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**Revised Clinical Study Protocol**

Study Code	PT010011
NCT #	NCT03311373
Version	Ver. 1
Date	11 September 2017

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**A Randomized, Double-Blind, Chronic Dosing (24 Weeks),  
Placebo-Controlled, Parallel Group, Multi-Center Study to Assess  
the Efficacy and Safety of PT003, PT005, and PT001 in Subjects  
with Moderate to Very Severe COPD, Compared with Placebo**

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

Amendment No.	Date of Amendment
Version 1	11 September 2017

## Clinical Trial Protocol: PT010011-00

**Study Title:** A Randomized, Open-label, Single-dose, Single-center, Crossover Study in Healthy Subjects to Assess the Relative Bioavailability of PT010 Administered With and Without a Spacer, and With and Without Oral Charcoal

**Study Number:** PT010011

**Study Phase:** I

**Product Name:** PT010: Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol, Metered Dose Inhaler (BGF MDI)

**Indication:** Chronic Obstructive Pulmonary Disease

**Investigators:** Single Center

**Sponsor:** Pearl Therapeutics, Inc.  
[REDACTED]  
[REDACTED]  
[REDACTED]

**Sponsor Contact:** [REDACTED]

	Version Number	Date
<b>Original Protocol:</b>	1.0	11 September 2017

### Confidentiality Statement

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## SYNOPSIS

**Sponsor:**

Pearl Therapeutics, Inc.  
[REDACTED]

**Name of Study Drug:**

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

**Name of Active Ingredient:**

Budesonide, Glycopyrronium, and Formoterol Fumarate

**Study Title:**

A Randomized, Open-label, Single-dose, Single center, Crossover Study in Healthy Subjects to Assess the Relative Bioavailability of PT010 Administered With and Without a Spacer, and With and Without Oral Charcoal

**Study Protocol Number:**

PT010011-00

**Study Phase: I****Primary Objectives:**

- To assess the total systemic exposure of budesonide, glycopyrronium, and formoterol administered as BGF MDI with and without a spacer device
- To assess the lung exposure of budesonide, glycopyrronium, and formoterol administered as BGF MDI with and without oral activated charcoal

**Secondary Objectives:**

- To characterize the pharmacokinetic (PK) profiles of budesonide, glycopyrronium, and formoterol administered as BGF MDI, with and without a spacer device, and with and without oral charcoal
- To assess the safety of single doses of BGF MDI in healthy subjects

**Study Design:**

This is a Phase I, randomized, open-label, single-dose, single-center, crossover study to assess the PK and safety of BGF MDI in healthy subjects (male or female). PK profiles of each active ingredient (budesonide, glycopyrronium, and formoterol), will be determined after administration of BGF MDI with a spacer device (test) and without a spacer device (reference), and with and without the concomitant administration of activated oral charcoal to estimate total systemic exposure and lung exposure, respectively.

The study will comprise the following:

- A screening period with a maximum duration of 28 days.

- Four Treatment Periods during which subjects will be resident from the afternoon before dosing with BGF MDI until at least 24 hours after dosing and discharged on the morning of Day 2 of each Treatment Period. There will be a washout period of 5 to 14 days between Treatment Periods 1, 2, and 3.
- A follow-up phone call will take place within 5 to 7 days following the last administration of BGF MDI.

After providing informed consent, subjects will undergo screening procedures. Subjects meeting eligibility criteria will be enrolled into the study and admitted to the study site as an inpatient on Day -1 of Treatment Period 1, at which time, continuing eligibility will be assessed. Device training will be conducted during screening, on admission to each Treatment Period, and prior to dosing on Day 1 of each Treatment Period. In addition to training with a placebo MDI device, additional inhalation training tools may be used to help ensure the subjects are able to use the MDI device correctly.

Study drug will be administered, under fasted conditions, on the morning of Day 1 of each Treatment Period, at approximately the same time of day throughout the study ( $\pm 30$  minutes). Eligible subjects will receive a single dose of BGF MDI 320/28.8/9.6  $\mu\text{g}$  administered as follows:

- Without a spacer device and without charcoal (regimen A)
- With a spacer device and without charcoal (regimen B)
- Without a spacer device and with charcoal (regimen C)
- With a spacer device and with charcoal (regimen D)

Subjects will receive all 4 regimens (1 regimen per Treatment Period) in 1 of 8 possible regimen sequences: AB CD, AB DC, BA CD, BA DC, CD AB, CD BA, DC AB, or DC BA. These regimen sequences allow for subjects who might drop out after 2 Treatment Periods only to be included in the PK statistical analysis.

Randomization will be performed on the morning of first dosing (Day 1, Treatment Period 1). Randomization codes will be assigned strictly sequentially in ascending order as subjects become eligible.

During their inpatient stay, subjects will undergo safety assessments and have an indwelling intravenous cannula for serial PK blood draws. Subjects will be discharged on the morning of Day 2 of each Treatment Period after all protocol-specified assessments are completed. There will be a washout period of 5 to 14 days between each Treatment Period.

A follow-up phone call will be conducted 5 to 7 days after Treatment Period 4 dosing or after the last dose of study drug, whichever comes first.

### Study Population:

This study will be conducted in healthy male and female subjects, 18 to 40 years of age (inclusive). Approximately 56 subjects will be randomized in order to have approximately 48 evaluable subjects.

### Test Product, Dose, and Mode of Administration:

Product Name & Dose	Product Strength	Dosage Form/ Fill Count	Administration
BGF MDI 320/28.8/9.6 µg ex-actuator	160/14.4/4.8 µg per actuation	MDI/ 120 inhalations	<p><b>Regimen A:</b> 2 inhalations BGF MDI; no spacer device; no oral charcoal – reference formulation/total systemic exposure</p> <p><b>Regimen B:</b> 2 inhalations BGF MDI; AeroChamber Plus Flow-Vu spacer device; no oral charcoal – test formulation/total systemic exposure</p> <p><b>Regimen C:</b> 2 inhalations BGF MDI; no spacer device; with oral charcoal – reference formulation/lung exposure</p> <p><b>Regimen D:</b> 2 inhalations BGF MDI; AeroChamber Plus Flow-Vu spacer device; with oral charcoal – test formulation/lung exposure</p>

### Non-Investigational Medicinal Product, Dose, and Mode of Administration:

Manufacturer:	Perrigo
Formulation:	Actidose-Aqua <sup>®</sup> (activated charcoal) 50 g for oral suspension
Strength/Concentration:	50 g/240 mL
Dose regimen:	<ul style="list-style-type: none"> <li>Immediately prior to study drug dose: 10g (approximately 48 mL of suspension) which will be mouth-rinsed and swallowed</li> <li>Immediately after study drug dosing: 10 g (approximately 48 mL of suspension) which will be mouth-rinsed and swallowed; repeat at 1 hour and 2 hours post-dose</li> </ul>
Route of administration:	Oral
Regimen:	<p><b>Regimen C:</b> 2 inhalations BGF MDI; no spacer device; with oral charcoal – reference formulation/lung exposure</p> <p><b>Regimen D:</b> 2 inhalations BGF MDI; AeroChamber Plus Flow-Vu spacer device; with oral charcoal – test formulation/lung exposure</p>

### Duration of Treatment:

Each subject will be involved in the study for approximately 13 weeks.

### PK Endpoints:

Pharmacokinetics following administration of BGF MDI will be assessed using plasma concentrations of budesonide, glycopyrronium, and formoterol pre-dose and at various times post-dose on Day 1 of each Treatment Period.

### Primary PK parameters

- Maximum plasma concentration ( $C_{\max}$ )
- Area under the plasma concentration-time curve from 0 the time of the last measurable plasma concentration ( $AUC_{0-t_{\text{last}}}$ )

**Secondary PK parameters**

- Time to maximum plasma concentration ( $t_{\max}$ )
- Area under the plasma concentration-time curve from 0 extrapolated to infinity ( $AUC_{0-\infty}$ );

**Safety Assessments:**

The safety and tolerability profile of BGF MDI will be assessed using adverse event reporting, vital sign values, clinical laboratory values, and findings from 12-lead electrocardiograms

**Statistical Methods:**

**PK:**

The PK analyses will be performed for the PK population. Pharmacokinetic parameters will be calculated using non-compartmental analysis.

The treatment ratio of BGF MDI with spacer versus BGF MDI without spacer, both in the presence and absence of charcoal, will be calculated for budesonide, glycopyrronium, and formoterol.

Treatment comparisons of primary PK parameters will be assessed on the difference of log transformed  $C_{\max}$ ,  $AUC_{0-t_{\text{last}}}$ , and  $AUC_{0-\infty}$  of budesonide, glycopyrronium, and formoterol using a 2-sided 90% confidence interval (CI) approach based on an analysis of variance model including period and sequence, regimen, and subject as fixed effects. Estimated geometric mean ratios with 90% CIs will be provided.

**Safety:**

All safety analyses will be performed on the Safety Population. Descriptive statistics will be provided for all safety assessments.

**Determination of sample size:**

Even though this study is being conducted for estimation purposes,

[REDACTED]

[REDACTED] a sample size of 48 subjects completing the study will provide 90% probability to observe a 1-sided 95% lower confidence bound for the geometric mean ratio (D/C) that is greater than 80%.

**Date of Original Protocol:** 11 September 2017

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AUC <sub>0-tlast</sub>	Area under the plasma concentration-time curve from 0 to the time of the last measurable plasma concentration
AUC <sub>0-∞</sub>	Area under the plasma concentration-time curve from 0 extrapolated to infinity
BFF MDI	Budesonide and Formoterol Fumarate Metered Dose Inhaler
BGF MDI	Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler
BP	Blood Pressure
CFR	Code of Federal Regulations
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation (according to National Kidney Disease Education Program)
CL/F	Apparent total body clearance
C <sub>max</sub>	Maximum plasma concentration
COPD	Chronic obstructive pulmonary disease
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FSH	Follicle stimulating hormone
FDA	Food and Drug Administration
FEV <sub>1</sub>	Forced expiratory volume in 1 second
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HbsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled corticosteroid

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IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISMPP	International Society for Medical Publications Professionals
IV	Intravenous
LABA	Long-acting $\beta_2$ -agonist
LAMA	Long-acting muscarinic antagonist
LLQ	Lower limit of quantification
$\lambda_z$	Terminal elimination rate constant
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
NCA	Non-compartmental analysis
OTC	Over-the-counter
PK	Pharmacokinetics
PT009	Budesonide and Formoterol Fumarate Inhalation Aerosol
PT010	Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol
QTcF	Fridericia's corrected QT interval
SAE	Serious adverse event
SAP	Statistical analysis plan
$t_{1/2}$	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
$t_{last}$	Time to last measurable plasma concentration
$t_{max}$	Time to maximum plasma concentration
US	United States
Vd/F	Apparent volume of distribution

## 1 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases, the most common of which is cigarette smoke. Exacerbations and comorbidities contribute to the overall severity in individual patients. Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality worldwide and results in a significant economic and social burden that is both substantial and increasing. Pharmacologic therapy in COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance as described in the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2017) guidelines.

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are  $\beta_2$ -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<sub>1</sub>) value of <60% of predicted. Withdrawal from treatment with ICS may lead to exacerbations in some patients. When combined with a long-acting  $\beta_2$ -agonist (LABA), an ICS is more effective than the individual components in improving lung function and quality of life and reducing exacerbations in subjects with moderate to very severe COPD (GOLD 2017).

Pearl Therapeutics, Inc. (hereinafter referred to as the Sponsor) is developing the fixed-dose ICS/long-acting muscarinic antagonist (LAMA)/LABA triple combination product, Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (PT010), hereafter referred to as Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler (BGF MDI), for the treatment of patients with COPD. Budesonide and Formoterol Fumarate Inhalation Aerosol (PT009), hereinafter referred to as Budesonide and Formoterol Fumarate (BFF) MDI, is also being developed as a twice daily (BID) fixed dose ICS/LABA treatment for patients with COPD.

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

Glycopyrronium is a LAMA that exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. Glycopyrronium is approved in many countries in multiple formulations for different indications, including for the treatment of COPD.

Formoterol fumarate is a selective LABA approved worldwide for use in asthma and COPD. In addition, formoterol fumarate is also approved worldwide in combination with budesonide (eg, Symbicort MDI, Symbicort Turbuhaler<sup>®</sup>) for use in patients with asthma and COPD. When inhaled, formoterol fumarate acts locally in the lung as a bronchodilator. Formoterol fumarate stimulates  $\beta_2$  adrenoreceptors in the airways, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction.

In order to improve coordination of inhaler actuation and inspiration, a valved holding chamber (or spacer) may be used with an MDI. A spacer may also reduce the amount of drug that is deposited in the oropharynx. The purpose of this study is to establish the relative bioavailability of budesonide, glycopyrronium, and formoterol after administration of BGF MDI with and without a spacer device in order to include the use of a spacer in the label as required in the European Union. Specifically, budesonide, glycopyrronium, and formoterol delivered via BGF MDI with a spacer device (test) and without a spacer device (reference) will be administered with and without the concomitant administration of activated oral charcoal to estimate total systemic exposure and lung exposure, respectively.

## **2 STUDY OBJECTIVES**

### **2.1 Primary Objectives**

The primary objectives of this study are the following:

- To assess the total systemic exposure of budesonide, glycopyrronium, and formoterol administered as BGF MDI with and without a spacer device
- To assess the lung exposure of budesonide, glycopyrronium, and formoterol administered as BGF MDI with and without activated oral charcoal

### **2.2 Secondary Objectives**

The secondary objectives of this study are the following:

- To characterize the pharmacokinetic (PK) profiles of budesonide, glycopyrronium, and formoterol administered as BGF MDI, with and without a spacer device, and with and without oral charcoal
- To assess the safety of single doses of BGF MDI in healthy subjects

### 3 STUDY ENDPOINTS

#### 3.1 Efficacy Endpoints

Not applicable

#### 3.2 PK Endpoints

The PK after single-dose administration of BGF MDI will be assessed using plasma concentrations of budesonide, glycopyrronium, and formoterol for each regimen.

##### 3.2.1 Primary PK Parameters

- Maximum plasma concentration ( $C_{\max}$ )
- Area under the plasma concentration-time curve from 0 the time of the last measurable plasma concentration ( $AUC_{0-t_{\text{last}}}$ )

##### 3.2.2 Secondary PK Parameters

- Time to maximum plasma concentration ( $t_{\max}$ )
- Area under the plasma concentration-time curve from 0 extrapolated to infinity ( $AUC_{0-\infty}$ );

##### 3.2.3 Other PK parameters

- Apparent terminal elimination half-life ( $t_{1/2}$ )
- Apparent total body clearance ( $CL/F$ )
- Apparent volume of distribution ( $V_d/F$ )<sub>P</sub>
- Termination elimination rate constant ( $\lambda_z$ )
- Time to last measurable plasma concentration ( $t_{\text{last}}$ )

#### 3.3 Safety Endpoints

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

## 4 INVESTIGATIONAL PLAN

### 4.1 Overall Study Design and Plan

This is a Phase I, randomized, open-label, single-dose, single-center, crossover study to assess the PK and safety of BGF MDI in healthy subjects (male or female). The PK profiles of each active ingredient (budesonide, glycopyrronium, and formoterol), will be determined after administration of BGF MDI with a spacer device (test) and without a spacer device (reference), and with and without the concomitant administration of activated oral charcoal to estimate total systemic exposure and lung exposure, respectively.

Figure 4-1 summarizes the overall study design, which will comprise the following:

- A screening period with a maximum duration of 28 days.
- Four Treatment Periods during which subjects will be resident from the afternoon before dosing with BGF MDI until at least 24 hours after dosing and discharged on the morning of Day 2 of each Treatment Period. There will be a washout period of 5 to 14 days between Treatment Periods 1, 2, and 3.
- A follow-up phone call will take place within 5 to 7 days following the last administration of BGF MDI.

After providing informed consent, subjects will undergo screening procedures. Subjects meeting eligibility criteria will be enrolled into the study and admitted to the study site as an inpatient on Day -1 of Treatment Period 1, at which time, continuing eligibility will be assessed. Device training will be conducted during screening, on admission to each Treatment Period, and prior to dosing on Day 1 of each Treatment Period. In addition to training with a placebo MDI device, additional inhalation training tools may be used to help ensure the subjects are able to use the MDI device correctly.

Study drug will be administered, under fasted conditions, on the morning of Day 1 of each Treatment Period, at approximately the same time of day throughout the study ( $\pm 30$  minutes). Eligible subjects will receive a single dose of BGF MDI 320/28.8/9.6  $\mu\text{g}$  administered as follows:

- Without a spacer device and without charcoal (regimen A)
- With a spacer device and without charcoal (regimen B)
- Without a spacer device and with charcoal (regimen C)
- With a spacer device and with charcoal (regimen D)

Subjects will receive all 4 regimens (1 regimen per Treatment Period) in 1 of 8 possible regimen sequences: AB CD, AB DC, BA CD, BA DC, CD AB, CD BA, DC AB, or DC BA.



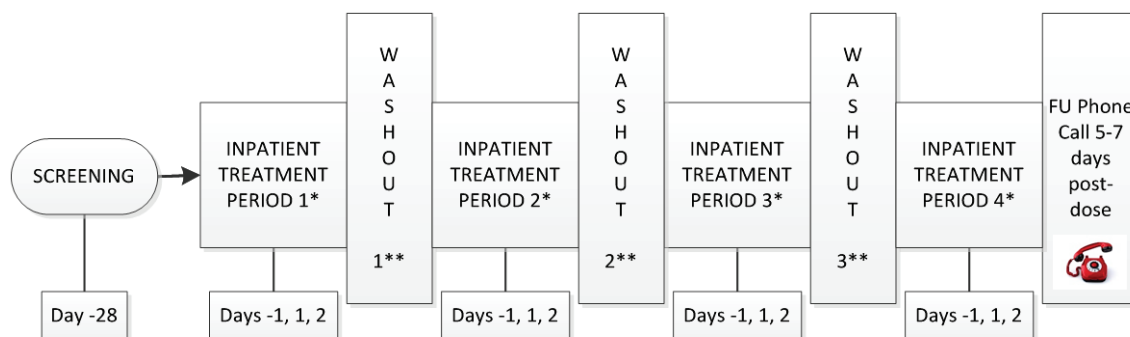
These regimen sequences allow for subjects who might drop out after 2 Treatment Periods only to be included in the PK statistical analysis.

Randomization will be performed on the morning of first dosing (Day 1, Treatment Period 1). Randomization codes will be assigned strictly sequentially in ascending order as subjects become eligible.

During their inpatient stay, subjects will undergo safety assessments and have an indwelling intravenous cannula for serial PK blood draws. Subjects will be discharged on the morning of Day 2 of each Treatment Period after all protocol-specified assessments are completed. There will be a washout period of 5 to 14 days between each Treatment Period.

A follow-up phone call will be conducted 5 to 7 days after Treatment Period 4 dosing or after the last dose of study drug, whichever comes first.

**Figure 4-1 Study Design**



\*BGF 320/28.8/9.6 µg will be administered at each Treatment Period:  
With and without spacer, with and without charcoal (4 regimens; 8 possible regimen sequences)

\*\* Washout is a minimum of 5 to a maximum of 14 days between each Treatment Period

## 4.2 Rationale for Study Design and Control Group

The purpose of this study is to evaluate budesonide, glycopyrronium, and formoterol lung and total systemic exposure following administration of BGF MDI. This will be accomplished by establishing the relative bioavailability of budesonide, glycopyrronium, and formoterol after single-dose administration of BGF MDI with and without a spacer and with and without concurrent oral charcoal administration.

A single dose of BGF MDI 320/28.8/9.6 µg (administered as 2 inhalations of BGF MDI 160/14.4/4.8 µg) will generate sufficient plasma exposure to budesonide, glycopyrronium, and formoterol for the assessment of relative bioavailability.

Considering the elimination half-life of the components of BGF MDI and the time period during which plasma concentrations are above the lower limit of quantification, the sampling period of 24 hours will be sufficient to adequately estimate the PK parameters.

### **4.3 Study Duration**

This study will include a Screening Period of up to 28 days and 4 single-dose Treatment Periods separated by a Washout Period (minimum of 5 days to a maximum of 14 days) for added scheduling flexibility. A follow-up phone call will be conducted 5 to 7 days after completion of the last Treatment Period. The maximum participation in the study for each subject is approximately 13 weeks. The study is anticipated to run for approximately 3 months and should not exceed 6 months.

## 5 STUDY POPULATION SELECTION

### 5.1 Study Population

Approximately 56 healthy male or female subjects will be randomized in this study in order to ensure approximately 48 subjects complete all 4 Treatment Periods. Subjects who withdraw from the study after receiving at least 1 dose of study drug will not be replaced. Subjects who are re-screened will maintain 1 screening number throughout the study. The study will be conducted at a single center in the United States (US).

### 5.2 Inclusion Criteria

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

1. Signed and dated Independent Ethics Committee (IEC)/Institutional Review Board (IRB)-approved Informed Consent Form (ICF) before any protocol-specific screening procedures are performed
2. Male and female subjects 18 to 40 years of age, inclusive
3. Be in good general health as determined by a thorough medical history and physical examination, ECG, vital signs, and clinical laboratory evaluation.
4. Willing and able to complete all study assessments and procedures
5. Agree to one of the following to prevent pregnancy:
  - Non-childbearing potential (ie, physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal, or surgically sterile [defined as having a bilateral oophorectomy, hysterectomy or tubal ligation])
  - Practicing abstinence
  - If a sexually active woman of childbearing potential agrees to prevent pregnancy by using one of the following methods of birth control from the date the ICF is signed until 2 weeks after the final dose of investigational product is taken:
    - Hormonal contraception (eg, oral contraceptive, contraceptive implant, or injectable hormonal contraceptive)
    - Double-barrier birth control (eg, condom plus intrauterine device, diaphragm plus spermicide or condom plus spermicide)
    - Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy
  - If a woman of childbearing potential, have a negative serum pregnancy test at screening
  - 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 study drug until 2 weeks after their last dose, and must not donate sperm during their study participation period.

6. Screening laboratory tests must be within normal range or determined to not be clinically significant by the Investigator. Subjects must also have normal glomerular filtration rate (normal estimated normal glomerular filtration rate [eGFR]  $\geq 90$  mL/min) using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI)
7. Screening ECG must be acceptable to the Investigator
8. Demonstrate correct MDI administration technique

### 5.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study unless otherwise stated:

1. Pregnant or nursing female subjects or subjects who are trying to conceive
2. For female subjects, a positive serum human chorionic gonadotropin (hCG) test at screening or a positive urine hCG at admission for any of the 4 Treatment Periods
3. Subjects with clinically significant neurologic, cardiovascular, hepatic, renal, endocrinologic, pulmonary, hematological, psychiatric, or other medical illness that would interfere with participation in this study
4. Subjects who have cancer that has not been in complete remission for at least 5 years
5. Supine blood pressure (BP)  $>140/90$  mmHg or resting heart rate  $\geq 100$  bpm at screening or baseline (pre-dose on Day 1 of the first Treatment Period)
6. Male subjects with symptomatic prostatic hypertrophy that is clinically significant in the opinion of the Investigator
7. Male subjects with a trans-urethral resection of the prostate or full resection of the prostate within 6 months prior to screening
8. Subjects with bladder neck obstruction or urinary retention that is clinically significant in the opinion of the Investigator
9. History of substance-related disorders (with the exception of caffeine-related and nicotine-related disorders) within 1 year of screening
10. History of smoking or the use of nicotine-containing products within 3 months of screening by self-reporting
11. A positive alcohol breathalyzer or urine drug screen for drugs of abuse at screening or at the beginning of each Treatment Period
12. Treatment with any prescription or non-prescription drugs including vitamins, herbal, and dietary supplements for 28 days or 5 half-lives, whichever is longer, before study drug use including restrictions per Sections 5.5 and 5.6
13. Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) prior to the beginning of the screening Period
14. Subjects with a history of an allergic reaction or hypersensitivity to any drug used in this study or to any component of the formulations used in this study
15. Subjects with anemia that is considered clinically significant by the Investigator.
16. Seropositivity for human immunodeficiency virus (HIV) at screening

17. Positive for hepatitis B surface antigen (HbsAg) or positive hepatitis C antibody at screening
18. Subjects with a history of major surgery within 4 weeks or minor surgery within 2 weeks of screening
19. Subjects with any flu-like syndrome or other respiratory infections within 2 weeks of drug administration or who have been vaccinated with an attenuated live virus within 4 weeks of drug administration
20. Any other condition and/or situation that causes the Investigator to deem a subject unsuitable for the study (eg, inability to medically tolerate the study procedures, or a subject's unwillingness to comply with study-related procedures)
21. Subjects who, in the opinion of the Investigator, have a clinically significant abnormal 12-lead ECG at screening. A clinically significant abnormal ECG includes, but is not limited to, the following:
  - Fridericia corrected QT interval (QTcF) >450 ms for males or >470 ms for females at screening
22. Study Investigators, sub-Investigators and coordinators, and their employees or immediate family members.

#### **5.4 Subject Identification**

All subjects who undergo screening procedures will be assigned a unique screening identification number at screening. Only subjects continuing to meet entry inclusion/exclusion criteria at Treatment Period 1 will be assigned a unique subject randomization number.

#### **5.5 Prior, Concomitant, and Prohibited Medications**

Apart from paracetamol/acetaminophen, hormone replacement therapy and systemic contraceptives, no concomitant medication or therapy will be allowed. The subjects should be instructed that no other medication is allowed, including herbal remedies, vitamin supplements and over the counter (OTC) products, without the consent of the Investigator.

When any medication is required, it should be prescribed by the Investigator. Following consultation with the Medical Monitor, the Investigator must determine whether or not the subject should continue in the study.

The Investigator or designated qualified personnel will assess and record concomitant medication usage on the electronic case report form (eCRF). Concomitant medication usage will be assessed at screening and throughout the study.

#### **5.6 Restrictions During the Study**

The following restrictions apply for the specified times during the study period:

1. On Day 1 of each Treatment Period, subjects will be fasted for at least 6 hours prior to dosing and until after the 4 hours post dose blood draw. No fluids will be allowed apart from water, which can be given until 1 hour prior to dosing and resumed 2 hours after dosing.  
Subjects should not lie fully supine (unless specified for certain assessments) for 4 hours after dosing with BGF MDI.
2. Subjects should not engage in any strenuous activity (eg, marathon, marathon training, or other similar activities) from 72 hours prior to dosing on Day 1 of the first Treatment Period until after Treatment Period 4.
3. Prior to each Treatment Period, subjects should abstain from alcohol for 72 hours prior to admission to the study unit until after their last PK sample is collected. Between Treatment Periods, subjects should consume no more than 2 units of alcohol per day.
4. Prior to each Treatment Period, subjects should abstain from xanthine and/or xanthine analogue (caffeine)-containing foods, beverages, and medications from 24 hours prior to admission to the study unit until discharge. Examples of such products include coffee, tea, chocolate, and cola. When not at the study site, subjects should limit their caffeine intake to the equivalent of 3 cups of coffee per day (1 cup = 360 mL soda, 180 mL coffee, or 240 mL tea) for the duration of the study.
5. Subjects should abstain from grapefruit or grapefruit juice, Seville oranges (including marmalade) and quinine (eg, tonic water) from 7 days prior to admission to the study unit on Day -1 of the first Treatment Period until after Day 2 of Treatment Period 4.
6. During the in-patient stay, subjects will receive a standard diet. No food or beverages should be consumed while in the clinic other than those provided by the study site.
7. During the outpatient periods, subjects should abstain from consuming high energy drinks (eg, Red Bull), food containing poppy seeds (eg, specialty breads and muffins), and any over-the-counter (OTC) medication or herbal preparations until after Day 2 of the fourth Treatment Period has been completed.
8. Subjects will be instructed to abstain from blood or plasma donation until 3 months after study completion.

## 5.7 Study Withdrawal

The Investigator or medically qualified designee may withdraw a subject at the occurrence of any one or more of the following:

- Protocol deviation
- AE
- Subject becomes pregnant
- Clinically significant change in laboratory parameter(s)
- Termination of the study by the Sponsor or Investigator
- Request by the subject to be withdrawn from the study

- Investigator's discretion

Subjects withdrawn from the study after receiving at least 1 dose of study drug will not be replaced.

## 6 CLINICAL SUPPLY LABELING, PACKAGING, STORAGE, DISPENSING, AND RETURN

### 6.1 Description of Study Drugs

In this protocol, “study drug” refers to an active ingredient or placebo being tested or used as a reference in the study (International Conference on Harmonisation E6 (R1)). The study drug used in this study is described in Table 6-1. Instructions for use/priming are provided in Section 6.5, Section 6.6, Section 6.7, Appendix 1 and Appendix 2.

**Table 6-1 Description of Study Drugs**

Product Name & Dose	Product Strength	Dosage Form/ Fill Count	Administration
BGF MDI 320/28.8/9.6 µg ex-actuator	160/14.4/4.8 µg/actuation	MDI 120 inhalations	Taken as 2 inhalations

Note: Study drug will be administered by oral inhalation. A single-dose of study drug will be administered on Day 1 of Treatment Periods 1 to 4. Administration of study drug should occur at approximately the same time of day.

### 6.2 Other Sponsor-Provided Medications Used in the Study

Other Sponsor-provided medications used during the study are described in Table 6-2.

**Table 6-2 Other Medications Provided by Sponsor**

Product Name & Dose	Product Strength	Dosage Form/ Fill Count	Administration
Placebo MDI <sup>a</sup>	Formulation does not contain active ingredient	MDI/ 120 inhalations	Subjects will use the placebo MDI for training purposes only to demonstrate proper use of the MDI at screening and on Day -1 and Day 1 of each Treatment Period
Actidose-Aqua <sup>®</sup> (activated oral charcoal suspension)	50 g/240 mL (0.208 g/mL)	Oral suspension	<ul style="list-style-type: none"> <li>Immediately prior to study drug dose: 10 g (approximately 48 mL of suspension) which is to be mouth-rinsed and swallowed</li> <li>Immediately after study drug dose: 10 g (approximately 48 mL of suspension) which is to be mouth-rinsed and swallowed; repeat at 1 hour and 2 hours post dose</li> <li>Administered during regimens C and D</li> </ul>

<sup>a</sup> Placebo MDI for training purposes. All placebos are created by the Sponsor in the image of the active test product, with no active moieties.



### 6.3 Packaging and Labeling

Clinical supplies will be packaged to support enrollment of the study. All treatments will be open-label.

Study drug will be packaged in a box and labeled with a single label. Inside the box will be a labeled foil pouch containing a labeled MDI canister and actuator.

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

Lot # (Packaging Lot Trace ID) Space for entry of screening # Component ID# Randomization # Fill Count and Dosage Form Treatment Period #	Storage conditions Protocol # Country regulatory requirements Sponsor address Translation Key
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Abbreviations: #=number; ID=identification

### 6.4 Storage Requirements

Prior to dispensing, BGF MDI should be stored below 25°C (77°F) in a dry place. Excursions permitted up to 30°C (86°F).

Actidose-Aqua<sup>®</sup> should be stored between 20°C to 25°C (68°F to 77°F) on its side.

All study supplies should be kept in a locked cabinet or room with limited access. The temperature of the site's storage area for study supplies must be monitored by site staff for temperature ranges consistent with those specified in this protocol. Documentation of temperature monitoring should be maintained at the site and available for review. All study supplies contain contents under pressure. Do not use or store near heat or open flame. Exposure to temperatures above 49°C (120°F) may cause bursting. Never throw canister into a fire or incinerator. Avoid spraying in eyes.

### 6.5 Instructions for Preparation of Study Drug for Administration and Dosing

Individual BGF MDIs will be packaged in a foil pouch and contained in an individual box. Both the box and the foil overwrap will have a label with a component ID number. The box will be labeled with a 2-part label.

For each subject, study drug will be administered as a single-dose on Day 1 of each of the 4 Treatment Periods. Study drug should be administered in the morning, at approximately the same time of day throughout the study ( $\pm 30$  minutes). A total of 56 subject identifiers will be randomly assigned to 1 of the following 8 possible regimen sequences: AB CD, AB DC,

BA CD, BA DC, CD AB, CD BA, DC AB or DC BA. These regimen sequences allow for subjects who might drop out after 2 Treatment Periods only to be included in the statistical analysis of the PK.

All MDIs must be primed before the first use. 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. Priming involves releasing 4 sprays into the air before the first use of the inhaler. The MDI must be primed in a separate room, away from the subject treatment area. Refer to Appendix 1 for full instructions on priming and administration of BGF MDI.

At screening, on admission to each Treatment Period, and on Day 1 of each Treatment Period, subjects will be instructed by site staff on how to use the MDI device correctly using placebo MDIs. In addition, MDI training will be supplemented using the Vitalograph AIM Aerosol Inhalation Monitor or an equivalent device.

Each dose will consist of 2 puffs from the MDI. BGF MDI will be administered in a separate room from the room where blood samples will be drawn. The in-clinic dosing time for study drug (BGF MDI) will be recorded as the time of administration of the second puff. During administration, subjects and clinic personnel will wear protective clothing and vinyl gloves, which will be discarded immediately after administration in the room used for inhalation, to avoid subsequent contamination of blood samples, according to the routines at the clinic.

## **6.6 Instructions for Administration of Activated Oral Charcoal**

Actidose—Aqua<sup>®</sup>, a ready-to-use activated oral charcoal suspension, will be provided by the Sponsor. Actidose-Aqua<sup>®</sup> provides 0.208 g of oral charcoal /mL of suspension.

Actidose-Aqua<sup>®</sup> will be administered during regimens C and D. Before dosing with study drug, subjects will receive 10 g of activated oral charcoal (approximately 48 mL) which they are to mouth-rinse and swallow. Immediately after study drug administration, subjects will receive another 10 g of activated oral charcoal to mouth-rinse and swallow. This will be repeated at 1 and 2 hours post-dose. Post-administration of each dose of oral charcoal, subjects will rinse their mouths twice with 30 to 60 mL of water which is to be mouth-rinsed and swallowed.

In total, subjects will receive 40 g activated oral charcoal (or 192 mL) in both regimens C and D.

## **6.7 Aerochamber Plus Flow-Vu Instructions for Administration and Dispensing of Treatments**

The Aerochamber Plus Flow-Vu VHC can be used directly out of the package. Before use the VHC cap is to be removed and the chamber is to be examined for any obvious defects.

At the time of first use, ensure that the BGF MDI is primed outside of the VHC according to the instructions in Section 6.5 and Appendix 1. Once the MDI is primed, shake the inhaler immediately before use per the instructions in Appendix 1. Insert the inhaler into the back

part of the chamber, which is the opposite end from the mouthpiece (refer to Appendix 2 for a diagram of the VHC).

The inhalation instructions should be followed for taking each dose and subjects should be instructed as follows: put the mouthpiece into your mouth and close your lips around the mouthpiece to ensure an effective seal. The **Flow-Vu** indicator only moves if there is a good seal. Breathe out gently and press the inhaler at the beginning of a slow inhalation. Use the Flow-Vu indicator to assist in the coordination of this step. Breathe in slowly and deeply through the mouth until a full breath has been taken. Hold your breath for 5-10 seconds. Slow down inhalation if you hear the Flow Signal whistle sound. This means you are inhaling too quickly. Administer 1 puff at a time. Shake the MDI prior to each dose inhalation during dosing and repeat VHC instructions for use. A new VHC is to be dispensed for each Treatment Period in which it is used. Each subject will also be provided with a separate VHC for use in practice sessions.

The VHC should not be cleaned.

Store the VHC at room temperature and keep dry.

Refer to Appendix 2 for instructions for use of the Aerochamber Plus Flow-Vu VHC.

## 6.8 Dispensing Study Drug

All subjects will receive BGF MDI without spacer and without oral charcoal (regimen A), BGF MDI with spacer and without oral charcoal (regimen B), BGF MDI without spacer and with oral charcoal (regimen C), and BGF MDI with spacer and with oral charcoal (regimen D) in a random assignment to 1 of 8 predetermined regimen sequences on the morning of the first dosing (Day 1, Treatment Period 1). Randomization codes will be assigned in ascending order as subjects become eligible. At screening, Day -1, and before study drug dosing on Day 1 of each Treatment Period, subjects will be trained on and must demonstrate proper use of an MDI using a bulk-supplied MDI (placebo). Subjects must demonstrate the ability to use the MDI correctly, including the ability to coordinate actuation with inspiration.

A new BGF MDI will be dispensed for each Treatment Period. On Day 1 of the Treatment Period, prior to dosing, the MDI device will be primed in the study site pharmacy by the pharmacist and delivered to the delegated staff (See Appendix 1 for MDI device priming instructions). On Day 1 of each Treatment Period, subjects will again be trained on and must demonstrate proper use of the MDI device. At the time of all study drug dosing, trained site staff will be present to ensure that the subject properly administers the required number of actuations from the MDI device. Any occurrence of cough, interruption of the inhalation process or leakage around the lips/mouth during inhalation will be recorded.

## 6.9 Study Drug Accountability/Return of Clinical Supplies

**Under no circumstance will the Investigator(s) allow the study drugs 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 secured location to which only the appropriate designated 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 is responsible for keeping accurate records of the clinical supplies received from the Sponsor, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the study. Study drug should be handled in accordance with Good Pharmacy Practices. The Medical 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 the Sponsor.

The study site should check with the Sponsor's representative for appropriate documentation that needs to be completed for drug accountability.

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

**Note:** Used study drug will be stored separately from unused study drug.

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

## 7 STUDY PROCEDURES

### 7.1 Informed Consent

The ICF must be executed prior to performing any study-related activities. The ICF must be approved by the reviewing IEC/IRB. Informed consent will be obtained for all subjects participating in the study. Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the Principal Investigator.

### 7.2 Subject Eligibility

Eligibility screening of healthy subjects will be completed within 28 days prior to administration of the first dose of study drug and will be documented on the eCRF. Eligibility will be confirmed at each clinic admission (Day -1).

Screen failures and the reason for failure to meet the study eligibility requirements will be documented in the study site source documents and documented in the eCRF.

### 7.3 PK Assessments

Pharmacokinetic sampling will occur during each Treatment Period. Sample collections will be scheduled for the nominal time point and actual collection times will be recorded in the source documents (Refer to Table 8-2).

#### 7.3.1 Blood Sample Collection Schedule

Approximately 10 mL of whole blood will be collected within 60 minutes *prior* to study drug dosing and then at 2, 6, 20, and 40 minutes post-dose and 1, 2, 4, 8, 12 and 24 hours post dose (see also Table 8-2 and Table 8-3).

Subjects must fast for at least 6 hours prior to study drug administration during each Treatment Period. Meals during each Treatment Period will be standard and will begin after the 4 hour post-dose blood draw.

The recommended time windows for post-dose PK assessments are as follows:

**Table 7-1 Time Window for Post-dose PK Assessments**

Time Point	Time Window
2 and 6 minutes	±1 minute
20 and 40 minutes and 1 hour	±2 minutes
2 and 4 hours	±5 minutes
8, 12, and 24 hours	±10 minutes

Collection and storage of PK samples will be provided in the laboratory manual

### 7.3.2 Procedure for Shipping Samples

Samples are to be shipped frozen by overnight courier to the bioanalytical laboratory for analysis. Instructions for sample handling, storage, and shipping will be provided in the laboratory manual.

### 7.3.3 Storage and Destruction of PK Samples

Samples for determination of drug concentration in plasma will be analyzed by the bioanalytical laboratory on behalf of the Sponsor using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Pharmacokinetic samples will be disposed of after the bioanalytical report finalization or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the clinical study report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the clinical study report but separately in a bioanalytical report.

## 7.4 Safety Assessments

### 7.4.1 Medical History

Relevant medical history will be obtained from the subject at screening and at each clinic admission (Day -1) and recorded on the source document. Medical history will capture the subject's family health history, history of hospitalization, and history of surgeries.

### 7.4.2 Physical Examination

A complete physical examination including height and weight will be performed at screening (height and weight at screening only) and on Day 2 at the end of Treatment Period 4. An abbreviated physical examination will be conducted at Day -1 of each Treatment Period. The findings of each examination will be recorded on the source documents and clinically significant abnormalities will be recorded on the Medical History eCRF (prior to any study drug administration) and on the AE eCRF during the randomized Treatment Period. The physical examination will include the following:

#### **COMPLETE PHYSICAL EXAMINATION**

The complete physical examinations will include an assessment of the general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, respiratory,

cardiovascular, musculoskeletal, abdominal, extremities, neurological and dermatological. Height and weight will be measured at screening only.

#### **BRIEF (ABBREVIATED) PHYSICAL EXAMINATION**

The brief physical examination will include an assessment of the general appearance, skin, abdomen, cardiovascular system, and respiratory.

##### **7.4.3 Vital Signs**

Vital signs (BP and heart rate) will be determined after a subject has rested for 5 minutes in a supine position at screening, on the day of each clinic admission (Day -1), on Day 1 prior to study drug administration, and on Day 2 of Treatment Period 4 (see Table 8-1).

##### **7.4.4 12-Lead Electrocardiogram**

Twelve-lead ECGs will be recorded at screening and on Day 2 of Treatment Period 4 (Table 8-1). Subjects should rest in a supine position for at least 5 minutes before and during the ECG recording procedure. Subjects with any ECG abnormality should be evaluated by the Investigator to determine if the abnormality is clinically significant. All clinically significant abnormalities after administration of randomized study drug will be reported as AEs and followed closely by the Investigator in order to assure the safety of the study subject.

##### **7.4.5 Clinical Laboratory Tests**

###### **7.4.5.1 Laboratory Parameters**

Laboratory testing (hematology with differential, chemistry, and urinalysis) will be performed using standard methods. Blood and urine samples for the clinical laboratory tests listed in Table 7-2 will be collected at screening and on Day 2 of Treatment Period 4 (Table 8-1). Subjects must fast for at least 6 hours prior to any scheduled clinical laboratory assessment blood draw.



**Table 7-2 List of Laboratory Tests**

Hematology	Chemistry	
Hematocrit <sup>a</sup>	Creatinine <sup>b</sup>	Bilirubin (direct)
Hemoglobin	Potassium	Alanine aminotransferase
Platelet count	Sodium	Aspartate aminotransferase
Red blood cell count	Chloride	Gamma-glutamyltransferase
White blood cell count	Magnesium	Alkaline phosphatase
WWhite blood cell differential	Calcium	Total protein
Mean corpuscular volume	Inorganic phosphate	Albumin
MCH concentration	Glucose	
	Urea	
	Bilirubin (total)	
<b>Urinalysis:</b> Macroscopic examination routinely including specific gravity, pH, protein, glucose, ketones, blood, and urobilinogen. A microscopic examination will be performed if warranted based on macroscopic results.		
<b>Urine drug screen:</b> A urine sample will be collected at screening and Day-1 of each Treatment Period and analyzed (positive or negative) for drugs of abuse including amphetamine, opiate, cocaine, barbiturates, benzodiazepines, cotinine and marijuana (tetrahydrocannabinol)		
<b>Alcohol breathalyzer test:</b> A breathalyzer test will be performed at screening and Day -1 of each Treatment Period for the presence of alcohol (positive or negative)		
<b>Serology:</b> Testing for HbsAg, Hepatitis C antibody, and HIV will be performed at screening only. Results of each serology test will be reported as either positive or negative.		
<b>For females who are not post-menopausal:</b> A <u>serum</u> hCG test at screening and <u>urine</u> hCG test at admission will be performed during each of the 4 Treatment Periods.		
<b>For females of non-childbearing potential:</b> A <u>serum</u> hCG test at screening will be performed. In addition, a serum FSH test for confirmation of non-childbearing status will be performed at screening.		

Abbreviations: FSH=follicle-stimulating hormone; MCH=mean cell hemoglobin

<sup>a</sup> Packed cell volume

<sup>b</sup> Serum creatinine value will be used to calculate eGFR using CKD-EPI.

#### 7.4.5.2 Sample Collection, Storage, and Shipping

Detailed instructions for laboratory sample collection, processing, and shipping instructions will be provided in the [REDACTED] laboratory manual. Approximately 480 mL of blood will be collected per subject during the study (approximately 440 mL for PK assessments and 40 mL for laboratory assessments).

Biological material will be stored and secured in a way that assures that unauthorized access is prohibited and the samples are not lost, deteriorated, or accidentally or illegally destroyed. Details for storage and shipping will be provided in the [REDACTED] laboratory manual.



## 7.5 Adverse Event Assessments

### 7.5.1 Performing Adverse Event (AE) Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's eCRF and on the AE Reporting Form. If the AE is unexpected, the Investigator should report the AE immediately to the Sponsor. In addition, certain AEs (as described in Section 7.5.7) are classified as 'serious' and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as a serious adverse event (SAE) to the Sponsor or its designee.

In the case of SAEs, after discussing the details of the AE, the Investigator and the Medical Monitor may withdraw the subject from the study.

### 7.5.2 AE Definitions

The following definitions of terms are guided by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, the US Code of Federal Regulations (21 CFR 312.32), and European Union 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 (eg, 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 (eg, 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 the following:

- 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 the following:

- medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, blood transfusion); the condition that led to the procedure is an AE (eg, bleeding esophageal varices, dental caries).

- overdose of either study drug or concurrent medication without any clinical signs or symptoms.
- abnormal laboratory values that are not clinically significant; if accompanied by signs/symptoms, the signs or symptoms are considered an AE.

### 7.5.3 Pre-Randomization AEs

Any AE occurring from the time the subject signs informed consent until the subject administers the first dose of study drug will be summarized as medical history and not as a AE unless the event meets the definition of an SAE as defined in Section 7.5.7.

### 7.5.4 Severity

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

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

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

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

### 7.5.5 Relationship to Study Drug

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

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as ‘yes’.

### 7.5.6 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 (eg., 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 the following:

- a laboratory abnormality that leads to a dose-limiting toxicity (eg, an abnormality that results in study drug dose reduction, suspension, or discontinuation).
- a laboratory abnormality that results in any therapeutic intervention (ie, concomitant medication or therapy).
- any other laboratory abnormality judged by the Investigator to be of any particular clinical concern (eg, significant fall in hemoglobin not requiring transfusion).

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

#### 7.5.7 SAEs

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

- Death
- A life-threatening AE
- Inpatient 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 medical judgment, they jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

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

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

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

#### 7.5.7.1 REPORTING SAEs

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 the Sponsor. All SAEs must be reported to the Sponsor 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 (eg, SAE Report Form). After the initial report, as necessary, the Investigator must provide any additional information on an SAE to the Sponsor within 2 working days after he/she receives that information. This follow up information will include a detailed summary of hospital records, case reports, autopsy reports, and other pertinent documents which will be summarized in the eCRF.

Post-study SAEs must be reported to the Sponsor as described in Section 7.5.9.

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

#### 7.5.8 Supplemental Investigation of SAEs

The Investigator and supporting personnel responsible for subject care should discuss with the Sponsor any need for supplemental investigations of SAEs. The results of these additional assessments conducted must be reported to the Sponsor. If a subject dies during participation and if a post-mortem examination is performed, a copy of the autopsy report must be submitted to the Sponsor.

#### 7.5.9 Post-Study Follow-Up of AEs

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

#### 7.5.10 Notification of Post-Treatment SAEs

Investigators are not obligated to actively follow subjects after the completion of the study. However, if the Investigator becomes aware of a post-treatment SAE occurring within the 5 to 7 days following the last dose of study drug, it must be reported to the Sponsor, whether or not the event is attributable to study drug. All SAEs must be reported to the Sponsor no later than 24 hours after the Investigator recognizes/classifies the event as an SAE.

#### 7.5.11 IRB/IEC Notification of SAEs

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

#### 7.5.12 Health Authority Safety Reports

The Sponsor 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 specified by each regulatory agency.

The Sponsor will send copies of each safety report to Investigators who are actively participating in a Pearl sponsored clinical study. Safety reports must also be submitted to the appropriate IRB/IECs as soon as possible. Documentation of the submission to the IRB/IEC must be retained for each safety report.

#### 7.5.13 Overdose

An overdose is defined as any dose greater than the highest dose investigated in this study, that results in clinical signs and symptoms. In the event of a study drug overdose, the Investigator should use their best clinical judgment in treating the overdose, and the Sponsor should be contacted. Investigators should refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drug(s) being administered. Such document(s) may include, but are not limited to: the Investigator Brochure for BGF MDI and approved product labeling for open-label products.

#### 7.5.14 Pregnancy

To ensure subject safety, each pregnancy from screening until study completion must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed in its entirety to ascertain outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be recorded on a Paper Pregnancy Report Form and reported by the Investigator to the Sponsor. Pregnancy follow-up should be recorded on the same pregnancy paper form and should include possible relationship to the study drug in response to the pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

#### 7.5.15 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 study drug 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.

## **7.6 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.

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

## 8 STUDY ACTIVITIES

A schedule of events is provided in Table 8-1. Detailed schedules of inpatient assessments for Treatment Periods 1, 2, and 3 are provided in Table 8-2 and in Table 8-3 for Treatment Period 4. Refer to Section 7 for study procedure details.

**Table 8-1 Schedule of Events for Screening, Treatment, and Follow-Up**

	Screening	Treatment Periods 1, 2, 3, and 4		Follow-up phone call 5 to 7 days post-final dose
		Day -1	Days 1 and 2	
Informed consent	X			
Medical history	X	X		
Demographics	X			
Physical exam <sup>a</sup>	X	X	X	
Vital signs (BP, heart rate) <sup>b</sup>	X	X	X	
Device training (pMDI and, where applicable, spacer) <sup>c</sup>	X	X	X	
12-lead ECG <sup>d</sup>	X		X	
Clinical laboratory testing <sup>e</sup>	X		X	
Viral serology <sup>f</sup>	X			
Urinary drug screen including cotinine	X	X		
Alcohol breathalyzer test	X	X		
Pregnancy testing (females only) <sup>g</sup>	X	X		
FSH (women not of child-bearing potential only)	X			
Eligibility review	X	X	X	
Inpatient admission		X		
Randomization <sup>h</sup>			X	
Study drug administration <sup>ij</sup>			X	
AEs <sup>k</sup>	X	X	X	X
Concomitant medication	X	X	X	X

**Table 8-1 Schedule of Events for Screening, Treatment, and Follow-Up**

	Screening	Treatment Periods 1, 2, 3, and 4		Follow-up phone call 5 to 7 days post-final dose
		Day -1	Days 1 and 2	
PK assessments <sup>l</sup>			X	
Inpatient discharge <sup>m</sup>			X	

Abbreviations: AE=adverse event; BP=blood pressure; ECG=electrocardiogram; FSH=follicle-stimulating hormone; HbsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; PK=pharmacokinetic; pMDI=pressurized metered-dose inhaler; SAE=serious adverse event

- <sup>a</sup> Refer to Section 7.4.2 for assessments to be included in the physical examination. A full physical examination is to be conducted at screening and on Day 2 of Treatment Period 4 (height and weight at screening only). A brief physical examination will be done on Day -1 of each Treatment Period.
- <sup>b</sup> Refer to Section 7.4.3 for details on the timing of vital sign assessments to be obtained during screening, on Day -1 and Day 1 of each Treatment Period, and on Day 2 of Treatment Period 4.
- <sup>c</sup> In addition to training with placebo MDIs, and spacer as applicable inhalation training tools may be used to help ensure the subjects are able to use the MDI device correctly. Device training will be conducted during screening, on admission to each Treatment Period, and prior to dosing on Day 1 of each Treatment Period.
- <sup>d</sup> Refer to Section 7.4.4 for details on the timing of ECG assessments to be obtained during screening and on Day 2 of Treatment Period 4.
- <sup>e</sup> Refer to Section 7.4.5 for details on the clinical laboratory assessments to be obtained during screening and on Day 2 of Treatment Period 4.
- <sup>f</sup> Refer to Table 7-2 for details on the serology assessments (HbsAg, hepatitis C antibody, and HIV)
- <sup>g</sup> Serum pregnancy test will be performed at screening. For women for child-bearing potential, urine pregnancy tests will be performed at Day -1 of each Treatment Period.
- <sup>h</sup> Randomization done on Day 1 of Treatment Period 1.
- <sup>i</sup> Activated oral charcoal dosing will be administered according to randomization. regimens A & B do not receive activated oral charcoal whereas regimens C & D do receive activated oral charcoal. Dosing is as follows: Immediately prior to study drug dosing, subjects will receive 10 g. immediately after study drug dosing, subjects will receive another 10 g; repeat at 1 hour and 2 hours post-dose. Each dose of activated oral charcoal will be followed by a mouth-rinse and swallow with 30-60 mL water.
- <sup>j</sup> Study drug is to be administered on Day 1 (0 h) of each Treatment Period at approximately the same time of day throughout the study ( $\pm 30$  minutes).
- <sup>k</sup> Any AEs collected before the first dose of study drug of Treatment Period 1 should be recorded as medical history and not as an AE unless it meets the criteria for an SAE.
- <sup>l</sup> Refer to Section 7.3, Table 8-2 and Table 8-3 for timing of PK assessments.
- <sup>m</sup> Discharge to take place after all PK samples have been collected on Day 2 of each Treatment Period. A washout period of at least 5 days to a maximum of 14 days, must occur after Treatment Periods 1, 2, and 3.



**Table 8-2 Timing of Assessments on Day 1 During Inpatient Treatment Periods 1, 2, and 3**

Procedure	Time Relative to Drug Administration											
	-60 min	0 hr	2 mins	6 mins	20 mins	40 mins	1 hr	2 hrs	4 hrs	8 hrs	12 hrs	24 hrs
PK sample collection	X <sup>a</sup>		X	X	X	X	X	X	X	X	X	X
Device training (pMDI and, where applicable, spacer) <sup>b</sup>	X											
Administer oral charcoal <sup>c</sup>	X	X					X	X				
Administration of study drug <sup>d</sup>		X										
AEs	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse event; PK=pharmacokinetic; pMDI=pressurized metered dose inhaler.

- <sup>a</sup> Within 60 minutes prior to dosing
- <sup>b</sup> In addition to training with placebo MDIs, and spacer as applicable inhalation training tools may be used to help ensure the subjects are able to use the MDI device correctly.
- <sup>c</sup> Administer activated oral charcoal immediately pre-dose and immediately post-dose, then 1 hour and 2 hours post dose for regimens C and D only (refer to Section 6.6 for details regarding activated oral charcoal administration).
- <sup>d</sup> Study drug will be administered by oral inhalation. A single-dose of study drug will be administered on Day 1 of each Treatment Period.

**Table 8-3 Timing of Assessments on Day 1 During Inpatient Treatment Period 4**

Procedure	Time Relative to Drug Administration											
	-60 min	0 hr	2 mins	6 mins	20 mins	40 mins	1 hr	2 hrs	4 hrs	8 hrs	12 hrs	24 hrs
PK sample collection	X <sup>a</sup>		X	X	X	X	X	X	X	X	X	X
Device training (pMDI and, where applicable, spacer) <sup>b</sup>	X											
Administer oral charcoal <sup>c</sup>	X	X					X	X				
Administration of study drug <sup>d</sup>		X										
12-lead ECG												X
Clinical laboratory tests <sup>e</sup>												X
Vital Signs												X
Physical Examination												X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse event; PK=pharmacokinetic; pMDI=pressurized metered dose inhaler.

<sup>a</sup> Within 60 minutes prior to dosing

<sup>b</sup> In addition to training with placebo MDIs, and spacer as applicable inhalation training tools may be used to help insure the subjects are able to use the MDI device correctly.

<sup>c</sup> Administer activated oral charcoal immediately pre-dose and immediately post-dose then 1 hour and 2 hours post dose for regimens C & D (refer to Section 6.6 for details regarding oral charcoal administration).

<sup>d</sup> Study drug will be administered by oral inhalation.

<sup>e</sup> Refer to Section 7.4.5; for laboratory testing (hematology with differential, chemistry, and urinalysis) to be performed using standard methods. Subjects must be fast for at least 6 hours prior to blood draw.

## **8.1 Screening (Days –28 to -1)**

The following procedures and assessments will be performed during screening and results documented in the eCRF and/or source documents:

- Obtain informed consent
- Review inclusion/exclusion criteria
- Obtain demographic data, including age, race, smoking history/status, and relevant medical history
- Conduct a serum pregnancy test for all female subjects (childbearing and non-childbearing potential)
- Obtain FSH test for women of non-childbearing potential
- Conduct complete physical examination including height and weight
- Obtain vital signs (heart rate and BP) after being supine for 5 minutes
- Obtain a 12-lead ECG
- Obtain a urine drug screen including cotinine
- Conduct an alcohol breathalyzer test
- Confirm subject's ability to use MDI and spacer correctly (provide training as needed)
- Document any prior and concomitant medications
- Obtain laboratory samples (hematology, serology, chemistry, and urinalysis)
- Document AEs (Note: AEs that occur prior to dosing will be recorded as medical history unless the event meets the definition of an SAE as defined in Section 7.5.7)

## **8.2 Treatment Periods 1, 2, 3, and 4**

### **8.2.1 Clinic Admission (Day -1)**

Subjects will be admitted to the clinic on Day -1, the day prior to administration of study drug for each Treatment Period. The results of the following procedures and assessments will be documented in the eCRF and/or source documents:

- Review inclusion/exclusion criteria and confirm subject eligibility to continue
- Review relevant medical history
- Review any prior and concomitant medications and document any changes
- Obtain a urine pregnancy test for all female subjects of childbearing potential
- Obtain a urine drug screen including cotinine

- Conduct alcohol breathalyzer test
- Conduct a brief physical examination
- Obtain vital signs (heart rate and BP) after being supine for 5 minutes
- Confirm subject's ability to use MDI and spacer correctly (provide training as needed)
- Document AEs (Note: AEs that occur prior to first dose of randomized study drug in Treatment Period 1 will be recorded as medical history unless the event meets the definitions of an SAE as defined in Section 7.5.7)

### 8.2.2 Treatment Days (Day 1 to Day 2)

The following study activities and assessments will be performed on Days 1 and 2 of each Treatment Period (unless otherwise indicated) and will be documented in the eCRF and/or source documents:

- Obtain vital signs (heart rate and BP) after being supine for 5 minutes (Day 1 of each Treatment Period and Day 2 of Treatment Period 4)
- Conduct brief physical examination
- Review inclusion/exclusion criteria and confirm subject eligibility
- Confirm subject's ability to use MDI and spacer correctly (provide training as needed)
- Collect pre-dose PK samples per Table 8-2 for Treatment Periods 1, 2 and 3 and per Table 8-3 for Treatment Period 4.
- Obtain subject randomization number and regimen assignment (with/without Aerochamber Plus VHC and with and without charcoal) information in Treatment Period 1
  - Allow proper time prior to dosing to remove the seal around the study day treatment box, and read any instructions for administration of study drug that are to be followed.
  - Refer to Section 6. for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
  - The subject is to be considered randomized after receiving a randomization number.
  - Ensure appropriate training for the MDI providing instructions for use to the subject. The subject should demonstrate proper MDI administration technique prior to dosing (with and without Aerochamber, with and without oral charcoal), using an AIM or equivalent device as appropriate
  - Administer activated oral charcoal pre-dose for regimens C and D only (refer to Section 6.6, Table 8-2 and Table 8-3 for details regarding oral charcoal administration).

- After priming of study drug by site staff, subject should self-administer dose of randomized study drug under supervision by site staff (refer to Section 6 and Appendix 1 for details regarding study drug priming, dispensing and administration)
- Administer activated oral charcoal post-dose for regimens C and D only (refer to Section 6.6, Table 8-2 and Table 8-3 for details regarding oral charcoal administration).
- Collect post-dose PK samples per Table 8-2 for Treatment Periods 1, 2 and 3 and per Table 8-3 for Treatment Period 4. The 24-hour post-dose sample will be collected on the morning of Day 2 of all Treatment Periods.
- Document any AEs (Note: AEs that occur prior to first dose of randomized study drug in Treatment Period 1 will be recorded as medical history unless the event meets the definition of an SAE as defined in Section 7.5.7)
- Document any use of concomitant medications
- For Treatment Periods 1, 2, and 3:
  - Discharge subject from the clinic following completion of all protocol-specified procedures and after all available safety data have been reviewed by the Investigator.
  - Schedule the next Treatment Period at least 5 days and no more than 14 days later.
- For Treatment Period 4:
  - Obtain 12-lead ECG (Treatment Period 4 Day 2 only)
  - Obtain laboratory samples: hematology, chemistry, and urinalysis (Treatment Period 4 Day 2 only)
  - Discharge subject from the clinic following completion of all protocol-specified procedures and after all available safety data have been reviewed by the Investigator
  - Schedule follow-up phone call to occur between 5 to 7 days after dosing in Treatment Period 4.

### **8.3 Follow-up Phone Call**

Upon completion of the study, a follow-up phone call will be conducted 5 to 7 days after Treatment Period 4 dosing or, if the subject withdraws from the study, 5 to 7 days after the last dose of study drug.

- Review and document any AEs and/or concomitant medications

## 9 PLANNED STATISTICAL METHODS

### 9.1 General Considerations

The general approach for statistical analyses are provided below. A detailed Statistical Analysis Plan (SAP) will be finalized prior to database lock.

### 9.2 Determination of Sample Size

Even though this study is being conducted for estimation purposes,

[REDACTED]

[REDACTED] a sample size of 48 subjects completing the study will provide [REDACTED] probability to observe a [REDACTED] lower confidence bound for the geometric mean ratio (D/C) that is greater than [REDACTED].

### 9.3 Analysis Populations

#### 9.3.1 Safety Population

Safety and tolerability analyses will be performed on data from all subjects in the Safety Population which includes all randomized subjects who received at least 1 dose of BGF MDI.

#### 9.3.2 PK Population

The PK Population will consist of all subjects in the Safety Population set for whom at least 1 of the primary PK parameters for a given analyte can be calculated and who have no important protocol deviations thought to impact on the analysis of the PK data (details to be provided and documented prior to database lock). Subjects will be analyzed according to treatment received rather than randomized.

Pharmacokinetic analysis will be performed using the PK Population.

### 9.4 Demographics and Baseline Characteristics

Demographic information will include age, gender, ethnicity, and race. Demographics and baseline characteristics will be summarized descriptively for both the Safety and PK Populations. Height and weight, which are considered baseline characteristics and documented as part of the physical examination performed at screening, will be reported with the demographic information listed above.

## 9.5 Statistical Analysis of PK Variables

### 9.5.1 PK Parameters

Pharmacokinetic parameters will be estimated by non-compartmental analysis (NCA) using [REDACTED] From the plasma budesonide, glycopyrronium and formoterol concentration-time data, the following PK parameters will be estimated for each subject where possible:

$AUC_{0-t_{last}}$	The area under the plasma concentration-time curve from 0 to the time of the last measurable plasma concentration
$AUC_{0-\infty}$	The area under the plasma concentration-time curve from 0 extrapolated to infinity
$C_{max}$	The maximum plasma concentration, expressed in concentration units
$t_{max}$	The time to reach maximum plasma concentration, expressed in hours
$t_{1/2}$	The apparent terminal elimination half-life, expressed in hours, calculated as $\ln 2 / \lambda_z$
$CL/F$	The apparent total body clearance
$Vd/F$	The apparent volume of distribution
$\lambda_z$	The terminal elimination rate constant, calculated from the slope of the terminal portion of the $\ln$ (drug concentration) versus time curve
$t_{last}$	The time to last measurable plasma concentration

The  $AUC_{0-t_{last}}$  and  $AUC_{0-\infty}$  will be calculated using the linear-log trapezoidal method.

The PK parameters  $C_{max}$  and  $t_{max}$  will be obtained from the observed values.

The  $\lambda_z$  will be estimated for each subject where feasible by linear regression analysis, calculated from the slope of the terminal portion versus time curve. Selection of data points to include in the estimation of  $\lambda_z$  for each subject for each Treatment Period will be based on the following criteria:

- All samples used should preferably fall in the log-linear elimination phase.
- At least 3 samples above the lower limit of quantification (LLQ) should be used in the estimation.
- $C_{max}$  must not be used in the estimation.
- The elimination rate constant will not be estimated where below LLQ values occur in the terminal phase between quantifiable (non-zero) values.

In order for the selection to take place the adjusted  $r^2$  value reported in [REDACTED] must be  $\geq 0.7$ .

### 9.5.2 Handling of Values that are Below the Limit of Quantification

Plasma concentration values that are reported as below the LLQ will be set to missing in the NCA. Actual sampling timepoints relative to dosing will be used for the NCA where available. If the actual sampling time is unknown, the scheduled protocol time may be used for the calculation of derived PK parameters. No formal “outlier” analysis is planned.

All values below LLQ, except pre-dose, will be assigned a value of  $\frac{1}{2}$  LLQ for all descriptive statistics categories.

### 9.5.3 Statistical Analysis of PK Data

Descriptive statistics for plasma concentrations of budesonide, glycopyrronium, and formoterol by regimen and nominal timepoint will be summarized on the linear and log-linear scale using the PK Population. Individual plasma concentrations at each nominal and actual time point for each regimen will be listed by subject using the Safety Population.

The treatment ratio of each of the test formulations (regimen B or regimen D) will be compared to the reference formulations (regimen A or regimen C) for budesonide, glycopyrronium, and formoterol.

The statistical analysis will be conducted separately for the following:

- Total systemic exposure: regimen B versus regimen A
- Lung exposure: regimen D versus regimen C

Treatment comparisons of primary PK parameters will be assessed on the difference of log-transformed  $C_{max}$ ,  $AUC_{0-t_{last}}$  and  $AUC_{0-\infty}$  of budesonide, glycopyrronium, and formoterol using a 2-sided 90% CI approach based on an analysis of variance model including period, sequence, regimen and subject as fixed effects. Estimated geometric mean ratios with 90% CIs will be provided.

Only the data for the comparison under investigation will be included in the statistical analysis, e.g., when comparing regimen B and regimen A, the data for the other regimens will be removed from the dataset. Subjects must have a primary PK parameter available for both regimens for the given analyte under consideration in order to be included in a specific analysis. A subject may therefore be included in the analysis for one parameter and not for another.

Descriptive statistics for PK parameters by regimen will be summarized. The number of observations (n), mean, coefficient of variation (CV) (%), standard deviation, standard error, median, minimum, maximum, geometric mean, and geometric coefficient of variation by regimen will be provided.

No hypothesis test will be performed for this study.



## 9.6 Safety Analysis

No formal statistical analysis of safety data is planned. Safety data will be summarized by regimen and listed based on the Safety Population.

### 9.6.1 AEs

Adverse events occurring during each Treatment Period will be summarized by the number of subjects experiencing an event and tabulated at the level of the Medical Dictionary for Regulatory Activities (MedDRA) preferred term, and system organ class. The version of MedDRA current at the time of database lock will be used for the final analysis of data. Tabulations will be broken down by severity, seriousness, AEs leading to discontinuation, and by relationship to study drug. No hypothesis tests will be performed. Tables will summarize the overall incidence of AEs and the incidence for each regimen, based on the four different conditions (with/without oral charcoal, with/without spacer).

### 9.6.2 Vital Signs

Subjects with out-of-range values will be listed.

### 9.6.3 Clinical Laboratory Measurements

Subjects with out-of-range values will be listed.

### 9.6.4 12-Lead ECGs

Subjects with out-of-range values will be listed.

## 9.7 Randomization

This study will be conducted as a 4-period, 8-sequence, 4-regimen, crossover design. The experimental design was chosen to be balanced with respect to period, sequence and first-order carryover effects. Thus, eligible subjects will be equally randomized to 1 of the following 8 regimen sequences: AB CD, AB DC, BA CD, BA DC, CD AB, CD BA, DC AB or DC BA.

## 9.8 Statistical Software

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

## **10 ADMINISTRATIVE CONSIDERATIONS**

### **10.1 Regulatory Authority Approval**

The Sponsor 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 IRB or IEC Approval**

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

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

The Investigator (or Sponsor, where applicable) is responsible for ensuring that this protocol, the site's ICF, and any other information that will be presented to potential subjects (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.

The Sponsor 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 the Sponsor promptly.

### **10.3 Subject Information and Consent**

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

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

## **10.4 Laboratory Accreditation**

Any laboratory facility intended to be used for analysis of clinical laboratory samples required by this protocol must provide evidence of adequate licensure or accreditation according to the prevailing regulations in that state and/or country. Reference values and/or normal ranges for the test results must be provided to the Sponsor. The Sponsor 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 the Sponsor that information furnished to the Investigator by the Sponsor 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 the Sponsor (or representative), IRB/IEC, or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor. 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**

The Sponsor 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 a clinical study.

## 10.7 Data Management

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

## 10.8 Study Monitoring

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

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

The Investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant concerns. Upon completion of the study, the monitor will conduct the following activities in conjunction with the Investigator or site staff, as appropriate:

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

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

files by the Sponsor's Quality Assurance auditors, and authorized representatives of the Food and Drug Administration (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 the Sponsor's Quality Assurance auditors and by all applicable regulatory authorities. The period of time these documents must be maintained is governed by applicable regulations. The Sponsor or its designee will inform the Investigator when these documents may be destroyed. The Sponsor or its designee must be notified in writing at least 6 months prior to the intended date of disposal of any study record related to this protocol to allow the Sponsor to make alternate storage arrangements.

## **10.10 Financial Disclosure**

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

## **10.11 Investigator's Final Report**

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

## **10.12 Publication Policy**

The Sponsor intends to publish the results of all of the clinical studies that it sponsors in compliance with the Declaration of Helsinki (<http://www.wma.net/en/10home/index.html>). Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from the Sponsor sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study. In addition, the Sponsor recognizes and adheres to the precepts of the International Society for Medical Publications Professionals (ISMPP) that provide guidance to the preparation of publications, providing disclosure of conflicts of interest, and the protection of intellectual property. Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor's personnel, the Investigators and others involved, such as statisticians.

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

1. **Responsibility:** Each Principal Investigator is responsible for the accuracy and completeness of all data from their site. the Sponsor (or its representatives) is responsible

for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.

2. **Authorship and Publication Committee:** The Sponsor, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE and ISMPP. It is anticipated that a publication committee will be formed to assume oversight of these activities. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
3. **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted at least 30 days prior to submission for publication or presentation to the Sponsor for review, approval, and to ensure consistency with the policy in this protocol. The Sponsor will have the right to request appropriate modification to correct facts and to represent its opinions, or the opinions of the publication committee, if these differ with the proposed publication.
4. **Confidentiality:** Investigators will conduct all interactions with the Sponsor and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of nonclinical studies, or chemical formulae) may still need to remain confidential.
5. **Medical Journal Review:** Consistent with the intention of the Sponsor to publish the study in a fair and accurate manner, the Sponsor supports diligence in the publication review process of medical journals. Accordingly, upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, eg, protocol and amendments, data tabulations, etc. The journal and reviewers will need to make arrangements to maintain the confidentiality of such supplemental information, where relevant, and the Sponsor will make suitable arrangements to ensure that the identity of journal reviewers is kept confidential. Records will be maintained of reviewers and the respective documents and datasets that were reviewed by each of them.
6. **Reporting of Clinical Trials Results:** To provide transparency in the conduct and reporting of randomized clinical trials, the Sponsor reports clinical findings based on the guidance of The CONSORT (CONsolidated Standards of Reporting Trials) Statement and a 25 item checklist which is intended to improve the reporting of a randomized controlled trial, and to facilitate reader understanding of the trial design, conduct, analysis and interpretation, and to support their ability to assess the validity of its results.
7. **Internet Clinical Trial Listing:** In addition, also consistent with the recommendations of the ICMJE, the Sponsor will make available appropriate information regarding the study via the internet. This will include registration and listing of the study on [www.clinicaltrials.gov](http://www.clinicaltrials.gov), the US National Institutes of Health listing of clinical trials.

## 11 REFERENCE LIST

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management, and Prevention of COPD-2017. <http://www.goldcopd.org/>. Accessed 31 January 2017.

SYMBICORT® (budesonide and formoterol fumarate dehydrate) inhalation aerosol [package insert]. Wilmington, DE. AstraZeneca; 2017.

## Appendix 1 Instructions for Use of BGF MDI

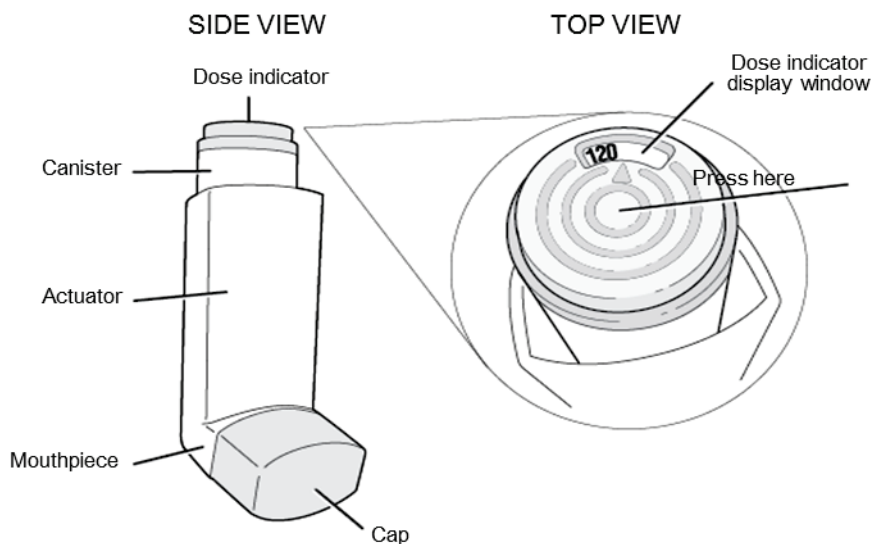
How do I store the inhaler (to be stored by study site personnel)?

- 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 120°F 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**.



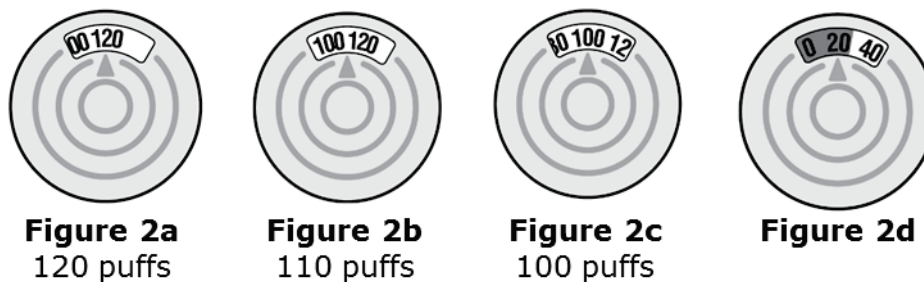
- The **Dose indicator** lets you know about how many puffs are left in your inhaler and is the part of the inhaler that is pressed to dispense a puff of medication. **See Figure 1.**
- The **Dose indicator** should be pointing just to the right of 120 when your inhaler is new. **See Figure 1.**
- The **Dose indicator** has numbers for every 20 puffs. The **Dose indicator** display will move after every tenth puff.
- For example, if the **Dose indicator** is pointing to 120 (see **Figure 2a**) and you take 10 puffs it will move between 120 and 100. This means that there are 110 puffs of medicine



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

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

**Figure 2**

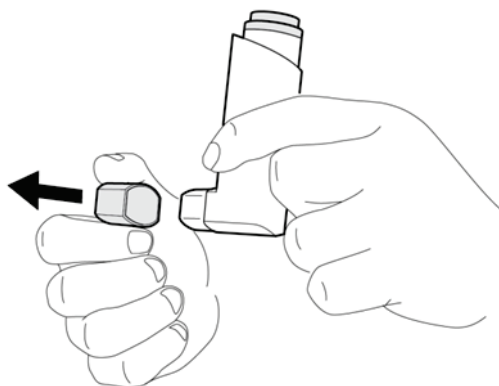


### **Preparing the Inhaler for Use (To be conducted by study site personnel):**

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**



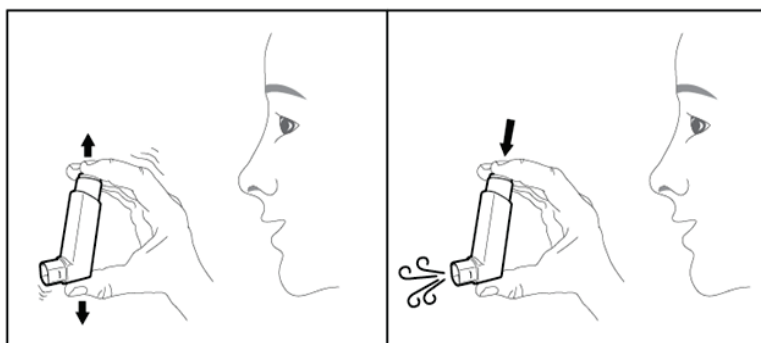
Prime the inhaler before you use it for the first time.

### Priming the Inhaler (To be conducted by study site personnel):

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

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

**Figure 4**



**Figure 4a**

**Figure 4b**

### Using the Inhaler:

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

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

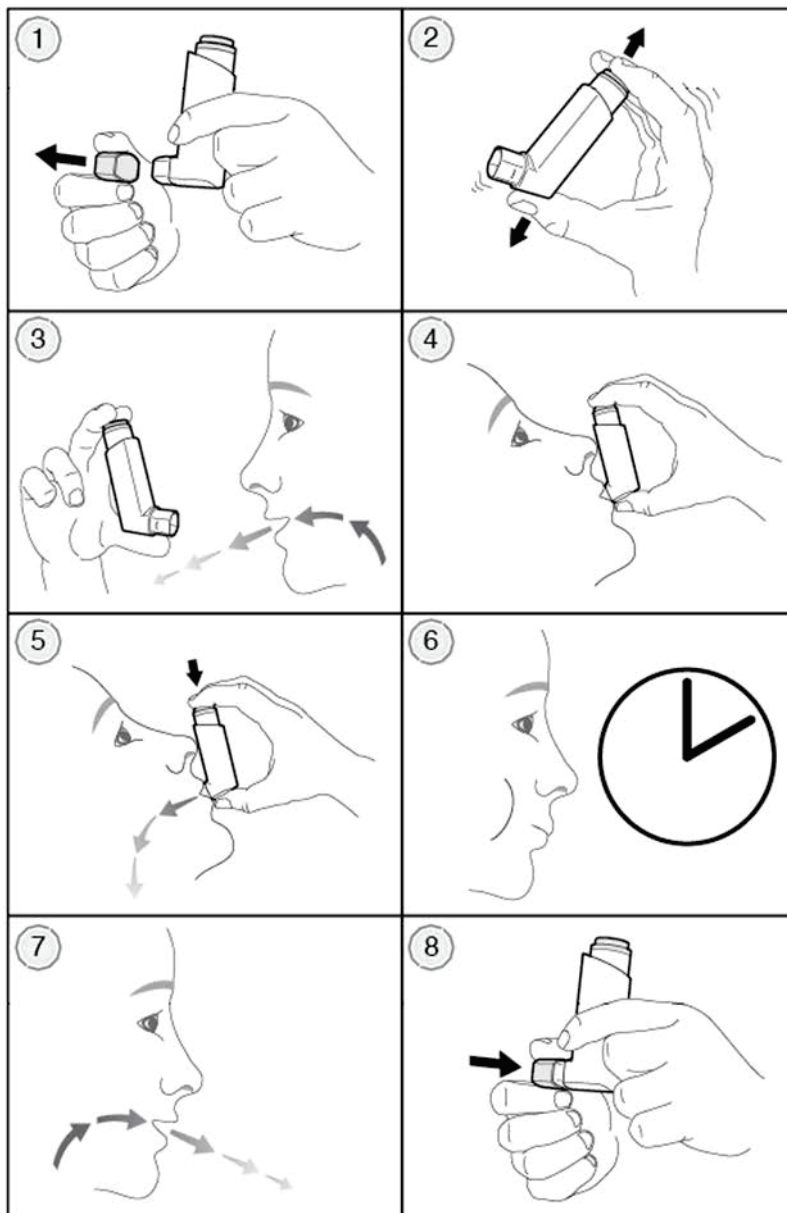
- **Step 1:** Remove the **Cap** from the **Mouthpiece**.
- **Step 2:** Shake the inhaler well before each puff.

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

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

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

**Figure 5**



## Appendix 2 Aerochamber Plus Flow-Vu Instructions for Use



### INDICATIONS FOR USE

This product is intended to be used by patients who are under the care or treatment of a physician or licensed healthcare professional. The device is intended to be used by these patients to administer aerosolized medication from most pressurized Metered Dose Inhalers. The intended environments for use include the home, hospitals and clinics.



Distributed by:  
**FOREST PHARMACEUTICALS, INC.**  
A Subsidiary of Forest Laboratories, LLC  
Forest Laboratories  
Monaghan Medical Corporation, 5 Latour Ave.,  
Suite 1000, Pittsborough, NY 12801

### INSTRUCTIONS FOR USE

THIS PRODUCT CAN BE USED RIGHT OUT OF PACKAGE. BEFORE USE, ENSURE THESE INSTRUCTIONS AND THE INSTRUCTIONS SUPPLIED WITH THE METERED DOSE INHALER (MDI) HAVE BEEN READ.

MOUTHPIECE			LARGE MASK		
1		2			

### Notes:

- Storage and operating range 5° C - 40° C (41° F - 104° F) at 15 to 95% relative humidity.
- Product may need to be replaced after 12 months of use. Environmental conditions, storage and proper cleaning can affect product life span.
- Do not share this medical device.
- If you notice medication build-up in your chamber, wash the inside of the chamber gently with a soft cloth.
- Dishwashing with overly dirty dishes is not recommended.
- Dishwasher validated up to 158°F (70°C).

### CAUTIONS:

1. PRODUCT MAY BE PERMANENTLY DAMAGED IF BOILED, STERILIZED OR CLEANED IN A DISHWASHER AT TEMPERATURE ABOVE 158°F (70°C).
2. Do not leave the chamber unattended with children.
3. Federal (USA) law restricts the sale of this device on or by the order of a physician.

**Rx Only**

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### **Appendix 3      Sponsor Signature**

**Study Title:**            A Randomized, Open-label, Single-dose, Single-center, Crossover  
Study in Healthy Subjects to Assess the Relative Bioavailability of  
PT010 Administered With and Without a Spacer, and With and  
Without Oral Charcoal

**Study Number:**        PT010011

**Final Date:**            11 September 2017

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

Signed:

A large black rectangular box redacting the signature of the sponsor.

Date: \_\_\_\_\_

A black rectangular box redacting the date of the signature.

## Appendix 4 Investigator's Signature

**Study Title:** A Randomized, Open-label, Single-dose, Single-center, Crossover Study in Healthy Subjects to Assess the Relative Bioavailability of PT010 Administered With and Without a Spacer, and With and Without Oral Charcoal

**Study Number:** PT010011

**Final Date:** 11 September 2017

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol. I agree:

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

Signed: \_\_\_\_\_

Date: \_\_\_\_\_

Name: \_\_\_\_\_

Site Name: \_\_\_\_\_