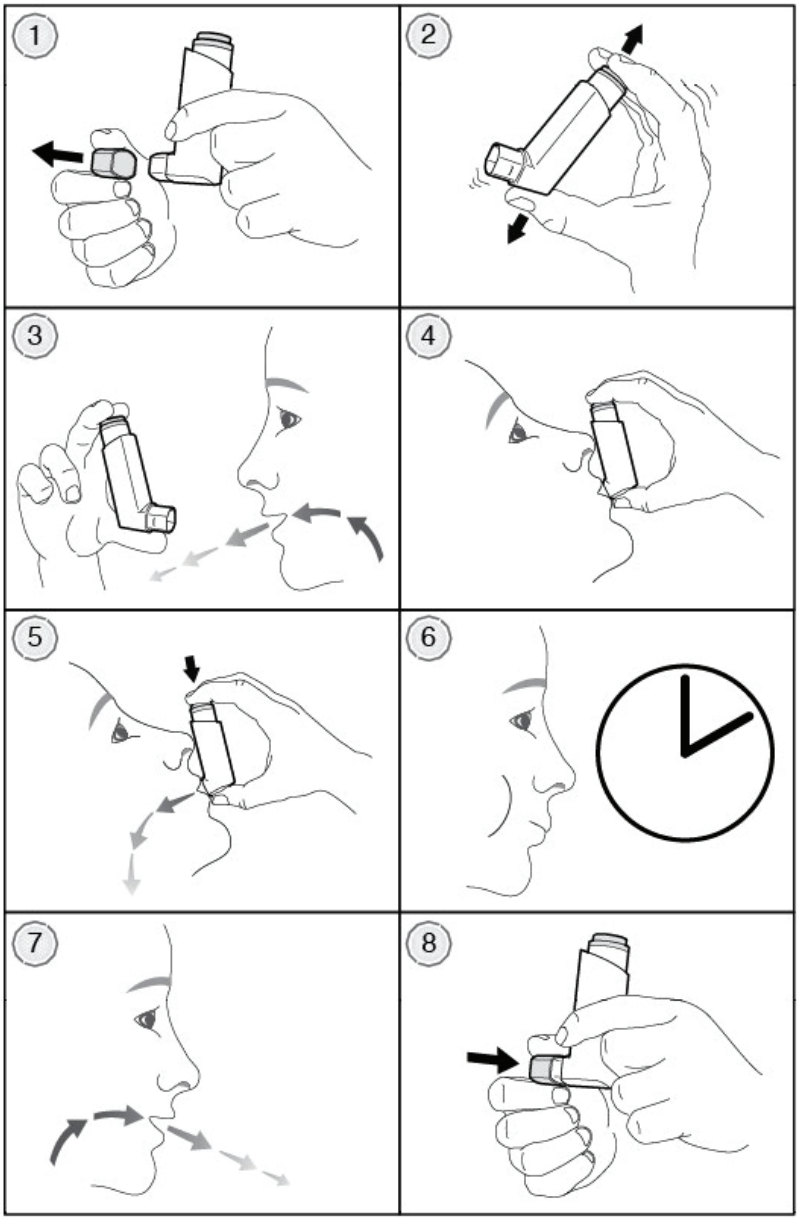


Figure 5

How to clean the Inhaler:

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

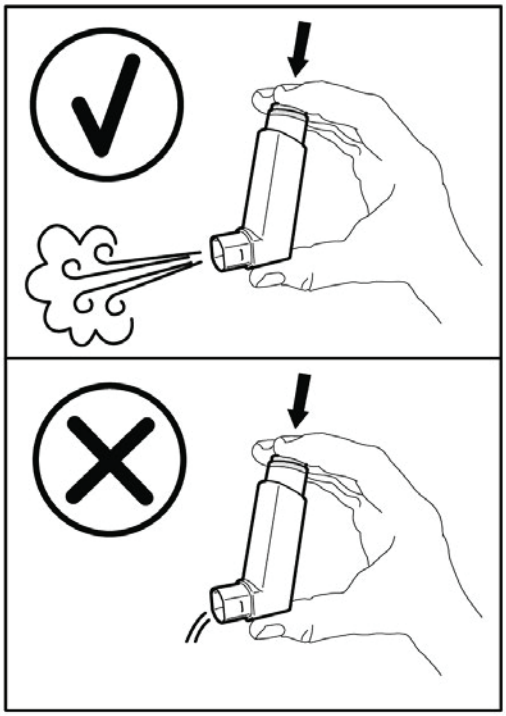
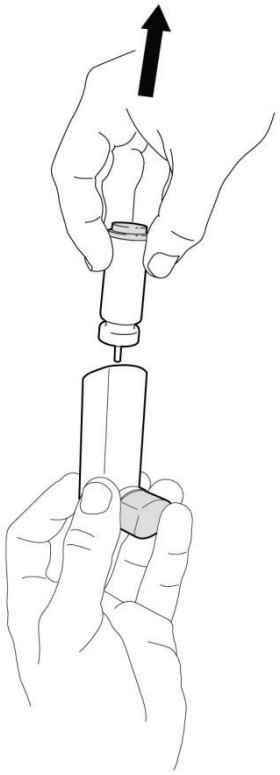


Figure 6

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**).

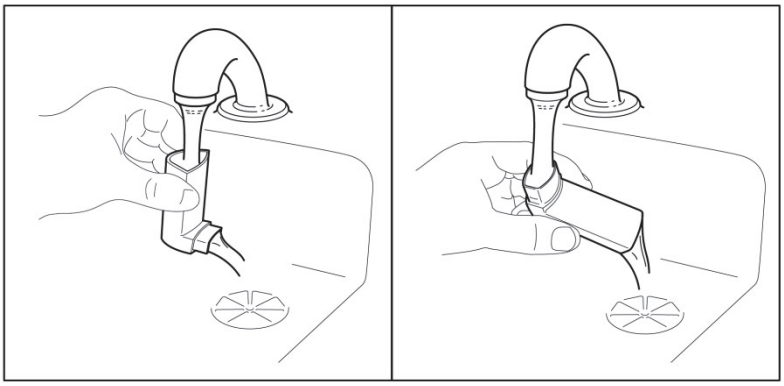


Figure 8

- **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.

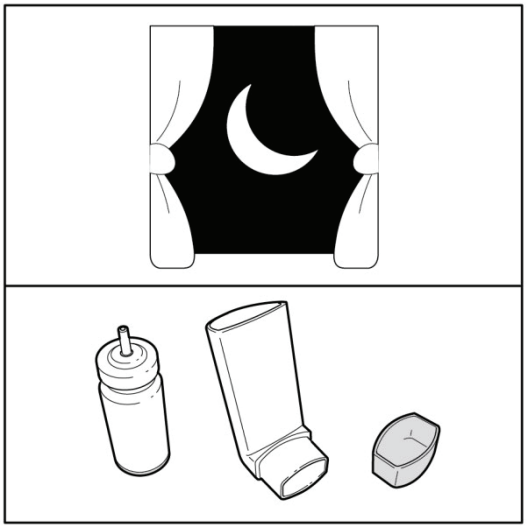


Figure 9

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.

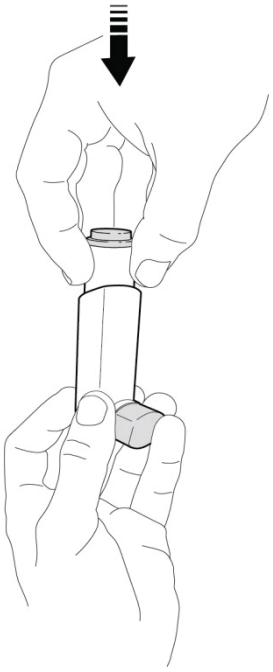


Figure 10

- 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 5 Instructions for Use of Atrovent® HFA Inhalation Aerosol Device

INSTRUCTIONS FOR USE
Atrovent® HFA
(ipratropium bromide HFA)
Inhalation Aerosol

Read the Instructions for Use before using your ATROVENT HFA and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

Use ATROVENT HFA exactly as your healthcare provider tells you to. Do not change your dose or how often you use ATROVENT HFA without talking with your healthcare provider.

Tell your doctor about all the medicines you take. ATROVENT HFA may affect the way some other medicines work and some other medicines may affect the way ATROVENT HFA works.

Important information about using ATROVENT HFA

- You do not have to shake ATROVENT HFA before using it.
- **ATROVENT HFA** should be "primed" 2 times before you use the first dose of a new ATROVENT HFA inhaler or when the inhaler has not been used for more than 3 days.
- To prime, push the canister against the mouthpiece (See Figure 1), allowing the medicine to spray into the air.
- **Do not spray the medicine into your eyes while priming ATROVENT HFA**.

Inhaler Description

ATROVENT HFA Inhalation Aerosol (Figure 1) consists of a metal canister containing the medicine and a mouthpiece that releases the medicine from the canister. The mouthpiece includes a clear colorless sleeve, a white plastic portion and a green protective dust cap.

The inhaler comes with a dose indicator you can see through a small window on the plastic mouthpiece (See Figure 1). A new inhaler first shows “200” in the dose indicator window. The dose indicator will show the approximate number of actuations (sprays) of medicine remaining in the inhaler. As you use the inhaler, the dose indicator will typically rotate during every 5 to 7 actuations (sprays) towards the next decreasing number (See Figure 2).

Figure 1

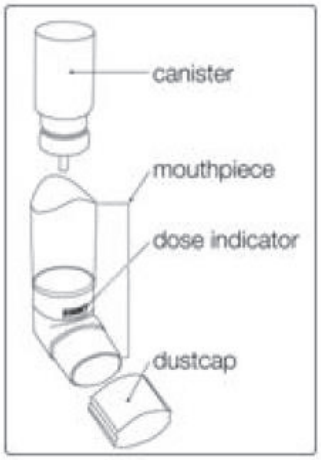


Figure 2

Instructions for Use:

1. **Insert the metal canister into the clear end of the mouthpiece (See Figure 1).** Make sure the canister is fully and firmly inserted into the mouthpiece.
   - The ATROVENT HFA canister is to be used only with the ATROVENT HFA mouthpiece.
   - Do not use the ATROVENT HFA mouthpiece with other inhaled medicines.
2. **Remove the green protective dust cap.** If the cap is not on the mouthpiece, make sure there is nothing in the mouthpiece before use. For best results, the canister should be at room temperature before use.
3. **Breathe out (exhale) deeply through your mouth.** Hold the inhaler upright (See Figure 3), between your thumb and first 2 fingers. Put the mouthpiece in your mouth and close your lips.

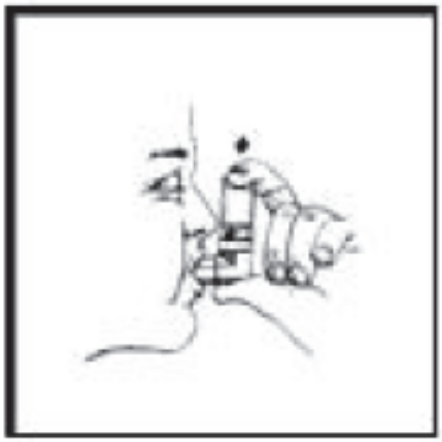
- Keep your eyes closed so that no medicine will be s prayed into your eyes . If sprayed into the eyes, ATROVENT HFA can cause blurry vision and other vision abnormalities, eye pain or discomfort, dilated pupils, or narrow-angle glaucoma or worsening of this condition. If any Combination of these symptoms develops, you should consult your physician immediately.

Figure 3

4. **Breathe in (inhale) slowly through your mouth and at the same time spray the ATROVENT HFA into your mouth.**

   - To spray ATROVENT HFA firmly press the canister against the mouthpiece 1 time (See Figure 4). Keep breathing in deeply.

Figure 4



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

Figure 5

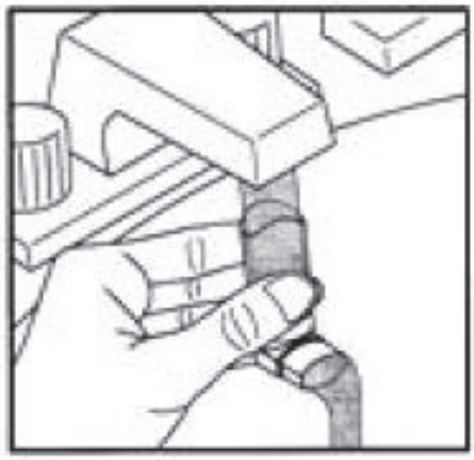
6. **Wait at least 15 seconds and repeat steps 3 to 5 again.**
7. **Replace the green protective dust cap after use.**
8. **Keep the mouthpiece clean.** At least once a week, wash the mouthpiece, shake it to remove excess water and let it air dry all the way (see **Mouthpiece Cleaning Instructions**).

Mouthpiece Cleaning Instructions:

Step A. Remove and set aside the canister and dust cap from the mouthpiece (See Figure 1).

Step B. Wash the mouthpiece through the top and bottom with warm running water for at least 30 seconds (See Figure 6). Do not use anything other than water to wash the mouthpiece.

Figure 6



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

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

Step E. Replace the green protective dust cap.

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

9. When to get a new ATROVENT HFA inhaler.

There are approximately 40 actuations (sprays) left when the dose indicator displays “40,” where the background changes from green to red (See Figure 7a). This is when you need to refill your prescription or ask your doctor if you need another prescription for ATROVENT HFA inhalation aerosol.

The background color will be all red when the indicator approaches 20. The indicator will stop moving at “0”. Discard the inhaler once the dose indicator displays “0” (See Figure 7b). Even though the canister may not be empty, you cannot be sure of the amount of medicine in each actuation (spray) once the dose indicator displays “0”.

Figure 7a

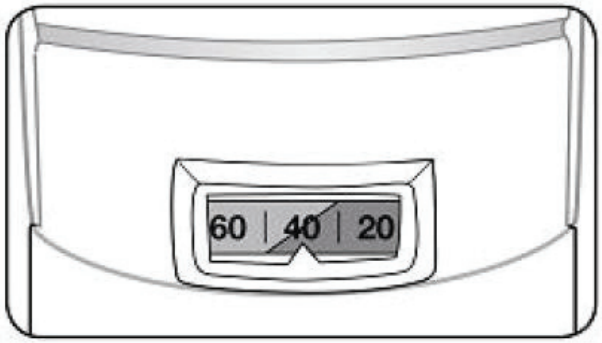
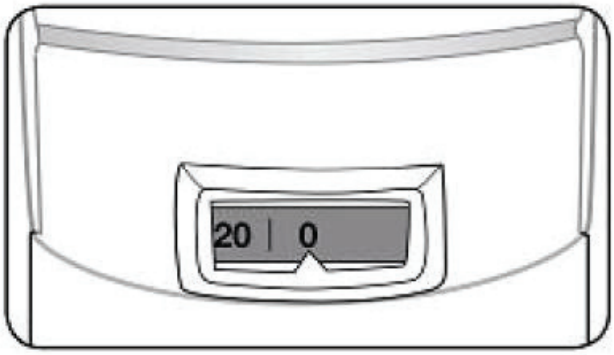


Figure 7b



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

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

Keep ATROVENT HFA and all medicines out of the reach of children.

Address medical inquiries to: http://us.boehringer-ingelheim.com, (800) 542-6257 or (800) 459-9906 TTY.

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

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA
Licensed from:
Boehringer Ingelheim International GmbH

IT1902II122012
10003001/09
Revised: August 2012

Atrovent HFA (ipratropium bromide HFA)
NDC 0597-0087-17
200 metered actuations

Appendix 6 Instructions for Use of Ventolin HFA Inhaler

Instructions for Use
For Oral Inhalation Only
Your VENTOLIN HFA inhaler

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

Figure A

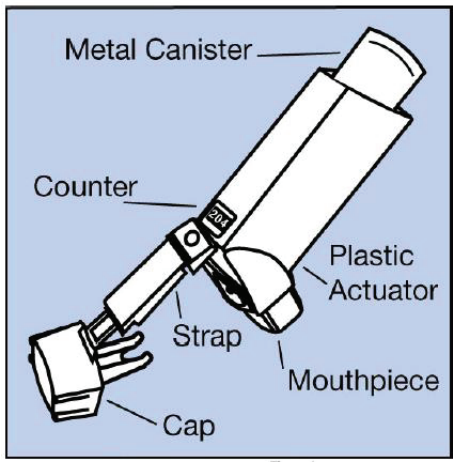


Figure A

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

Figure B

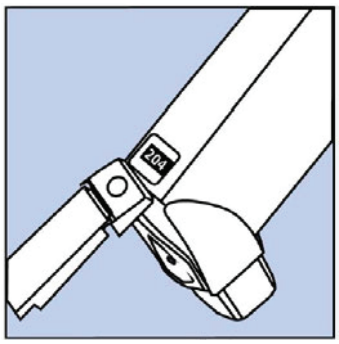


Figure B

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

Before using your VENTOLIN HFA inhaler

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

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

Figure C

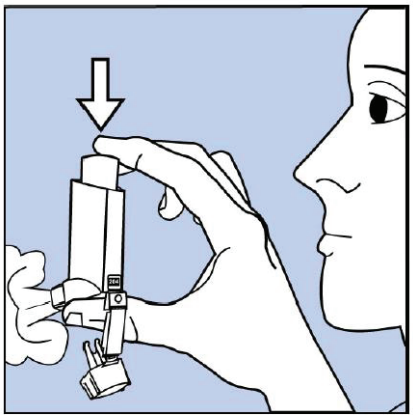


Figure C

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

Figure D

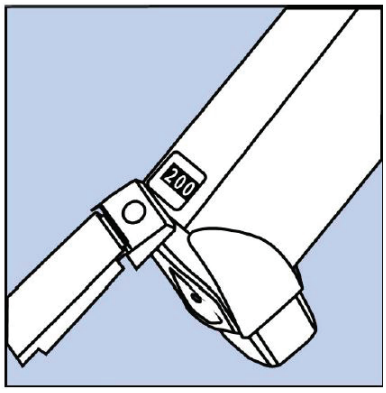


Figure D

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

How to use your VENTOLIN HFA inhaler

Follow these steps every time you use VENTOLIN HFA.

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

Shake the inhaler well before each spray.

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

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

Figure E

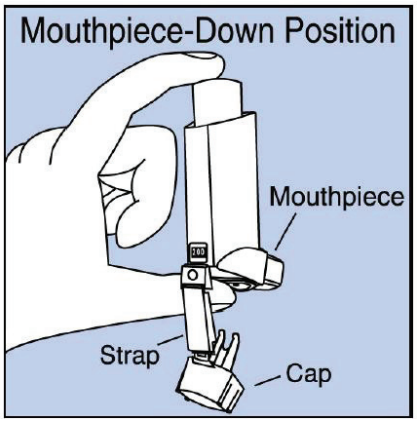


Figure E

Step 3. Breathe out through your mouth and push as much air from your lungs as you can. Put the mouthpiece in your mouth and close your lips around it. **See Figure F.**

Figure F

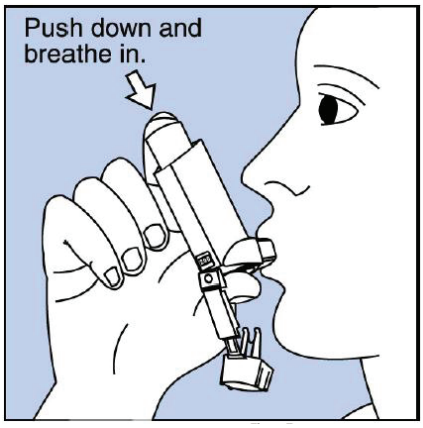


Figure F

Step 4. Push the top of the canister **all the way down** while you breathe in deeply and slowly through your mouth. **See Figure F.**

Step 5. After the spray comes out, take your finger off the canister. After you have breathed in all the way, take the inhaler out of your mouth and close your mouth.

Step 6. **Hold your breath for about 10 seconds,** or for as long as is comfortable. **Breathe out slowly as long as you can.**

If your healthcare provider has told you to use more sprays, wait 1 minute and shake the inhaler again. Repeat Steps 2 through Step 6.

Step 7. Put the cap back on the mouthpiece after every time you use the inhaler. Make sure it snaps firmly into place.

Cleaning your VENTOLIN HFA inhaler

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

Figure G

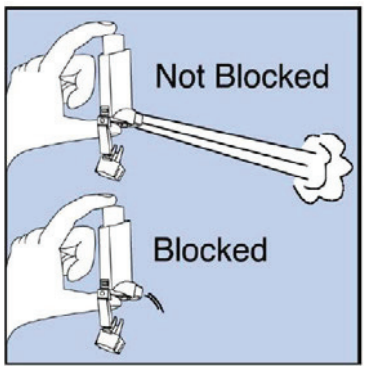


Figure G

Step 8. Take the canister out of the actuator and take the cap off the mouthpiece. The strap on the cap will stay attached to the actuator.

Step 9. Hold the actuator under the faucet and run warm water through it for about 30 seconds. **See Figure H.**

Figure H

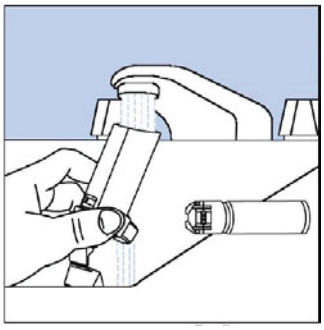


Figure H

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

Figure I

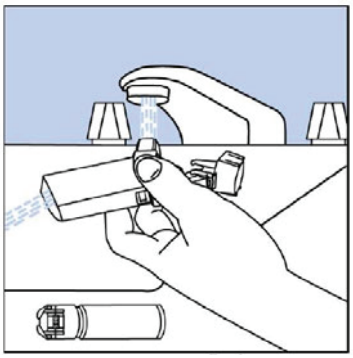


Figure I

Step 11. Shake off as much water from the actuator as you can. Look into the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat Steps 9 and 10.

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

Figure J

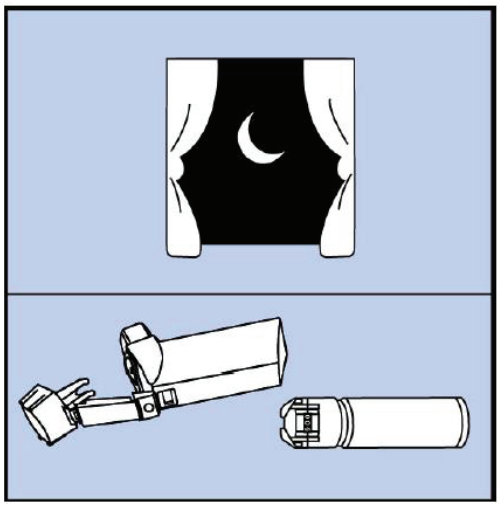


Figure J

Step 13. When the actuator is dry, put the protective cap on the mouthpiece and then put the canister in the actuator and make sure it fits firmly. Shake the inhaler well, remove the cap, and spray the inhaler once into the air away from your face. (The counter will count down by 1 number.) Put the cap back on
the mouthpiece.

If you need to use your inhaler before the actuator is completely dry:

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

Replacing your VENTOLIN HFA inhaler:

- **When the counter reads 020**, you should refill your prescription or ask your healthcare provider if you need another prescription for VENTOLIN HFA.
- **Throw the inhaler away** when the counter reads **000** or 12 months after you opened the foil pouch, whichever comes first. You should not keep using the inhaler when the counter reads **000** because you will not receive the right amount of medicine.

- **Do not use the inhaler** after the expiration date, which is on the packaging it comes in.

For correct use of your VENTOLIN HFA inhaler, remember:

- The canister should always fit firmly in the actuator.
- Breathe in deeply and slowly to make sure you get all the medicine.
- Hold your breath for about 10 seconds after breathing in the medicine. Then breathe out fully.
- Always keep the protective cap on the mouthpiece when your inhaler is not in use.
- Always store your inhaler with the mouthpiece pointing down.
- Clean your inhaler at least 1 time each week.

If you have questions about VENTOLIN HFA or how to use your inhaler, call GlaxoSmithKline (GSK) at 1-888-825-5249 or visit www.ventolin.com.

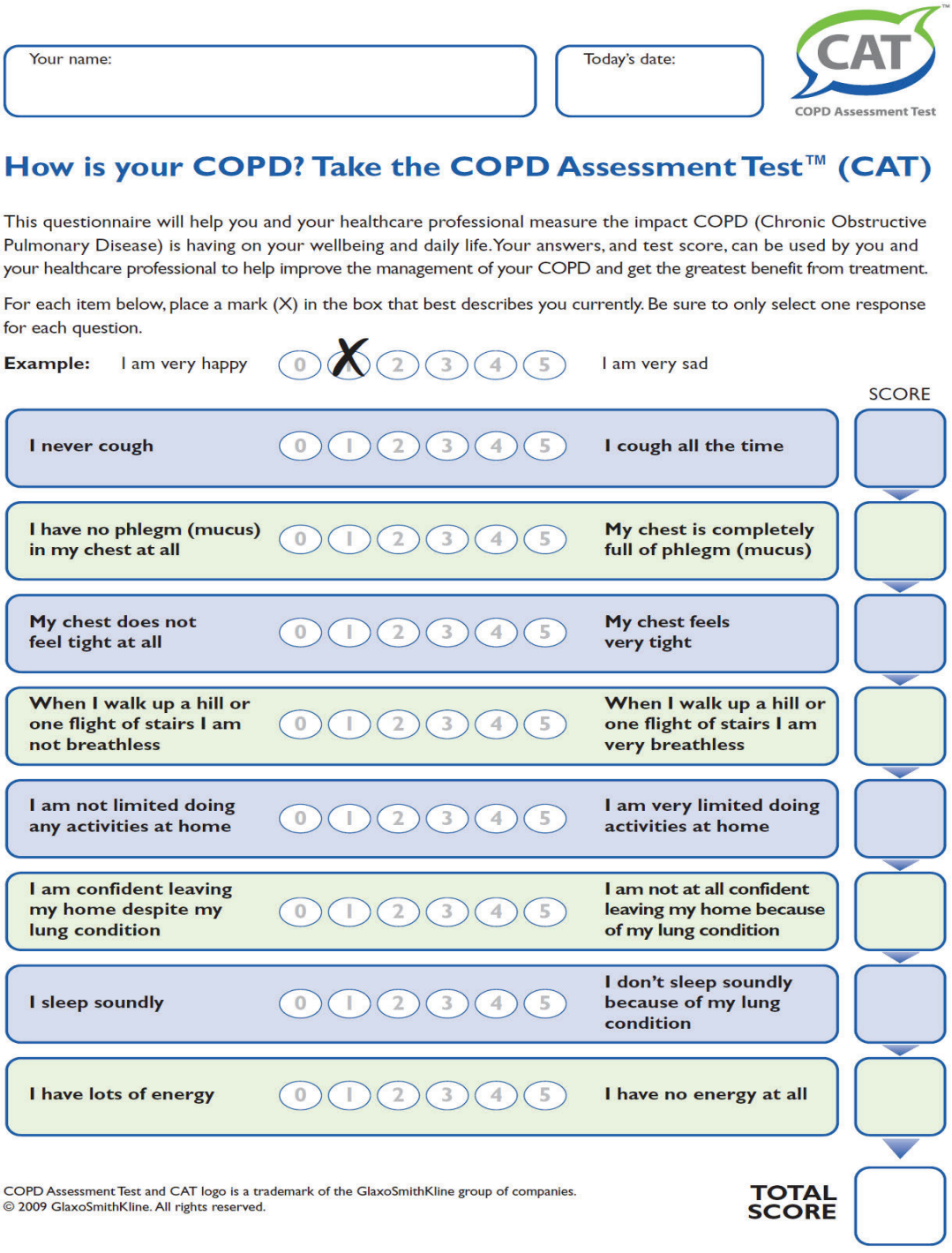
This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

VENTOLIN is a registered trademark of the GSK group of companies.
GlaxoSmithKline
Research Triangle Park, NC 27709

December 2014
VNT:9PIL

Appendix 7 COPD Assessment Test

(The CAT in English is found online at: www.catestonline.org/english/indexEN.htm); the CAT in other languages is found online at: http://www.catestonline.org/)



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	

COPD Assessment Test and CAT logo is a trademark of the GlaxoSmithKline group of companies.
© 2009 GlaxoSmithKline. All rights reserved.

Appendix 8 St. George's Respiratory Questionnaire

(*The sample provided here is for illustrative purposes only*)

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

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

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

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

Before completing the rest of the questionnaire:

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

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

P.W. Jones, PhD FRCP
Professor of Respiratory Medicine,
St. George's University of London,
Jenner Wing,
Cranmer Terrace,
London SW17 ORE, UK.

Tel. +44 (0) 20 8725 5371
Fax +44 (0) 20 8725 5955

USA / US English version 1

continued...

f:\institut\cultadep\project\gsk1881\question\final versions\sgrqusaq.doc 18/04/03

St. George's Respiratory Questionnaire
PART 1

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

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

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

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

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

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

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

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

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

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

USA / US English version 2

continued…

f:\inadhu\cu\adap\project\gsk1881\question\final versions\sgrqusaq.doc 18/04/03

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

continued…

f:\institut\cu\tadap\project\gsk1881\questionl\final versions\sgrqusaq.doc 18/04/03

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

continued…

f:\institut\cutedap\project\gsk18811\questionnaire versions\sgrqusaq.doc 18/04/03

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...

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

f:\inst\tu\cultadap\project\gsk1881\question\final versions\sgqusaq.doc 18/04/03

Appendix 9 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 10 EuroQol 5 Dimensions 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 ☐

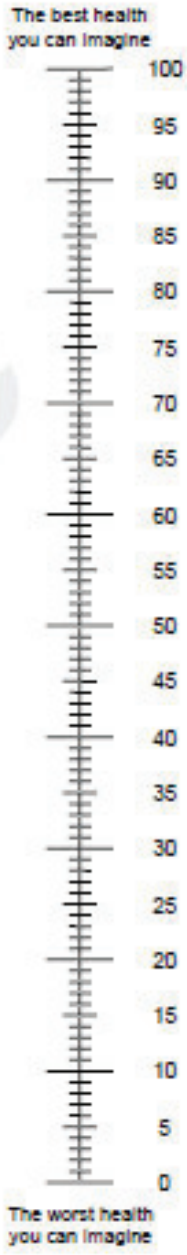
ANXIETY / DEPRESSION

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 = ☐



3

Appendix 11 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
Copyright	EXACT© 2013, Evidera, Inc. All rights reserved.	EXACT© 2013, Evidera, Inc. All rights reserved.

Training Material	Recommended Text	Translation (if available)
Standardized instruction given to patients with PDA training and with take-home instruction manual	Please complete your diary every evening, just before you go to bed.	Please complete your diary every evening, just before you go to bed.

Appendix 12 Dose Indicator Display Reading Instructions

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

130 Count (Actuation) Version Shown				
 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 13 Rules for Evaluation of Abnormal Liver Laboratory Values

INTRODUCTION

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

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

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

DEFINITIONS

- Potential Hy's Law

The levels of AST or ALT ≥3x ULN 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, e.g., elevated ALP indicating cholestasis, viral hepatitis, or another drug. The elevations do not have to occur at the same time or within a specified time frame.

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

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

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

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

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

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

FOLLOW-UP

Potential Hy's Law Criteria not met

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

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

Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

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

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

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

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

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

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

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

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

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

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

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

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

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

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

Appendix 14 Sponsor Signatory

Study Title:	A Randomized, Double Blind, Multi Center, Parallel Group Study to Assess the Efficacy and Safety of PT010 Relative to PT003 and PT009 on COPD Exacerbations over a 52 Week Treatment Period in Subjects With Moderate to Very Severe COPD
Study Number:	PT010005-05
Final Date:	Version 6.1, 21 June 2019

Signature: [redacted]

Name: [redacted]

Title: [redacted]

Appendix 15 Investigator's Agreement and Signature Page

Study Title: A Randomized, Double Blind, Multi Center, Parallel Group Study to Assess the Efficacy and Safety of PT010 Relative to PT003 and PT009 on COPD Exacerbations over a 52 Week Treatment Period in Subjects With Moderate to Very Severe COPD

Study Number: PT010005-05 **Final Date:** Version 6.1, 21 June 2019

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with the protocol and with any other study conduct procedures provided by Pearl Therapeutics, Inc. (hereafter referred to as Pearl)
- Not to implement any changes to the protocol without agreement from Pearl and prior review and written approval from the IRB/IEC, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am aware of and will comply with 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 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 eCRFs.
- To allow authorized representatives of Pearl or regulatory authority representatives to conduct on-site visits to review, audit and copy study documents. I will personally meet with these representatives to answer any study-related questions.

Signature:_____ Date:_____

Name:_____

Site Name: _____