## 12.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

This appendix includes the following approved original protocol and protocol amendments:

- Protocol Version 1.0 - [redacted]
- Protocol Amendment Version 2.0 - [redacted]

# Clinical Trial Protocol: PT010003-00

| | |
|---|---|
| **Title:** | A Phase I, Randomized, Double-Blind, Placebo-Controlled, Two-Period, Ascending Dose, Crossover Study to Assess the Safety and Pharmacokinetics of Two Doses of PT010 in Healthy Adult Subjects of Japanese Descent Following a Single Dose and After Chronic Dosing for 7 Days |
| **Study Number:** | PT010003-00 |
| **Study Phase:** | Phase I |
| **Product Name:** | Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol; PT010,<br>Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler; (BGF MDI) |
| **IND Number** | 118313 |
| **Investigators:** | Single study center; United States |
| **Sponsor:** | Pearl Therapeutics, Inc.<br>[redacted] |
| **Sponsor Contact:** | [redacted] |

| | Version Number | Date |
|---|---|---|
| **Original Protocol:** | Version 1.0 | [redacted] |

**Confidentiality Statement**

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# SYNOPSIS

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|---|
| **Sponsor:**<br>Pearl Therapeutics, Inc. |
| **Names of Finished Products:**<br>Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (PT010)<br>Budesonide, Glycopyrronium, and Formoterol Fumarate (BGF) Metered Dose Inhaler; BGF MDI<br>Matching Placebo MDI |
| **Name of Active Ingredients:**<br>Budesonide<br>Glycopyrronium<br>Formoterol fumarate |
| **Study Title:**<br>A Phase I, Randomized, Double-Blind, Placebo-Controlled, Two-Period, Ascending Dose, Crossover Study to Assess the Safety and Pharmacokinetics of Two Doses of PT010 in Healthy Adult Subjects of Japanese Descent Following a Single Dose and After Chronic Dosing for 7 Days |
| **Study Number:** PT010003-00 |
| **Study Phase:** I |
| **Primary Objectives:**<br>The primary objective of this study is to assess the safety and tolerability of two doses of BGF MDI in healthy adult subjects of Japanese descent after single dosing and during chronic (7 days) dosing. |
| **Secondary Objectives:**<br>The secondary objective of the study is to describe the PK profile of two doses of BGF MDI healthy adult subjects of Japanese descent after single dosing and after chronic (7 days) dosing. |
| **Safety Objective:**<br>The safety and tolerability profile of BGF MDI will be characterized by using physical examination assessments; adverse event (AE) reporting; vital sign measurements; clinical laboratory test values; and results from 12-lead electrocardiogram (ECG) procedures. |

**Study Design:**

PT010003 is a Phase I, single-center, randomized, double-blind, placebo-controlled, two-period, ascending dose, cross-over study to assess safety/tolerability and PK of two different doses of BGF MDI in healthy adult subjects of Japanese descent. Pharmacokinetics will be assessed following a single dose and after 7 days of chronic dosing. Safety will be assessed during the 7-day treatment and throughout the entire study until subjects are released from participation. All 3 study drugs will be administered by oral inhalation. It is planned that the study will enroll and randomize an estimated 20 eligible subjects to one of three treatment sequences. Subjects will receive two of the following treatments:

BGF MDI 320/14.4/9.6 µg
BGF MDI 160/14.4/9.6 µg
Placebo MDI

This study includes a Screening Period of up to 28 days and two Treatment Periods of 8 days each, separated by a minimum Washout Period of 7 days to a maximum of 21 days for added scheduling flexibility. A follow-up phone call will be conducted at least 5 days, but no longer than 7 days after completion of the last dose date on Treatment Period 2. The maximum participation in the study for each subject is not expected to exceed 65 days. The study is anticipated to run for approximately 3 months and should not exceed 6 months.

| Treatment Sequence | Number/Subjects | Treatment Period 1 (7 Days) | Washout Prior to Crossover | Treatment Period 2 (7 Days) |
|---|---|---|---|---|
| Sequence 1 | 4 Subjects | Placebo MDI (Matching) | Approximate 7-21 Day Duration | BGF MDI 320/14.4/9.6 µg |
| Sequence 2 | 12 Subjects | BGF MDI 160/14.4/9.6 µg | | BGF MDI 320/14.4/9.6 µg |
| Sequence 3 | 4 Subjects | BGF MDI 160/14.4/9.6 µg | | Placebo MDI (Matching) |

Abbreviations: BGF=budesonide, glycopyrronium, and formoterol fumarate inhalation aerosol; MDI=metered dose inhaler; µg=microgram.

**Note:** All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7, with a final single-dose administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

This single-center study will be conducted in the United States (US).

**Study Duration:**

Study PT010003 was planned to include a Screening Period of up to 28 days and two 7-day Treatment Periods (a single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7 of each Treatment Period, with a final single-dose administration of study drug occurring on the morning of Day 8.) separated by a Washout Period (minimum of7 days; maximum of 21 days) to ensure scheduling flexibility. Subject-participation in the study is anticipated to be approximately 25 to 65 days.

**Study Population:**

The planned study population includes a total of approximately 20 male and female adult healthy subjects of Japanese descent. Subjects will be enrolled and randomized in the study to provide approximately 16 subject completers. Inclusion and exclusion criteria are listed in Section 5 .

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

Investigational materials will be provided by Pearl Therapeutics, as summarized.

| Product Name & Dose | Product Strength | Dosage Form | Administration |
|---|---|---|---|
| BGF MDI 320/14.4/9.6 µg ex-actuator | 160/7.2/4.8 µg/actuation | MDI | Taken as 2 inhalations |
| BGF MDI 160/14.4/9.6 µg ex-actuator | 80/7.2/4.8 µg/actuation | MDI | Taken as 2 inhalations |
| Matching Placebo MDI | Formulation does not contain active ingredient | MDI | Taken as 2 inhalations |

Abbreviations: BGF MDI = budesonide, glycopyrrolate, and formoterol fumarate inhalation aerosol; MDI=metered dose inhaler.
**Note**: All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7, with a final single administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day. Placebo MDI is equivalent to the test products without the active ingredients.

**Pharmacokinetic Assessments:**

Pharmacokinetics of BGF MDI will be assessed and compared using plasma concentrations of budesonide, glycopyrronium, and formoterol. For the single dose administration, timepoints for PK blood sample collection will occur within a 1-hour window prior to dosing, and blood samples will be collected again post-dose at 2, 6, 20, and 40 minutes and at 1, 2, 4, 8, 10, 12, 16, and 24 hours. After 7 days of chronic dosing in each Treatment Period, timepoints for PK blood sample collection will occur within a 30-minute window prior to dosing, and blood samples will be collected again post-dose at 2, 6, 20, and 40 minutes and at 1, 2, 4, 8, 10, and 12 hours.

Approximately 500 mL of blood will be collected per subject during the study.

Pharmacokinetic parameters calculated at the first day (Day 1) and last dose (Day 8) in each Treatment Period will include maximum plasma concentration ($C_{max}$), area under the plasma concentration-time curve from 0 to 12 hours ($AUC_{0-12}$), area under the plasma concentration-time curve from 0 to the time of the last measureable plasma concentration ($AUC_{0-t}$); area under the plasma concentration-time curve from 0 extrapolated to infinity ($AUC_{0-\infty}$) (only calculated for Day 1); time to maximum plasma concentration ($t_{max}$); elimination half-life ($t_{½}$); apparent total body clearance (CL/F); apparent volume of distribution (Vd/F); terminal elimination rate constant ($\lambda_z$); accumulation ratio for $C_{max}$ (RAC [$C_{max}$]); accumulation ratio for $AUC_{0-12}$ (RAC [$AUC_{0-12}$]). Other PK parameters may be calculated, as appropriate.

**Safety Assessments:**

The safety and tolerability profile of BGF MDI will be assessed using physical examination findings, adverse event (AE) reporting, vital sign values, clinical laboratory values, and findings from 12-lead electrocardiograms (ECGs).

**Statistical Methods:**

Two subject populations will be used for data analyses during the study and are defined as follows:

**Safety Population:** All subjects who receive at least one dose of any study drug.

**PK Population:** All subjects in the Safety Population who have sufficient data to reliably calculate at least one PK parameter at either dose level of BGF MDI and do not have major protocol deviations (to be determined prior to unblinding).

Safety Analyses: Safety and tolerability analyses will be based on descriptive statistics for ECG, vital signs, and laboratory measurements as appropriate, and also on frequencies of AEs and the number of subjects with AEs.

PK Analyses: Summary statistics without model adjustment will be used to describe the PK parameters after treatment with two doses of BGF MDI as compared with Placebo MDI.

*Sample Size*:

The planned sample size of approximately 20 randomized subjects is selected to provide approximately 16 completers and initial safety information in healthy adult subjects of Japanese descent.

**Date of Original Approved Protocol:** [redacted]

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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| API | Active Pharmaceutical Ingredients |
| AST | Aspartate Aminotransferase |
| $AUC_{0-12}$ | Area Under the Curve From 0 to 12 Hours |
| $AUC_{0-t}$ | Area Under the Curve From 0 the Time of the Last Measureable Plasma Concentration |
| $AUC_{0-\infty}$ | Area Under the Curve From 0 Extrapolated to Infinity |
| BGF MDI | Budesonide, Glycopyrrolate, and Formoterol Fumarate Metered Dose Inhaler |
| BID | Bis In Die, Twice Daily |
| BP | Blood Pressure |
| CBC | Complete Blood Cell (count) |
| CFR | Code of Federal Regulations |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration Equation (according to National Kidney Disease Education Program) |
| CL/F | Apparent Total Body Clearance |
| $C_{max}$ | Maximum plasma concentration |
| COPD | Chronic Obstructive Pulmonary Disease |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| ECG | Electrocardiogram |
| EDTA | Ethylenediaminetetraacetic Acid |
| eg | Exempli Gratia, For Example |
| eCRF | Electronic Case Report Form |
| FDA | Food and Drug Administration |
| $FEV_1$ | Forced Expiratory Volume in 1 Second |
| FF MDI | Formoterol Fumarate Metered Dose Inhaler |
| FSH | Follicle Stimulating Hormone |

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| GCP | Good Clinical Practice |
| GFF MDI | Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler |
| GFR | Glomerular Filtration Rate |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| GP MDI | Glycopyrrolate Metered Dose Inhaler |
| HbsAg | Hepatitis B Surface Antigen |
| hCG | Human Chorionic Gonadotropin |
| HFA | Hydrofluoroalkane |
| HIV | Human Immunodeficiency Virus |
| HR | Heart Rate |
| IB | Investigators Brochure |
| ICF | Informed Consent Form |
| ICS | Inhaled Corticosteroid |
| ICMJE | International Committee of Medical Journal Editors |
| ie | Id Est, That Is |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| ISMPP | International Society for Medical Publications Professionals |
| IV | Intravenous |
| JRS | Japanese Respiratory Society |
| LABA | Long-acting β2 Agonist |
| LAMA | Long-acting Muscarinic Antagonist |
| $\lambda_z$ | Terminal Elimination Rate Constant |
| MDI | Metered Dose Inhaler |
| µg | Microgram |
| mL | Milliliter |
| mm | Millimeter |
| mmHg | Millimeter of Mercury |

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| msec (ms) | Millisecond |
| PK | Pharmacokinetics |
| QTcF | QT Corrected Using Fridericia's Formula |
| RAC($C_{max}$) | Accumulation ratio for $C_{max}$ |
| RAC($AUC_{0-12}$) | Accumulation ratio for $AUC_{0-12}$ |
| SABA | Short-acting β2-agonists |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| [redacted] | [redacted] |
| SOP | Standard Operating Procedure |
| $t_{½}$ | Apparent Terminal Elimination Half-life |
| [redacted] | [redacted] |
| TEAE | Treatment-emergent Adverse Event |
| $t_{max}$ | Time To Maximum Plasma Concentration |
| US | United States |
| Vd/F | Apparent Volume of Distribution |

# TRADEMARK INFORMATION

Trademarks not owned by Pearl Therapeutics, Inc. include:

Aerolizer

Aqua

Breezhaler

Cuvposa

Foradil

Oxis

Pulmicort

Respules

Rhinocort

Robinul

Robinul Forte

Spiriva

Symbicort

Turbuhaler

Ziploc

Vacutainer

# 1 INTRODUCTION AND STUDY RATIONALE

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

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are $\beta_2$-agonists, muscarinic antagonists, and methylxanthines which may be 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. Combining bronchodilators from different pharmacological classes may improve efficacy and decrease the risk of side effects compared with increasing the dose of a single bronchodilator [GOLD, 2014]. Long-acting $\beta_2$-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) reduce bronchoconstriction through different mechanisms, and there is a long history of combination therapy for COPD with short-acting agents in these classes.

Regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function, quality of life, and reduces the frequency of exacerbations in subjects with COPD and a forced expiratory volume in 1 second ($FEV_1$) value of <60% of predicted. Withdrawal from treatment with ICS may lead to exacerbations in some patients. When combined with a LABA, an ICS is more effective than the individual components in improving lung function, quality of life, and reducing exacerbations in subjects with moderate to very severe COPD. Furthermore, the addition of a LABA/ICS combination to the muscarinic antagonist tiotropium improves lung function and quality of life and may further reduce exacerbations, but more studies of triple therapy are needed [GOLD, 2014]. Pearl Therapeutics, Inc. (hereinafter referred to as Pearl) is developing the ICS/LAMA/LABA 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 COPD.

Glycopyrrolate (Robinul® and Robinul Forte®) is an antimuscarinic drug that is marketed in the United States (US) in both oral and parenteral formulations. Glycopyrrolate is a quaternary ammonium derivative, that when inhaled results in minimal mucosal absorption and systemic side effects. Glycopyrrolate is approved for respiratory inhalation in Japan for the treatment of COPD. In addition, tiotropium bromide (Spiriva® [Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA]) is approved worldwide as a powder for inhalation. It has been shown to reduce the rate of COPD exacerbations and to improve the effectiveness of pulmonary rehabilitation [Niewoehner, 2005; Casaburi, 2005].

Formoterol fumarate is a selective LABA approved in the US (eg., Foradil® Aerolizer®[ Merck Sharp & Dohme Corporation, a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA]) and worldwide (eg, Oxis® Turbuhaler®[Worldwide AstraZeneca Group of Companies; London, UK] Foradil) for use in asthma and COPD. Formoterol fumarate is also approved in the US and worldwide in combination with budesonide (eg., Symbicort® MDI, Symbicort® Turbuhaler® [AstraZeneca, LP, Wilmington Delaware]) 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.

Although formoterol fumarate is classified as a LABA, it has a rapid onset of action similar to short-acting $\beta_2$-agonists (SABAs). Formoterol fumarate is highly potent, displays high intrinsic activity, and can result in greater than 80% relaxation even under induced tone [Anderson, 1993]. Studies in subjects with COPD have demonstrated that the onset of action with formoterol fumarate is faster than with antimuscarinic agents or salmeterol, and similar to that of SABAs, such as albuterol, and that the duration of action is ≥12 hours [Berger, 2008]. Five large, placebo-controlled clinical studies of up to 12 months in duration in nearly 2500 patients demonstrated that formoterol fumarate is effective and well tolerated in patients with COPD [Dahl, 2001; Rossi, 2002; Albers R 2002;Campbell 2005; Campbell 2007].

Budesonide is a well-established corticosteroid approved worldwide in mono- and combination therapies for treatment of asthma and allergic rhinitis. It is available in both intranasal and inhaled formulations. Budesonide formulations currently approved and marketed in the US by AstraZeneca LP, Wilmington DE, USA, include: Rhinocort® Nasal Inhaler, Rhinocort Aqua® Nasal Spray, Pulmicort® Turbuhaler®, Pulmicort Respules®, and as the ICS component of Symbicort Inhalation Aerosol (Symbicort MDI). Inhaled budesonide as a mono therapy (Pulmicort) and in combination with formoterol fumarate dehydrate (ie, Symbicort) is approved for use in patients with COPD.

In clinical studies, Symbicort MDI 320/9 µg administered twice-daily (BID) demonstrated significant improvements in lung function compared with Budesonide MDI 320 µg BID, formoterol fumarate (Oxis Turbuhaler) 9 µg BID, or placebo in patients with COPD. In the clinical studies, improvements in secondary endpoints of morning and evening peak expiratory flow and reduction in rescue medication use were supportive of the efficacy of Symbicort MDI 320/9 µg [Symbicort Inhalation Aerosol Prescribing Information, 2012; Rennard, 2009; Tashkin, 2008]. The GOLD COPD guidelines acknowledge that combination therapy with an ICS and LABA is more effective than the individual components in improving lung function and health status, and reducing exacerbations in patients with moderate to very severe COPD [GOLD, 2014].

Pearl is developing BGF MDI using its porous particle technology platform. This technology is based on spray-dried porous particles comprised of distearoylphosphatidylcholine and calcium chloride that are co-suspended with micronized active pharmaceutical ingredients (APIs) in a hydrofluoroalkane (HFA) propellant to form stable suspension-based MDIs.

## 1.1 Study Rationale

BGF MDI is a proprietary, fixed-dose triple combination MDI product formulated with budesonide, glycopyrrolate, and formoterol fumarate for treatment of subjects with COPD. As described in the GOLD COPD guidelines, in some patients, the addition of a LABA/ICS to a LAMA improves lung function, quality of life, and may further reduce exacerbations. For patients with many symptoms and at high-risk of exacerbations (GOLD Category D [GOLD], 2014]), one treatment option is a combination of all three drug classes, which provides support to the use of a triple therapy (ICS/LAM/LABA).

The purpose of this study is to characterize the pharmacokinetics (PK) and safety and tolerability profile of two doses of BGF MDI (320/14.4/9.6 µg and 160/14.4/9.6 µg doses) following a single dose and after chronic dosing (7 days) , compared with Placebo MDI in healthy adult subjects of Japanese descent.

The safety/tolerability and efficacy of the individual components, budesonide, glycopyrronium, and formoterol fumarate are well characterized. Pearl has conducted an initial Phase I single-dose PK and safety study in healthy adult subjects (Study PT010001) with three doses of the triple combination product, BGF MDI compared with two doses of Symbicort® MDI and a single dose of the Pearl dual combination product Glycopyrronium and Formoterol Fumarate Metered Dose (GFF MDI; PT003).
The study demonstrated that formoterol and glycopyrronium plasma concentrations following administration of all BGF MDI doses were similar to those following GFF MDI administration. The budesonide plasma concentrations were comparable between BGF MDI and Symbicort MDI. All treatments were well tolerated with a low frequency of adverse events (AEs), and no untoward safety signals were observed. The results of Study PT010001 support the evaluation of BGF MDI 320/14.4/9.6 µg and lower doses in further clinical studies and suggest that the addition of budesonide to GFF MDI does not impact the systemic levels of either component. Based on these findings in Western subjects, Study PT010003 is being conducted to identify the appropriate dose(s) for evaluation in the Japanese population.

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective of this study is to assess the safety and tolerability of two doses of BGF MDI in healthy adult subjects of Japanese descent after single dosing and during chronic (7 days) dosing.

## 2.2 Secondary Objective

The secondary objective of the study is to describe the PK profile of two doses of BGF MDI healthy adult subjects of Japanese descent after single dosing and after chronic (7 days) dosing.

## 2.3 Safety Objective

The safety and tolerability profile of BGF MDI will be characterized by using physical examination assessments; adverse event (AE) reporting; vital sign measurements; clinical laboratory test values; and results from 12-lead electrocardiogram (ECG) procedures.

# 3 STUDY ENDPOINTS

## 3.1 Efficacy Endpoint

This study is being conducted to assess in healthy subjects. Therefore, efficacy will not be evaluated.

## 3.2 Safety Endpoint

The safety and tolerability of BGF MDI will be assessed from physical examination findings, AE reporting including serious AE (SAE) reporting, vital signs (blood pressure [BP], heart rate [HR], respiratory rate, and body temperature), clinical laboratory values (hematology, chemistry, and urinalysis), and findings from 12-lead safety electrocardiograms (ECGs).

## 3.3 Pharmacokinetic Endpoint

Pharmacokinetics of BGF MDI will be assessed and compared using plasma concentrations of budesonide, glycopyrronium, and formoterol. For the single dose administration, timepoints for PK blood sample collection will occur within a 60-minute window prior to dosing, and blood samples will be collected again post-dose at 2, 6, 20, and 40 minutes and at 1, 2, 4, 8, 10, 12, 16, and 24 hours. After 7 days of chronic dosing in each Treatment Period, timepoints for PK blood sample collection will occur within a 60-minute window prior to dosing, and blood samples will be collected again post-dose at 2, 6, 20, and 40 minutes and at 1, 2, 4, 8, 10, and 12 hours. Pharmacokinetic parameters calculated at the first day (Day 1) and last dose (Day 8) in each Treatment Period will include the following:

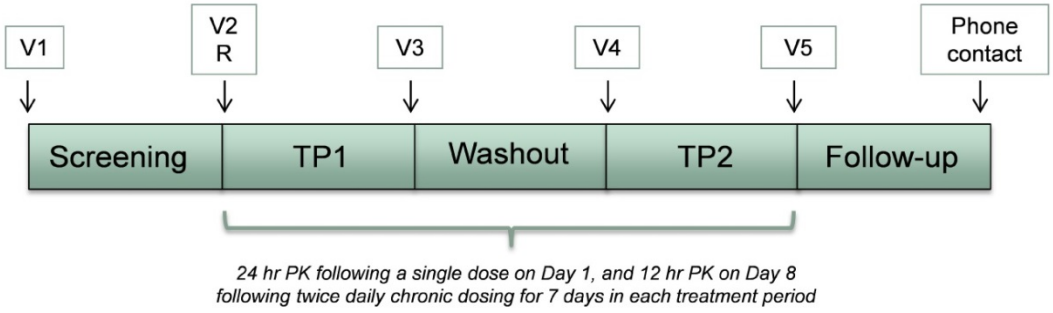
- Maximum plasma concentration ($C_{max}$)
- Area under the plasma concentration-time curve from 0 to 12 hours ($AUC_{0-12}$)
- Area under the plasma concentration-time curve from 0 to the time of the last measureable plasma concentration ($AUC_{0-t}$)
- Area under the plasma concentration-time curve from 0 extrapolated to infinity ($AUC_{0-\infty}$) (Calculated for Day 1 *only*)
- Time to maximum plasma concentration ($t_{max}$)
- Elimination half-life ($t_{½}$)
- Apparent total body clearance (CL/F)
- Apparent volume of distribution (Vd/F)
- Terminal elimination rate constant ($\lambda_z$)
- Accumulation ratio for $C_{max}$ (RAC [$C_{max}$])
- Accumulation ratio for $AUC_{0-12}$ (RAC [$AUC_{0-12}$])

# 4 INVESTIGATIONAL PLAN

## 4.1 Overall Study Design and Plan

This is a Phase I, single-center, randomized, double-blind, placebo-controlled, two-period, ascending dose, cross-over study to assess safety and PK of two doses of BGF MDI in healthy adult subjects of Japanese descent following a single dose and after chronic dosing for 7 days. The overall study design is summarized and illustrated in Figure 4-1.

**Figure 4-1. Study Design**




[1] Abbreviations: R=randomization; TP=Treatment Period

**Note**: All study drugs are administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7 of each Treatment Period, with a final single administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

Subjects who provide informed consent, undergo Screening procedures, and qualify for the study will be randomized to one of three treatment sequences, as shown in Table 4-1.

**Table 4-1. Treatment Sequences**

| Treatment Sequence | n | Treatment Period 1 | | Treatment Period 2 |
|---|---|---|---|---|
| 1 | 4 | Placebo MDI | **Wash-out** | BGF MDI 320/14.4/9.6 µg |
| 2 | 12 | BGF MDI 160/14.4/9.6 µg | | BGF MDI 320/14.4/9.6 µg |
| 3 | 4 | BGF MDI 160/14.4/9.6 µg | | Placebo MDI |

Abbreviations: BGF=budesonide, glycopyrrolate, and formoterol fumarate inhalation aerosol; MDI=metered dose inhaler

**Note**: All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7 of each Treatment Period, with a final single administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

Approximately 20 subjects are planned to be randomized, with four subjects in each of the two sequences that include a Placebo MDI treatment group, and 12 subjects in the BGF MDI (160/14.4/9.6 µg)/ BGF MDI (320/14.4/9.6 µg) treatment sequence.

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Subjects will be admitted as inpatients to the Clinical Research Unit (CRU; hereinafter referred to as "clinic") during the Treatment Periods. The inpatient Treatment Periods will be separated by a Washout Period of at least 7 calendar days and not exceeding 21 days between doses. For each Treatment Period, subjects will report to the clinic on Day-1 (the day prior to dosing), at which time, continuing eligibility will be assessed. If the subject continues to meet eligibility criteria, the subject will be admitted into the inpatient study unit.

Safety data will be closely monitored, and baseline and post-dosing serial blood draws (Section 7.9) for PK analysis (Refer to Table 8-2 and Table 8-3) will be obtained during each inpatient Treatment Period. After all scheduled assessments are completed and all available safety data have been reviewed by the Principal Investigator, subjects will be discharged from the clinic. Following the first Treatment Period, subjects will return to the clinic after their Washout Period of at least 7 calendar days between doses for their second inpatient Treatment Period. Other safety assessments will be obtained as listed in Table 8-2 and Table 8-3. A follow-up phone call will be conducted 5 days, but no later than 7 days, after completion of the last dose date on Treatment Period 2.

## 4.2 Study Duration and Dates

This study will include a Screening Period of up to 28 days and two Treatment Periods of 8 days each, separated by a minimum Washout Period of 7 days to a maximum of 21 days for added scheduling flexibility. A follow-up phone call will be conducted at least 5 days, but no longer than 7 days after completion of the last dose date on Treatment Period 2. Subject-participation duration is not expected to exceed 65 days. The study is anticipated to run for approximately 3 months and is not expected to exceed 6 months.

# 5 STUDY POPULATION SELECTION

Approximately 20 healthy male or female subjects will be randomized in this study. Subjects who withdraw from the study after receiving at least one single-dose treatment will not be replaced. Subjects who are randomized but did not receive treatment will be replaced. Subjects who are re-evaluated will maintain one screening number throughout the study.

## 5.1 Inclusion Criteria

Healthy subjects who meet all of the following inclusion criteria will be eligible for entry into this study:

1. Signed and dated Institutional Review Board (IRB)-approved Informed Consent Form (ICF) before any protocol specific screening procedures are performed.
2. Male and female first generation Japanese subjects ranging in age between18 to 55 years, inclusive:
3. First generation subjects who were born in Japan to two parents and four grandparents also born in Japan of full Japanese descent
4. Subjects must be an expatriate of Japan residing outside of Japan for less than five years
5. Subjects must have a valid Japanese passport
6. Subjects who have a body weight ≥50 kg (110 lbs) at the Screening Visit and body mass index between 18.5 and 32 kg/$m^2$, inclusive
7. Be in good general health as determined by a thorough medical history and physical examination, ECG, vital signs, and clinical laboratory evaluation.
8. Willing and able to complete all study assessments and procedures.
9. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception from the Screening Period through the Final Telephone Follow-up: hormonal contraception, condom with spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, injectable contraceptive, or intra-uterine device. A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. Subjects must agree to practice the above birth control methods through the Final Telephone Follow-up as a safety precaution.
10. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months, do not require contraception during the study. Post-menopausal must be confirmed by a serum follicle-stimulating hormone (FSH) test at Screening.
11. Males with female partners of childbearing potential must agree to use a highly effective, medically acceptable form of contraception from the Screening Period through the Final Telephone Follow-up. Males with female partners of childbearing potential who themselves are surgically sterile (status post-vasectomy) must agree to use condoms with spermicide over the same period of time. Male subjects must agree to practice the above birth control methods through the Final Telephone Follow-up as a safety precaution.

12. Results of complete blood cell (CBC) count (including white blood cell count, hematocrit, hemoglobin, platelet count, differential), serum creatinine, electrolytes (Na+, K+), serum glucose, aspartate aminotransferase/alanine aminotransferase (AST/ALT), and total bilirubin must be within normal ranges or determined to be not clinically significant by the Investigator.

## 5.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible for entry into this study:

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 each of the two 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 with a history of ECG abnormalities including PR>220 msec; QRS complex >110 msec; QT Corrected Using Fridericia's Formula (QTcF) >450 ms in both males and females; or any significant morphological changes other than non-specific T-wave changes;
   - In addition, subjects who demonstrate any of these or any other significant 12-lead ECG abnormalities prior to the first Treatment Period (ie, 12-lead ECGs performed at Screening, baseline (pre-dose on Day 1 of the first Treatment Period [ECG obtained within 1 hour prior to dosing on Day 1 of Treatment Period 1]) will be excluded from participation in the study;
5. A history of additional risk factors for Torsades de Pointes (eg, heart failure, family history of Long QT Syndrome);
6. Subjects with the inability to coordinate the use of the Placebo MDI under supervision from site staff;
7. Subjects who have cancer that has not been in complete remission for at least 5 years;
8. Supine BP >140/90 mmHg or resting HR≥100 beats per minute at Screening (pre-dose on Day 1 of the first Treatment Period);
9. Male subjects with symptomatic prostatic hypertrophy that is clinically significant in the opinion of the Investigator;
10. Male subjects with a trans-urethral resection of the prostate or full resection of the prostate within 6 months prior to Screening;
11. Subjects with bladder neck obstruction or urinary retention that is clinically significant in the opinion of the Investigator;
12. Subjects with a diagnosis of glaucoma that in the opinion of the Investigator has not been adequately treated;
    - All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective β-blockers such as betaxolol, carteolol, levobunolol, metipranolol, prostaglandin analogues, and timolol;

13. History of substance-related disorders (with the exception of caffeine-related and nicotine-related disorders) as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM), fourth edition, text revision within 1 year of Screening;
14. History of smoking or the use of nicotine containing products or electronic cigarettes within 3 months of Screening by self-reporting;
15. A positive alcohol breathalyzer or urine drug screen for drugs of abuse at the Screening Visit or at the beginning of each inpatient period;
16. Treatment with an investigational drug within 30 days or five half-lives (whichever is longer) prior to the beginning of the Screening Period;
17. Treatment with any prescription or non-prescription drugs (including vitamins, herbal, and dietary supplements) within 30 days or five half-lives (whichever is longer) prior to Visit 2 (Day 1);
    - Acetaminophen will be permitted at doses of ≤2 grams/day. In females, oral and/or implanted contraceptive medication is permitted;
18. Subjects with a history of an allergic reaction or hypersensitivity to any drug or who develop allergic reaction or hypersensitivity to any component of the formulation(s) used in this study;
19. Blood collection of greater than 500 mL within 56 days prior to Screening;
20. Subjects with pre-existing blood conditions, as described:
    a. Subjects with anemia at Screening: defined as hemoglobin < 13.8 and < 11.3 for males and females, respectively, ***or***
    b. Hematocrit < 40.2 % and < 34.4 % for males and females, respectively;
21. Seropositivity for human immunodeficiency virus (HIV) at Screening;
22. Positive for hepatitis B surface antigen (HbsAg) or positive hepatitis C antibody at Screening;
23. Subjects with a chronic medical condition that requires ongoing treatment with medication;
24. Subjects with a history of major surgery within 4 weeks or minor surgery within 2 weeks of drug administration;
25. 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;
26. Any other condition and/or situation that causes the Investigator to deem a subject unsuitable for the study (eg, due to expected study drug non-compliance, inability to medically tolerate the study procedures, or a subject's unwillingness to comply with study-related procedures);
27. Subjects with abnormal-glomerular filtration rate (GFR; estimated GFR <90 mL/min) using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI);
28. Subjects who have participated in a previous Pearl study involving BGF or its individual components budesonide, glycopyrronium, or formoterol fumarate.

## 5.3 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.

## 5.4 Prior, Concomitant, and Prohibited Medications

Investigational therapies are not permitted within 30 days or five half-lives (whichever is longer) prior to beginning the Screening Period.

All medications approved for control of intraocular pressure are allowed including topical ophthalmic non-selective β-blockers such as betaxolol, carteolol, levobunolol, metipranolol, prostaglandin analogues (eg, bimatoprost), and timolol). Otherwise, the use of prescription or over-the counter medications within 30 days or five half-lives (whichever is longer) prior to Visit 2 (Day 1) is not permitted. Acetaminophen will be permitted at doses of ≤2 grams/day as determined to be necessary by the Investigator. With the exception of treatments for control of intraocular pressure and contraceptives in female subjects, ongoing treatment for chronic conditions will not be allowed.

Any medications that were being taken prior to signing the ICF will be documented as prior study drugs and must be stopped prior to entry.

## 5.5 Other Study Restrictions

### 5.5.1 Surgical Procedure/Intervention Restrictions

Major surgical interventions are not permitted within 4 weeks of study drug administration and minor surgical interventions are not allowed within 2 weeks of study drug administration.

### 5.5.2 Dietary Restrictions

For scheduled clinical laboratory assessment blood draws, subjects will be fasting for at least 4 hours. Meals during the dosing day of each Treatment Period will be standardized after the 4-hour post-dose clinical laboratory draw. There are no restrictions regarding clear fluid intake.

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

### 5.5.3 Illicit Drugs and/or Drugs of Abuse Restriction

Illicit drugs and/or drugs of abuse will not be allowed from within 1 year of Screening to whenever the subject discontinues the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented. Refer to Exclusion Criterion 13 and 26 in Section 5.2)

### 5.5.4 Smoking Restrictions

Smoking is prohibited duration of the study and 3 months prior to screening. Electronic cigarettes will be treated the same way as smoking is considered in the protocol.

## 5.6 Removal of Subjects from the Study or Study Drug

The Investigator may withdraw a subject at the occurrence of any or all of the following:

- Protocol deviation
- AE
- Clinically significant change in a laboratory parameter(s)
- Termination of the study by the Sponsor or Investigator
- Request by the subject to be discontinued from the study
- Investigator's discretion

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

## 6.1 Subject Information

Clinical supplies will be packaged to support enrollment of the study. All treatment arms will be blinded. The characteristics of the BGF MDI and Placebo MDI doses that will be administered during the study are presented in Table 6-2.

An unblinded pharmacist at the site will be provided with a written randomization scheme for allocation of subjects to one of three treatment sequences and to manage the distribution of clinical supplies. The three treatment sequences are listed in the following table (Table 6-1):

**Table 6-1. Treatment Sequences**

| Treatment Sequence | Number/Subjects | Treatment Period 1 (7 Days) | Washout Prior to Crossover | Treatment Period 2 (7 Days) |
|---|---|---|---|---|
| Sequence 1 | 4 Subjects | Placebo MDI (Matching) | Approximate 7-21 Day Duration | BGF MDI 320/14.4/9.6 µg |
| Sequence 2 | 12 Subjects | BGF MDI 160/14.4/9.6 µg | | BGF MDI 320/14.4/9.6 µg |
| Sequence 3 | 4 Subjects | BGF MDI 160/14.4/9.6 µg | | Placebo MDI (Matching) |

Abbreviations: BGF=budesonide, glycopyrronium, and formoterol fumarate inhalation aerosol; MDI=metered dose inhaler; µg=microgram.

**Note:** All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7 of each Treatment Period, with a final single administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

For each subject, single dose administration (Day 1),BID dosing (Day 2 through Day 7), and single-morning dose (Day 8) administration of study drug for chronic dosing of 7 days during each of the two Treatment Periods should occur at approximately the same time of day.

## 6.2 Dispensing Study Drug

All subjects will receive BGF MDI (320/14.4/9.6 µg), BGF MDI (160/14.4/9.6 µg), or Placebo MDI by random assignment to one of three predetermined treatment sequences (Refer to Section 6.1). At Screening, subjects will be instructed on the proper use of an MDI using a bulk-supplied Placebo MDI and, at that time, must demonstrate the ability to coordinate use of the MDI.

On Day 1 of each Treatment Period, prior to the first MDI administration, the MDI device will be primed in the study site pharmacy by the pharmacist and delivered to the inpatient clinic. Just prior to dosing, subjects will again be given detailed instruction regarding the proper use of the MDI device to ensure comprehension of its use. At the time of all study drug-dosing, a healthcare provider will be present to ensure that the subject properly administers the required number of activations of the MDI device.

## 6.3 Study Drug Product Descriptions

The BGF MDI active drug substances are budesonide, glycopyrronium, and formoterol fumarate dihydrate. Investigational materials will be provided by Pearl as summarized in the following table (Table 6-2):

### Table 6-2. Product Descriptions

| Product Name & Dose | Product Strength | Dosage Form | Administration |
|---|---|---|---|
| BGF MDI 320/14.4/9.6 µg ex-actuator | 160/7.2/4.8 µg/actuation | MDI | Taken as 2 inhalations |
| BGF MDI 160/14.4/9.6 µg ex-actuator | 80/7.2/4.8 µg/actuation | MDI | Taken as 2 inhalations |
| Matching Placebo MDI | Formulation does not contain active ingredient | MDI | Taken as 2 inhalations |

Abbreviations: BGF MDI = budesonide, glycopyrrolate, and formoterol fumarate inhalation aerosol; MDI=metered dose inhaler.
**Note**: All study drugs will be administered by oral inhalation. Placebo is formulated by Pearl in the image of the active test product(s) (ie, matching).

Following Screening and determination of eligibility, dosing will span two Treatment Periods based on three treatment sequences. The treatment and study visit schedule is illustrated in Table 4-1.

## 6.4 Study Drug Packaging and Box Labeling Information

Study drug will be provided as packaged supplies. Each subject will be randomized to one of three treatment sequences.

**BGF MDI and Placebo MDI:** Each of the formulations (approximately 10.8 grams) is contained within a coated aluminum canister fitted with a metering valve and plastic actuator. The products are foil overwrapped with desiccant. The products are formulated with sufficient suspension to ensure delivery of 120 inhalations from the nominal 50 µL valve over the shelf-life of the product.

## 6.5 Unblinding Procedures

The Sponsor will provide disclosure cards with the clinical supplies for the purpose of unblinding. The Investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject.

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

## 6.6 Study Drug Storage Requirements

**BGF MDI and Placebo MDI:** Prior to dispensing, BGF MDI and Placebo MDI should be stored according to the product label.

Clinical supplies for this study will be provided to the study site pharmacy by [redacted].
The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this protocol or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained.

## 6.7 Preparation of Study Products for Dispensing and Administration

Instructions regarding the administration of study drug are provided in Appendix 1.

## 6.8 Study Drug Accountability/Return of Clinical Supplies

**NOTE: 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 assistants have access. Storage conditions for the clinical supplies should be observed, monitored, and documented. Clinical supplies are to be dispensed only in accordance with the protocol. The Investigator is responsible for keeping accurate records of the clinical supplies received from [redacted], 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 Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned to [redacted].

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

For each subject, all used study drug materials will be collected and placed in a plastic bag (Ziploc® or similar type bag) and labeled with the subject number. Used subject supplies will be kept at 20°C to 25°C (68°F to 77°F) in a secure and locked cabinet until returned to [redacted].

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

# 7 STUDY PROCEDURES

## 7.1 Informed Consent

The informed consent form (ICF) must be executed *prior* to performing any and all study-related activities. The ICF must be approved by the Independent Ethics Committee (IEC)/IRB that is reviewing the studydocuments. 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 Eligibility of Subjects

Eligibility screening of healthy subjects will be completed within 28 days prior to administration of the first study drug and will be documented on the eCRF. Confirmation of eligibility will be performed at clinic admission (Day -1), Day 1, and Day 8 for each of the two Treatment Periods. Screening failures and the reason for screen-failure will be documented in the study site source documents.

## 7.3 Medical History

Relevant medical history, based on the opinion of the Investigator, will be obtained from the subject at Screening, on the day of each clinic admission (Day -1), and during the Follow-up telephone call, 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 Use of Concomitant Medications

The Investigator or designated qualified personnel will assess subject-use of concomitant medications at the Screening Visit, on the day of each clinic admission (Day -1), on Day 1 and Day 8 of each Treatment Period, and during the Final Telephone Follow-up. Concomitant medication use will be recorded on the eCRF. Specific information regarding use of concomitant medication and/or prior therapies is provided in Section 5.4.

## 7.5 Physical Examination

A complete physical examination including height and weight will be performed at the time of Screening and on the day of each clinic admission (Day -1). The findings of each examination will be recorded on the source documents and clinically significant abnormalities will be recorded on the eCRF.

The physical examination will include:

- Documentation of height (Screening only)
- Documentation of weight (Screening only)
- General appearance
- Head, eyes, ears, nose, and throat
- Respiratory
- Cardiovascular
- Musculoskeletal
- Gastrointestinal
- Neurologic
- Extremities
- Dermatologic
- Lymphatic

## 7.6 Vital Signs

Vital sign determinations, including BP, HR, respiratory rate, and body temperature will be performed after the subject has been supine for a 5-minute period at the Screening Visit, on the day of each clinic admission (Day -1), and on Day 1 and Day 8 of each Treatment Period, within 1 hour prior to administration of study drug and 30 minutes, 2 hours, 12 hours, and 24 hours (Day 1 only) post administration of study drug (Refer to Table 8-2 and Table 8-3).

## 7.7 Electrocardiography

Twelve-lead ECGs will be recorded at Screening and on the day of each clinic admission (Day -1) (baseline represents pre-dose on Day 1 of the first Treatment Period). On each treatment day (Day 1 and Day 8), 12-lead ECGs will be obtained within 1 hour prior to dosing and at 30 minutes and 2, 12, and 24 (Day 1 only) hours post-dosing (Refer to Table 8-2 and Table 8-3). Subjects should be supine and resting for at least 5 minutes before and during the ECG recording procedure. Subjects with any ECG abnormalities should be evaluated by the Investigator to determine if each abnormality is clinically

significant. All clinically significant abnormalities will be reported as AEs and followed closely by the Investigator in order to assure the safety of the study subject.

## 7.8 Clinical Laboratory Tests

### 7.8.1 Laboratory Parameters

**Note:** Subjects must be **fasting for at least 4 hours prior** to any scheduled clinical laboratory assessment blood draw.

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 7-1 will be collected at Screening and on the day of each clinic admission (Day -1 of each Treatment Period).

At 12 hours post administration of study drug on Day 1 and Day 8 during each of the two Treatment Periods, chemistry and hematology samples will be collected.

Additionally, blood samples will be drawn for assessments of glucose and potassium level determination within 60 minutes *prior* to dosing and at 30 minutes and 2 and 4 hours *post*-administration of study drug on Day 1 and Day 8 (Refer to Table 8-2 and Table 8-3).

Meals during the dosing day of each Treatment Period (Day 1 and Day 8) will be standardized after the 4-hour post-dose clinical laboratory draw.

There are no restrictions regarding clear fluid intake.

## Table 7-1. Laboratory Tests

| Hematology | Chemistry | |
|---|---|---|
| Hematocrit [a]<br>Hemoglobin<br>Serum Iron<br>Ferritin<br>Platelet count<br>Red blood cell (RBC) count<br>White blood cell (WBC) count<br>WBC differential<br>Mean corpuscular volume (MCV)<br>Mean cell hemoglobin (MCH)<br>MCH concentration (MCHC) | Creatinine [b]<br>Potassium (K+) [c]<br>Sodium (Na+)<br>Chloride (Cl-)<br>Magnesium (Mg++)<br>Calcium<br>Inorganic phosphate<br>Glucose [c]<br>Urea<br>Bilirubin (Total) | Bilirubin (direct)<br>Alanine aminotransferase (ALT)<br>Aspartate aminotransferase (AST)<br>Gamma-glutamyltransferase (GGT)<br>Alkaline phosphatase<br>Total Protein<br>Albumin |
| **Urinalysis:** 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. | | |
| **Urine drug screen:** A urine sample will be collected and analyzed (positive or negative) for drugs of abuse including amphetamine, opiate, cocaine, barbiturates, benzodiazepines, and marijuana [tetrahydrocannabinol]. | | |
| **Breathalyzer Test:** A breathalyzer test will be performed for the presence of alcohol (positive or negative). | | |
| **Serology:** 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. | | |
| **For females who are not post-menopausal:** A serum hCG test at Screening and urine hCG test at admission for each of the two Treatment Periods. | | |
| **For females of non-childbearing potential:** A serum hCG test at Screening and urine hCG test at admission for each of the two Treatment Periods. In addition, a serum FSH test for confirmation of non-childbearing status will be performed at Screening only. | | |

Abbreviations: CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration Equation; eGFR=estimated glomerular filtration rate; HbsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; FSH=follicle-stimulating hormone.

a Packed cell volume
b Serum creatinine value will be used to calculate eGFR using CKD-EPI.
c Additionally, within 60 minutes prior to dosing and at 30 minutes, 2 hours, and 4 hours post-dose of each Treatment Period

### 7.8.2 Laboratory Sample Collection, Storage and Shipping

Detailed instructions for laboratory sample collection, processing, and shipping instructions will be provided in the [redacted] laboratory manual. Approximately 500 mL of blood will be collected per subject during the study.

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.

## 7.9 Pharmacokinetic Assessments

**Note:** Pharmacokinetic sampling will occur in conjunction with Treatment Periods 1 and 2. Sample collections will be scheduled for the nominal timepoint and actual collection times will be recorded in the source documents (Refer to Table 8-2and Table 8-3).

### 7.9.1 Blood Sample Collection Schedule

***PRE-Dose Administration Sample Collection-On Day 1 AND Day 8:***

Approximately 10 mL of whole blood will be collected within 1 hour *prior* to administration of study drug.

***POST-Dose Administration –On Day 1 ONLY:***

Approximately 10 mL of whole blood will be collected at 2, 6, 20, and 40 minutes, and at Hour(s) 1, 2, 4, 8, 10, 12, 16 , and 24.

***POST-Dose Administration Sample Collection –On Day 8 ONLY:***

Approximately 10 mL of whole blood will be collected at 2, 6, 20, and 40 minutes.

### 7.9.2 Procedure for Sample Collection

Samples will be collected via an indwelling intravenous (IV) cannula (per the study site's Standard Operating Procedure [SOP]) or, if necessary, by direct venipuncture into vacuum collection tubes (for example Vacutainer™ [redacted] plasma collection tube) containing thylenediaminetetraacetic acid (EDTA) tripotassium. After processing, the plasma for each sample will be harvested, divided into two approximately equal aliquots, and transferred into cryotubes appropriate for plasma. Aliquots are to be frozen at≤-60°C. Refer to Appendix 2 for plasma collection, processing, and handling.

### 7.9.3 Procedure for Shipping Samples

Samples are to be shipped frozen by overnight courier to the bioanalytical laboratory [redacted] for analysis. Plasma levels of budesonide,

glycopyrronium, and formoterol will be determined using validated High Performance Liquid Chromatography tandem Mass Spectrometry methodology. Instructions for sample handling, storage, and shipping will be provided in the [redacted] laboratory manual.

## 7.10 Safety Assessments

#### 7.10.1.1 Performing Adverse Events Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's case report form and on the AE Reporting Form. If the AE is "alarming," the Investigator must report the AE immediately to Pearl Therapeutics. In addition, certain AEs (as described in Section 7.10.1.2) are classified as "serious" and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as a serious AE (SAE) to Pearl Therapeutics or its designee.

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

#### 7.10.1.2 Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonization, the U.S. 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:

- 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.
- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, blood transfusion) are considered AEs and the condition that results in the procedure is also considered an AE (eg, bleeding esophageal varices, dental caries).

An AE does **not** include:

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

#### 7.10.1.3 Pre-Randomization Adverse Events

Adverse events that occur between the time subject signs the ICF for the study and the time when that subject is randomized will be summarized as medical history and not as a treatment-emergent adverse event (TEAE) unless the event meets the definition of an SAE as defined in Section 7.10.1.8

#### 7.10.1.4 Treatment Emergent Adverse Events

All AEs that occur at the time of and following the first administration of study drug through the Final Telephone Follow-up will be considered as being TEAEs.

#### 7.10.1.5 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.

#### 7.10.1.6 Relationship

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

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

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

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

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

#### 7.10.1.7 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 BUN and creatinine in the setting of an AE of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). In such cases, the laboratory abnormality itself (eg, elevated creatinine in a setting of renal failure) does not need to be recorded as an AE. However, isolated laboratory abnormalities should be reported as AEs if they are considered to be clinically significant by the Investigator.

Criteria for a "clinically significant" laboratory abnormality are:

- A laboratory abnormality that leads to a dose-limiting toxicity (eg, an abnormality that results in study drug dose reduction, suspension, or discontinuation)
- A laboratory abnormality that results in any therapeutic intervention (ie, concomitant medication or therapy)
- Other laboratory abnormality judged by the Investigator to be of any particular clinical concern (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.

#### 7.10.1.8 Serious Adverse Events

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

- Death
- A life-threatening AE
- In patient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

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

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

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

An unexpected AE means any AE in which the specificity or severity is not consistent with the current Investigator's Brochure (IB).

#### 7.10.1.8.1 Reporting Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for AE identification, documentation, grading, assignment of causality, and prompt notification of SAEs to Pearl Therapeutics' Medical Monitor or designee. All SAEs must be reported to Pearl Therapeutics no later than 24 hours after the Investigator recognizes/classifies the event as a SAE. At a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report using the appropriate form (eg, SAE Report Form). After the initial report, as necessary, the Investigator must provide any additional information regarding the SAE to the Medical Monitor within two working days after he/she receives that information. This follow-up information will be a detailed written report that may include copies of hospital records, case reports, and autopsy reports, and other pertinent documents.

Post-study SAEs following the last dose of study drug must be reported to Pearl Therapeutics as described in Section 7.10.1.11.

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

#### 7.10.1.9 Supplemental Investigations of SAEs

The Investigator and supporting personnel responsible for subject care should discuss with the Medical Monitor any need for supplemental investigations of SAEs. The results of these additional assessments conducted must be reported to Pearl Therapeutics.

If a subject dies during participation in the study and a post-mortem examination is performed, a copy of the autopsy report must be submitted to Pearl Therapeutics.

#### 7.10.1.10 Post-Study Follow-Up of Adverse Events

All AEs, including a worsening of clinically significant laboratory values or physical examination findings compared with baseline values, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost-to-follow-up.

Adverse events ongoing at the Follow-up/Final Visit will be followed for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes or resolves. If resolved, a resolution date should be documented on the case report form or reported to Pearl Therapeutics if the case report forms have been locked.

The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. Activities at Follow-up may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals as is practical.

#### 7.10.1.11 Notification of Post-Study Serious Adverse Events

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

#### 7.10.1.12 International Review Board/Independent Ethics Committee Notification of Serious Adverse Events

The Investigator is responsible for promptly notifying her/his investigational research board/independent ethics committee (IRB/IEC) of all SAEs, including any follow-up information, occurring at her/his site and any SAE regulatory report, including any follow-up reports that he/she receives from Pearl Therapeutics. Documentation of the submission to the IRB/IEC must be retained for each safety report. The Investigator is also responsible for notifying Pearl Therapeutics if their IRB/IEC requires revisions to the informed consent form or other measures based on its review of an SAE report.

#### 7.10.1.13 Health Authority Safety Reports

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

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

### 7.10.2 Overdose

An overdose is defined as a dose greater than the high dose level evaluated in this study as described in Section 6.3 (Product Descriptions) that results in clinical signs and symptoms. In the event of an overdose of study medication, the Investigator should use clinical judgment in treating the overdose and contact the study Medical Monitor. The Investigator should refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drug(s) being used in this study. Such document may include, but not be limited to, the Investigator's brochure for BGF MDI.

### 7.10.3 Pregnancy

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

## 7.11 Termination of the Study

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

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

# 8 STUDY ACTIVITIES

A time and events schedule is provided in Table 8-1 schedules of inpatient assessments on Day 1 and Day 8 are provided in Table 8-2 and Table 8-3, respectively.

## Table 8-1 Schedule of Events for Screening, Treatment Sequences, and Follow-up

| Procedure | Screening | Inpatient Treatment Sequence 1 | | | | Inpatient Treatment Sequence 2 | | | Follow up |
|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 | Clinic Admission Day -1 | Visit 2 Day 1 | Visit 3 Day 8 | Washout | Clinic Admission Day -1 | Visit 4 Day 1 | Visit 5 Day 8 | Telephone Follow up |
| **Study Day** | **-28 to -2** | **-1** | **1** | **8** | **7 (+14 days)** | **-1** | **1** | **8** | **5 to7 days** |
| **Informed Consent** | X | | | | | | | | |
| **Medical History** | X | X | | | | X | | | X |
| **Demographics** | X | | | | | | | | |
| **Physical Examination** | X | X | | | | X | | | |
| **Vital Signs (BP, Temperature, HR, Respiratory Rate)** | X | X | X | X | | X | X | X | |
| **Eligibility Review** | X | X | X | X | | X | X | X | |
| **Placebo MDI Usage Demonstration/Practice** [a] | X | | X | X | | | X | X | |
| **12-lead ECG** | X | X | X | X | | X | X | X | |
| **Clinical Laboratory Testing** | X | X | X | X | | X | X | X | |
| **Adverse Events** | | X | X | X | | X | X | X | X |
| **Concomitant Medications** | X | X | X | X | | X | X | X | X |
| **Urine Drug Screen** | X | X | | | | X | X | X | |
| **Alcohol Breathalyzer** | X | X | | | | X | X | X | |
| **Pregnancy Test (women only)** [b] | X [c] | X | | | | X | X | X | |
| **Serology: (HIV, HBsAg, HepC)** | X | | | | | | | | |

| Procedure | Screening | Inpatient Treatment Sequence 1 | | | | Inpatient Treatment Sequence 2 | | | Follow up |
|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 | Clinic Admission Day -1 | Visit 2 Day 1 | Visit 3 Day 8 | Washout | Clinic Admission Day -1 | Visit 4 Day 1 | Visit 5 Day 8 | Telephone Follow up |
| **Study Day** | **-28 to -2** | **-1** | **1** | **8** | **7 (+14 days)** | **-1** | **1** | **8** | **5 to7 days** |
| **PK Assessment** | | | X | X | | | X | X | |
| **Study Drug Administration** | | | X [d] | X [d] | | | X [d] | X [d] | |
| **Inpatient Admission** | | X | | | | X | | | |
| **Inpatient Discharge** | | | | X | | | | X | |

Abbreviations: BP=blood pressure; ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; Hep C=hepatitis C; HIV=human immunodeficiency virus; HR=heart rate; MDI=metered dose inhaler; PK=pharmacokinetic(s).

[a] Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.

[b] For all women (childbearing potential and non-childbearing potential) (serum at Screening and urine thereafter).

[c] Follicle-stimulating hormone test for women of non-childbearing potential at Screening only.

[d] See the Schedule of Inpatient Period Assessments (Table 8-2; Table 8-3) for details regarding times and events for the Screening and baseline 12-lead ECG, vital signs, drug administration, and PK assessments during Treatment Periods 1 and 2. All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7, with a final single-dose administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

## Table 8-2 Schedule of Assessments on Day 1 of Each Inpatient Treatment Period (Visits 2 and 4)

| Procedure | Time Relative to Drug Administration | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **-60 min** | **0 hr** | **2 min** | **6 min** | **20 min** | **30 min** | **40 min** | **1 hr** | **2 hrs** | **4 hrs** | **8 hrs** | **10 hrs** | **12 hrs** | **16 hrs** | **24 hrs** |
| **PK Blood Draw** [e] | X[a] | | X | X | X | | X | X | X | X | X | X | X | X | X |
| **Administration of Study Medication** [b] | | X | | | | | | | | | | | | | |
| **12-lead Safety ECG** [b] | X[a] | | | | | X | | | X | | | | X | | X |
| **Clinical Laboratory Tests** | X[c] | | | | | X[c] | | | X[c] | X[c] | | | X[d] | | |
| **Vital Signs** | X[a] | | | | | X | | | X | | | | X | | X |
| **Adverse Events** | | X | X | 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 | X | X |

Abbreviations: ECG=electrocardiogram; PK=pharmacokinetic

[a] Within 1 hour of dosing

[b] All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7, with a final single-dose administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

[c] Twelve-lead safety ECGs will be recorded at the Screening Visit, on Day -1 to confirm eligibility, within 1 hour prior to dosing, and as scheduled above.

[d] Glucose and potassium only

[e] Complete clinical laboratory testing - chemistry and hematology

[f] For additional details, refer to Table 8-2. and Table 8-3.

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

## Table 8-3. Schedule of Assessments on Day 8 of Each Inpatient Treatment Period (Visits 3 and 5)

| Procedure | Time Relative to Drug Administration | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **-60 min** | **0 hr** | **2 min** | **6 min** | **20 min** | **30 min** | **40 min** | **1 hr** | **2 hrs** | **4 hrs** | **8 hrs** | **10 hrs** | **12 hrs** |
| **PK Blood Draw** | X[a] | | X | X | X | | X | X | X | X | X | X | X |
| **Administration of Study Medication** [b] | | X | | | | | | | | | | | |
| **12-lead Safety ECG** [b] | X[a] | | | | | X | | | X | | | | X |
| **Clinical Laboratory Tests** | X[c] | | | | | X[c] | | | X[c] | X[c] | | | X[d] |
| **Vital Signs** | X[a] | | | | | X | | | X | | | | 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: ECG=electrocardiogram; PK=pharmacokinetic

[a] Within 1 hour of dosing

[b] All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7, with a final single-dose administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

[c] Twelve-lead safety ECGs will be recorded at the Screening Visit, on Day -1 to confirm eligibility, within 1 hour prior to dosing, and as scheduled above.

[d] Glucose and potassium only

[e] Complete clinical laboratory testing - chemistry and hematology

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

## 8.1 Screening Visit 1 (Days -28 to Day -2, Prior to Randomization)

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

After obtaining written and signed informed consent, the following procedures and assessments will be performed during the Screening period, prior to randomization, and results will be documented in the eCRF and/or source documents:

- Informed consent (obtain first, prior to other study procedures)
- Demographics and relevant medical history
- Physical examination
- Vital signs
- Review of eligibility criteria
- Placebo MDI usage demonstration and practice
- 12-lead ECG
- Clinical laboratory evaluations (including urinalysis)
- Urine drug testing
- Alcohol breathalyzer test
- Serum pregnancy test (women only; for all women of childbearing potential and non-childbearing potential)
- Follicle-stimulating hormone test for women of non-childbearing potential
- Serology (HIV, HBsAg, and hepatitis C)
- Document concomitant medications

## 8.2 Admission to Clinic (Day -1 of Treatment Period 1)

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

After the subject is admitted to the study center, the following procedures will be obtained and/or performed:

- Medical history
- Physical examination

- Vital signs
- Review of eligibility criteria
- 12-lead ECG
- Clinical laboratory evaluations (including urinalysis)
- Documentation of AEs
- Documentation of concomitant medications
- Urine drug screen
- Alcohol breathalyzer test
- Urine pregnancy test for all women (of childbearing *and* non-childbearing potential)

## 8.3 Visit 2 (Day 1 of Treatment Period 1)

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

The following study activities and assessments will be performed on Day 1 in conjunction with the first Treatment Period and results will be documented in the eCRF and/or source documents:

- Review of eligibility criteria
- Randomization and treatment assignment
- Placebo MDI usage demonstration and practice
- Pre- and post-dose documentation of vital signs per Table 8-2
- Administration of study drug; a single dose of study drug will be administered by oral inhalation. (Refer to Appendix 1 for details regarding study drug dispensing and administration).
  - **Note:** Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.
- Collect pre- and post-dose PK samples per Table 8-2
- Collect blood samples for clinical laboratory testing per Table 8-2
- Perform 12-lead ECG per Table 8-2
- Documentation of 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 7.10.1.8)
- Documentation of concomitant medications

After all scheduled assessments are complete and all available safety data has been reviewed by the Investigator, schedule next visit. Subjects will remain in the clinic until completion of Treatment Period 1.

## 8.4 Visit 5 (Day 2 of Treatment Period 1)

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

- Administration of study drug; study drug will be administered BID by oral inhalation. (Refer to Appendix 1 for details regarding study drug dispensing and administration).
  - It is recommended that the timing of study drug administration is anchored to the timing of the first dose, such that the volunteer is dosed every 12 hours: between 8 to 10 am for the morning dose; and between 8 to 10 PM for the evening dose.
    - **Note**: Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.
- Documentation of 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 7.10.1.8)

## 8.5 Days 3–7 of Treatment Period 1

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

- Administration of study drug; study drug will be administered BID by oral inhalation. (Refer to Appendix 1 for details regarding study drug dispensing and administration).
    - **Note:** Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.
- Documentation of 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 7.10.1.8)

## 8.6 Day 8 of Treatment Period 1

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

The following study activities and assessments will be performed on Day 8 in conjunction with the first Treatment Period and results will be documented in the eCRF and/or source documents:

- Review of eligibility criteria
- Placebo MDI usage demonstration and practice
- Pre- and post-dose documentation of vital signs per Table 8-3
- Administration of study drug; only a single morning dose of study drug will be administered by oral inhalation. (Refer to Appendix 1 for details regarding study drug dispensing and administration)
    - **Note:** Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.
- Collect pre- and post-dose PK samples per Table 8-3
- Collect blood samples for clinical laboratory testing per Table 8-3
- Perform 12-lead ECG per Table 8-3
- Documentation of AEs
- Documentation of concomitant medications

After all scheduled assessments are complete and all available safety data has been reviewed by the Investigator, discharge from the clinic upon completion of all protocol-specified procedures and complete a Washout Period of at least 7 calendar days, and not exceeding 21 days between doses. Prior to discharge from the clinic for Treatment Period 1, schedule the clinic admission for Treatment Period 2.

## 8.7 Visit 5 (Day 8 of Treatment Period 2)

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

The following study activities and assessments will be performed on Day 8 in conjunction with the second Treatment Period and results will be documented in the eCRF and/or source documents:

- Review of eligibility criteria
- Placebo MDI usage demonstration and practice
- Pre- and post-dose documentation of vital signs per Table 8-3
- Administration of study drug (Refer to Appendix 1 for details regarding study drug dispensing and administration)

- **Note:** Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.

- Collect pre- and post-dose PK samples per Table 8-3
- Collect blood samples for clinical laboratory testing per Table 8-3
- Perform 12-lead ECG per Table 8-3
- Documentation of AEs
- Documentation of concomitant medications

After all scheduled assessments are complete and all available safety data has been reviewed by the Investigator, and discharge from the clinic upon completion of all protocol-specified procedures.

## 8.8 Follow-Up Telephone Call

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

Upon completion of the study, a follow-up phone call with each subject will be completed at least 5 days but no longer than 7 days from the last dose date. Subjects will be asked about any new or outstanding AEs, any new concomitant medication, and any changes to birth control method. This will be documented appropriately in the subject source documents and eCRFs.

- Review of medical history
- Documentation of AEs and concomitant medications
- Documentation of changes to birth control

# 9 PLANNED STATISTICAL METHODS

## 9.1 General Considerations

A detailed Statistical Analysis Plan (SAP) will be finalized prior to database lock and unblinding.

## 9.2 Analysis Populations

Two subject populations will be evaluated during this study and are defined as follows:

- **Safety Population:** All subjects who receive at least one dose of any study drug.
- **PK Population:** All subjects in the Safety Population who have sufficient data to reliably calculate at least one PK parameter at either dose level of BGF MDI and do not have major protocol deviations (to be determined prior to unblinding).

Safety and tolerability analyses will be performed on data from all subjects in the Safety Population.

Pharmacokinetic analysis will be performed using the PK population.

## 9.3 Demographics and Baseline Characteristics

Demographic information will include date of birth, 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.

## 9.4 Analysis of Pharmacokinetic Variables

Pharmacokinetic analysis will be performed using the PK population.

Pharmacokinetic parameters at both doses will include $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{0-12}$, $AUC_{0-t}$, $AUC_{0-\infty}$, CL/F, Vd/F, $\lambda_z$, RAC ($C_{max}$), and RAC ($AUC_{0-12}$). Other PK parameters may be calculated, as appropriate.

The initial calculation of PK parameters will be performed using non-compartmental analysis. Model-based parameter estimation may be performed following examination of the data. Summary statistics will be used to describe the plasma concentrations and PK parameters for budesonide, glycopyrronium, and formoterol by treatment.

## 9.5 Safety Analyses

No formal statistical analysis of safety data is planned. Safety data will be summarized by treatment and listed. The safety of BGF MDI will be assessed from physical examination

findings, AE reporting including SAE reporting, vital signs (BP, HR, respiratory rate, and body temperature), clinical laboratory values (hematology, chemistry, and urinalysis), and findings from 12-lead ECGs. The incidence of AEs and SAEs will be tabulated by treatment. Summary statistics of assessed laboratory values will be tabulated by treatment.

## 9.6 Interim Analysis

No interim analysis is planned for the study.

## 9.7 Randomization

Following determination of study eligibility, subjects will be randomized to one of three treatment sequences shown below in a 1:3:1 ratio where A, B, and C each represent Placebo MDI, BGF 160/14.4/9.6 µg, and BGF 320/14.4/9.6 µg, respectively.

**AC BC BA**

The design allows the lower dose of BGF MDI to be examined in the first period prior to administering the higher dose in the second period.

## 9.8 Determination of Sample Size

The anticipated sample size of approximately 20 randomized subjects was selected to provide approximately 16 completers. No formal criteria for the evaluation of PK were used to determine the sample size, but the chosen size is expected to provide reasonable estimates of the PK parameters in healthy adult subjects of Japanese descent.

## 9.9 Analysis Plan

All analyses will be specified in a detailed statistical analysis plan (SAP) that will be accompanied by table and data listing shells with mock graphical representations. The SAP will be approved by signature before database lock and prior to unblinding.

# 10 ADMINISTRATIVE CONSIDERATIONS

## 10.1 Regulatory Authority Approval

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

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

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

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

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

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

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

## 10.4 Laboratory Accreditation

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

## 10.5 Confidentiality

### 10.5.1 Confidentiality of Data

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

### 10.5.2 Confidentiality of Subject/Patient Records

By signing this protocol, the Investigator agrees that Pearl Therapeutics (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 Pearl Therapeutics. In addition, the Investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable laws (ie, Health Insurance Portability and Accountability Act), rules and regulations.

## 10.6 Quality Control and Assurance

Pearl Therapeutics is responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

## 10.7 Data Management

Data management procedures and information for this protocol will be provided by Pearl Therapeutics or their designee.

## 10.8 Study Monitoring

In accordance with applicable regulations, GCP, and Pearl Therapeutics 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 issues.

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

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

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

## 10.9 Retention of Data

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

## 10.10 Financial Disclosure

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

## 10.12 Publication Policy

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

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

1. **Responsibility:** Each principal Investigator is responsible for the accuracy and completeness of all data from their site. Pearl Therapeutics (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.
2. **Authorship and Publication Committee:** Pearl Therapeutics, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE. It is anticipated that a publication committee will be formed to assume oversight of these activities.
   All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
3. **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted at least 30 days prior to submission for publication or presentation to Pearl Therapeutics for review, approval, and to ensure consistency with the policy in this protocol. Pearl Therapeutics will have the right to request appropriate modification to correct facts and to represent its opinions, or the opinions of the publication committee, if these differ with the proposed publication.
4. **Confidentiality:** Investigators will conduct all interactions with Pearl Therapeutics and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of nonclinical studies, or chemical formulae) may still need to remain confidential.
5. **Medical Journal Review:** Consistent with the intention of Pearl Therapeutics to publish the study in a fair and accurate manner, Pearl Therapeutics 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 Pearl Therapeutics will make suitable arrangements to ensure that the identity of journal reviewers is kept confidential. Records will be maintained of reviewers and the respective documents and datasets that were reviewed by each of them.
6. **Reporting of Clinical Trials Results:** To provide transparency in the conduct and reporting of randomized clinical trials, Pearl reports clinical findings based on the guidance of The CONSORT (CONsolidated Standards of Reporting Trials) Statement [CONSORT, 2010] and a 25-item checklist which is intended to improve the reporting of a randomized controlled 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, Pearl Therapeutics will make available appropriate information regarding the

study via the internet. This will include registration and listing of the study on www.clinicaltrials.gov, the US National Institutes of Health listing of clinical trials, and other clinical trial listings as appropriate.

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

# Appendix 1 Administration of Study Drug

All subjects will receive two treatments by random assignment to one of three predetermined treatment sequences as listed in Section 6.1of this protocol. This is a double-blind study. The Pearl products (BGF MDI and Placebo MDI) are identical in form and function and indistinguishable from each other.

At the Screening Visit, subjects will be instructed in the proper use of the MDI and, at that time, must demonstrate the ability to coordinate use of the MDI using a bulk-supplied Placebo MDI.

**BGF MDI and Placebo MDI Administration:** For specific guidance for the Handling and Instructions for Use of BGF MDI and BFF MDI, please refer to Section 3.3 of the Investigator Brochure (IB). For each BGF MDI and Placebo MDI administration, the MDI device will be primed (four actuations to waste) in the study site pharmacy by the pharmacist and then delivered to the inpatient clinic. Just prior to dosing, subjects will again be given detailed instruction regarding the proper use of the MDI device to ensure comprehension of its use. At the time of dosing, a healthcare provider will be present to ensure that the two activations of the MDI device are properly administered by the subject. The dosing time must be documented on the eCRF. The three MDI treatments are:

- BGF MDI 320/14.4/9.6 µg
- BGF MDI 160/14.4/9.6 µg
- Placebo MDI

The dose delivery specifications for the three treatments are provided in the following table:

## Table A1-1. Dose Delivery Specifications

| Product Name & Dose | Product Strength | Dosage Form | Administration |
|---|---|---|---|
| BGF MDI 320/14.4/9.6 µg ex-actuator | 160/7.2/4.8 µg/actuation | MDI | Taken as 2 inhalations |
| BGF MDI 160/14.4/9.6 µg ex-actuator | 80/7.2/4.8 µg/actuation | MDI | Taken as 2 inhalations |
| Placebo MDI | Formulation does not contain active ingredient | MDI | Taken as 2 inhalations |

[2] Abbreviations: BGF MDI=budesonide, glycopyrrolate, and formoterol fumarate inhalation aerosol; MDI=metered dose inhaler
**Note:** All study drugs are administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7 of each Treatment Period, with a final single administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

# Appendix 2 Plasma Collection, Processing, and Handling (PK Samples)

- Collect approximately 10 mL of blood into a 2 tubes containing EDTA tripotassium ($4 \times 10^{3}$M in phosphate buffered saline). Care should be taken to minimize hemolysis during sample collection.
- Place all tubes on wet ice immediately after collection.
- Centrifuge the blood within 30 minutes of collection at >1000 x g (~2500 rpm) for 10 to 15 minutes.
- Transfer approximately equal aliquots (Aliquot A and Aliquot B) of plasma into duplicate labeled polypropylene test tubes with a snap or screw cap. Care should be taken to minimize contamination with red blood cells during transfer of plasma.
- Securely cap the labeled tubes. Please ensure the following when labeling the plasma aliquots:
  - Sample vials must be clearly and accurately labeled using a solvent resistant ink (do not use ballpoint pen) or using supplied labels.
  - The information on the labels should correspond to the information recorded on the PK Sample Log worksheet for each subject.
  - The actual date and clock time (24-hour clock) of sample collection should be entered on the PK Sample Log worksheet.
  - The plasma samples should then be placed in a freezer capable of maintaining a temperature of at least -60°C as soon as possible after aliquoting for storage. Store Aliquot A samples separate from Aliquot B samples as these will be shipped separately.
- Ship frozen plasma samples within dry ice using a supplied cooler and labeling according to the procedure provided by the courier service.
- Ship samples only on a Monday, Tuesday, or Wednesday or at least 3 days prior to a holiday via priority overnight delivery.
- Ship Aliquot A samples first.
- Aliquot B samples should be retained frozen until receipt of Aliquot A samples is confirmed and then shipped according to instruction.

**Shipping Address:**

[redacted]

**ATTENTION: Sample Management**

Phone: [redacted]
E-mail: [redacted]

## Appendix 3 Sponsor Signatory

**Study Title:** A Phase I, Randomized, Double-Blind, Placebo-Controlled, Two-Period, Ascending Dose, Crossover Study to Assess the Safety and Pharmacokinetics of Two Doses of PT010 in in Healthy Adult Subjects of Japanese Descent Following a Single Dose and After Chronic Dosing for 7 Days

**Study Number:** PT010003-00

**Final Date:** [redacted]

**Signature:** [redacted] Date: [redacted]

**Name:** [redacted]

**Title:** [redacted] Pearl Therapeutics, Inc.

# Appendix 4 Investigator's Agreement and Signature Page

**Study Title:** A Phase I, Randomized, Double-Blind, Placebo-Controlled, Two-Period, Ascending Dose, Crossover Study to Assess the Safety and Pharmacokinetics of Two Doses of PT010 in in Healthy Adult Subjects of Japanese Descent Following a Single Dose and After Chronic Dosing for 7 Days

**Study Number:** PT010003-00

**Final Date:** [redacted]

**I agree:**

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

Signature:_[redacted] Date:_[redacted]

Name:_[redacted]

Affiliation: _[redacted]

# Clinical Trial Protocol: PT010003-01

| | |
|---|---|
| **Title:** | A Phase I, Randomized, Double-Blind, Placebo-Controlled, Two-Period, Ascending Dose, Crossover Study to Assess the Safety and Pharmacokinetics of Two Doses of PT010 in Healthy Adult Subjects of Japanese Descent Following a Single Dose and After Chronic Dosing for 7 Days |
| **Study Number:** | PT010003-01 |
| **Study Phase:** | Phase I |
| **Product Name:** | Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol; PT010,<br>Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler; (BGF MDI) |
| **IND Number** | 118313 |
| **Investigators:** | Single study center; United States |
| **Sponsor:** | Pearl Therapeutics, Inc.<br>[redacted] |
| **Sponsor Contact:** | [redacted] |

| | Version Number | Date |
|---|---|---|
| **Original Protocol:** | Version 1.0 | [redacted] |
| **Amendment 1:** | Version 2.0 | [redacted] |

**Confidentiality Statement**

**Property of Pearl Therapeutics**

**This document is confidential and may not be used, divulged, published or otherwise disclosed without consent of Pearl Therapeutics Inc**

# SUMMARY OF CHANGES TO ORIGINAL PROTOCOL VERSION 1.0, DATED [redacted]

Based on the points which required clarification in an Administrative Letter dated [redacted] the following changes have been incorporated into Amendment 1 (Version 2.0) of the Study PT010003 protocol.

1. In the Synopsis and in Section 2.1: The Safety Objective has been merged with the Primary Objective to better reflect the objectives of the study. The Table of Contents has been revised accordingly.

2. In Section 7.9.1: The last paragraph was incomplete and has been revised to provide clarification: *"POST-Dose Administration Sample Collection –On Day 8 ONLY: Approximately 10 mL of whole blood will be collected at 2, 6, 20, and 40 minutes, and at Hour(s) 1, 2, 4, 8, 10, and 12."*

3. In Section 7.10.1.2: The last bullet point under "*Adverse events include, but are not limited to:"* has been corrected as follows: *"Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, blood transfusion) are not considered AEs, the condition that results in the procedure is considered an AE (eg, bleeding esophageal varices, dental caries)."*

4. In Section 8.2: An additional bullet point was listed under *"After the subject is admitted to the study center, the following procedures will be obtained and/or performed: Placebo MDI usage demonstration and practice"*

5. In Table 8-2 Schedule of Assessments on Day 1 of Each Inpatient Treatment Period (Visits 2 and 4) the following corrections were incorporated to align lines items contained in the Timed Assessments with their correct footnote:

    a. Footnote **e** Complete clinical laboratory testing – chemistry and hematology has been attached to the 12-hour timepoint for Clinical Laboratory Tests

    b. Footnote **b** has been deleted from the12-lead Safety ECG line in the table.

    c. Footnote **c** has been attached to the 12-lead Safety ECG line in the table.

    d. Footnote **d** glucose and potassium only has been attached to the following Clinical Laboratory Tests time-points instead: -60 min, 30 min, 2 hrs, and 4 hrs as complete clinical laboratory testing – chemistry and hematologly is collected at -60 min and 12 hour time-points

6. In Table 8-3 Schedule of Assessments on Day 8 of Each Inpatient Treatment Period (Visits 3 and 5) the following corrections were incorporated to align items in the table with their correct footnote:

    a. Footnote **b** has been deleted from the12-lead Safety ECG line in the table.

    b. Footnote **c** has been attached to the 12-lead Safety ECG line in the table.

    c. In Footnote **d** glucose and potassium only has been attached to the following Clinical Laboratory Tests time-points instead: -60 min, 30 min, 2 hrs, and 4 hrs.

    d. Footnote **e** complete clinical laboratory testing, chemistry and hematology has been attached to the 12-hour timepoint for Clinical Laboratory Tests as complete clinical laboratory testing – chemistry and hematologly is collected the 12 hour time-points.

7. In Section 8.6 and Section 8.7, the first bullet point ”Review of eligibility criteria” has been removed as eligibility is reviewed at the Screening Visit and at Day 1 of each Treatment Period.

8. In Appendix 1: The second sentence under the header **BGF MDI and Placebo MDI Administration,** *“For each BGF MDI and Placebo MDI administration, the MDI device will be primed (four actuations to waste) in the study site pharmacy by the pharmacist and then delivered to the inpatient clinic.”* has been abridged and replaced with the following: *“On Day 1 of each Treatment Period, prior to the first MDI administration, the MDI device will be primed in the study site pharmacy by the pharmacist and delivered to the inpatient clinic.”*

9. In addition, the opportunity was taken to address other minor protocol inconsistencies and typographical errors including updates to the abbreviation and reference lists.

# SYNOPSIS

| |
|---|
| **Sponsor:**<br>Pearl Therapeutics, Inc. |
| **Names of Finished Products:**<br>Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (PT010)<br>Budesonide, Glycopyrronium, and Formoterol Fumarate (BGF) Metered Dose Inhaler; BGF MDI<br>Matching Placebo MDI |
| **Name of Active Ingredients:**<br>Budesonide<br>Glycopyrronium<br>Formoterol fumarate |
| **Study Title:**<br>A Phase I, Randomized, Double-Blind, Placebo-Controlled, Two-Period, Ascending Dose, Crossover Study to Assess the Safety and Pharmacokinetics of Two Doses of PT010 in Healthy Adult Subjects of Japanese Descent Following a Single Dose and After Chronic Dosing for 7 Days |
| **Study Number:** PT010003-01 |
| **Study Phase:** I |
| **Primary Objectives:**<br>The primary objective of this study is to assess the safety and tolerability of two doses of BGF MDI in healthy adult subjects of Japanese descent after single dosing and during chronic (7 days) dosing. The safety and tolerability profile of BGF MDI will be characterized by using physical examination assessments; adverse event (AE) reporting; vital sign measurements; clinical laboratory test values; and results from 12-lead electrocardiogram (ECG) procedures. |
| **Secondary Objectives:**<br>The secondary objective of the study is to describe the PK profile of two doses of BGF MDI healthy adult subjects of Japanese descent after single dosing and after chronic (7 days) dosing. |

**Study Design:**

PT010003 is a Phase I, single-center, randomized, double-blind, placebo-controlled, two-period, ascending dose, cross-over study to assess safety/tolerability and PK of two different doses of BGF MDI in healthy adult subjects of Japanese descent. Pharmacokinetics will be assessed following a single dose and after 7 days of chronic dosing. Safety will be assessed during the 7-day treatment and throughout the entire study until subjects are released from participation. All 3 study drugs will be administered by oral inhalation. It is planned that the study will enroll and randomize an estimated 20 eligible subjects to one of three treatment sequences. Subjects will receive two of the following treatments:

BGF MDI 320/14.4/9.6 µg
BGF MDI 160/14.4/9.6 µg
Placebo MDI

This study includes a Screening Period of up to 28 days and two Treatment Periods of 8 days each, separated by a minimum Washout Period of 7 days to a maximum of 21 days for added scheduling flexibility. A follow-up phone call will be conducted at least 5 days, but no longer than 7 days after completion of the last dose date on Treatment Period 2. The maximum participation in the study for each subject is not expected to exceed 65 days. The study is anticipated to run for approximately 3 months and should not exceed 6 months.

| Treatment Sequence | Number/Subjects | Treatment Period 1 (7 Days) | Washout Prior to Crossover | Treatment Period 2 (7 Days) |
|---|---|---|---|---|
| Sequence 1 | 4 Subjects | Placebo MDI (Matching) | Approximate 7-21 Day Duration | BGF MDI 320/14.4/9.6 µg |
| Sequence 2 | 12 Subjects | BGF MDI 160/14.4/9.6 µg | | BGF MDI 320/14.4/9.6 µg |
| Sequence 3 | 4 Subjects | BGF MDI 160/14.4/9.6 µg | | Placebo MDI (Matching) |

Abbreviations: BGF=budesonide, glycopyrronium, and formoterol fumarate inhalation aerosol; MDI=metered dose inhaler; µg=microgram.

**Note:** All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7, with a final single-dose administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

This single-center study will be conducted in the United States (US).

**Study Duration:**

Study PT010003 was planned to include a Screening Period of up to 28 days and two 7-day Treatment Periods (a single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7 of each Treatment Period, with a final single-dose administration of study drug occurring on the morning of Day 8.) separated by a Washout Period (minimum of7 days; maximum of 21 days) to ensure scheduling flexibility. Subject-participation in the study is anticipated to be approximately 25 to 65 days.

**Study Population:**

The planned study population includes a total of approximately 20 male and female adult healthy subjects of Japanese descent. Subjects will be enrolled and randomized in the study to provide approximately 16 subject completers. Inclusion and exclusion criteria are listed in Section 5 .

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

Investigational materials will be provided by Pearl Therapeutics, as summarized.

| Product Name & Dose | Product Strength | Dosage Form | Administration |
|---|---|---|---|
| BGF MDI 320/14.4/9.6 µg ex-actuator | 160/7.2/4.8 µg/actuation | MDI | Taken as 2 inhalations |
| BGF MDI 160/14.4/9.6 µg ex-actuator | 80/7.2/4.8 µg/actuation | MDI | Taken as 2 inhalations |
| Matching Placebo MDI | Formulation does not contain active ingredient | MDI | Taken as 2 inhalations |

Abbreviations: BGF MDI = budesonide, glycopyrrolate, and formoterol fumarate inhalation aerosol; MDI=metered dose inhaler.
**Note**: All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7, with a final single administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day. Placebo MDI is equivalent to the test products without the active ingredients.

**Pharmacokinetic Assessments:**

Pharmacokinetics of BGF MDI will be assessed and compared using plasma concentrations of budesonide, glycopyrronium, and formoterol. For the single dose administration, timepoints for PK blood sample collection will occur within a 1-hour window prior to dosing, and blood samples will be collected again post-dose at 2, 6, 20, and 40 minutes and at 1, 2, 4, 8, 10, 12, 16, and 24 hours. After 7 days of chronic dosing in each Treatment Period, timepoints for PK blood sample collection will occur within a 30-minute window prior to dosing, and blood samples will be collected again post-dose at 2, 6, 20, and 40 minutes and at 1, 2, 4, 8, 10, and 12 hours.

Approximately 500 mL of blood will be collected per subject during the study.

Pharmacokinetic parameters calculated at the first day (Day 1) and last dose (Day 8) in each Treatment Period will include maximum plasma concentration ($C_{max}$), area under the plasma concentration-time curve from 0 to 12 hours ($AUC_{0-12}$), area under the plasma concentration-time curve from 0 to the time of the last measureable plasma concentration ($AUC_{0-t}$); area under the plasma concentration-time curve from 0 extrapolated to infinity ($AUC_{0-\infty}$) (only calculated for Day 1); time to maximum plasma concentration ($t_{max}$); elimination half-life ($t_{½}$); apparent total body clearance (CL/F); apparent volume of distribution (Vd/F); terminal elimination rate constant ($\lambda_z$); accumulation ratio for $C_{max}$ (RAC [$C_{max}$]); accumulation ratio for $AUC_{0-12}$ (RAC [$AUC_{0-12}$]). Other PK parameters may be calculated, as appropriate.

**Safety Assessments:**

The safety and tolerability profile of BGF MDI will be assessed using physical examination findings, adverse event (AE) reporting, vital sign values, clinical laboratory values, and findings from 12-lead electrocardiograms (ECGs).

**Statistical Methods:**

Two subject populations will be used for data analyses during the study and are defined as follows:

**Safety Population:** All subjects who receive at least one dose of any study drug.

**PK Population:** All subjects in the Safety Population who have sufficient data to reliably calculate at least one PK parameter at either dose level of BGF MDI and do not have major protocol deviations (to be determined prior to unblinding).

Safety Analyses: Safety and tolerability analyses will be based on descriptive statistics for ECG, vital signs, and laboratory measurements as appropriate, and also on frequencies of AEs and the number of subjects with AEs.

PK Analyses: Summary statistics without model adjustment will be used to describe the PK parameters after treatment with two doses of BGF MDI as compared with Placebo MDI.

*Sample Size*:

The planned sample size of approximately 20 randomized subjects is selected to provide approximately 16 completers and initial safety information in healthy adult subjects of Japanese descent.

**Date of Original Approved Protocol:** [redacted]

**Date of Amendment 1:** [redacted]

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## LIST OF IN-TEXT TABLES



## LIST OF IN-TEXT FIGURES



## LIST OF APPENDICES

# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| API | Active Pharmaceutical Ingredients |
| AST | Aspartate Aminotransferase |
| $AUC_{0-12}$ | Area Under the Curve From 0 to 12 Hours |
| $AUC_{0-t}$ | Area Under the Curve From 0 the Time of the Last Measureable Plasma Concentration |
| $AUC_{0-\infty}$ | Area Under the Curve From 0 Extrapolated to Infinity |
| BGF MDI | Budesonide, Glycopyrrolate, and Formoterol Fumarate Metered Dose Inhaler |
| BID | Bis In Die, Twice Daily |
| BP | Blood Pressure |
| CBC | Complete Blood Cell (count) |
| CFR | Code of Federal Regulations |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration Equation (according to National Kidney Disease Education Program) |
| CL/F | Apparent Total Body Clearance |
| $C_{max}$ | Maximum plasma concentration |
| COPD | Chronic Obstructive Pulmonary Disease |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| ECG | Electrocardiogram |
| EDTA | Ethylenediaminetetraacetic Acid |
| eg | Exempli Gratia, For Example |
| eCRF | Electronic Case Report Form |
| FDA | Food and Drug Administration |
| $FEV_1$ | Forced Expiratory Volume in 1 Second |
| FF MDI | Formoterol Fumarate Metered Dose Inhaler |
| FSH | Follicle Stimulating Hormone |

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| GCP | Good Clinical Practice |
| GFF MDI | Glycopyrrolate and Formoterol Fumarate Metered Dose Inhaler |
| GFR | Glomerular Filtration Rate |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| GP MDI | Glycopyrrolate Metered Dose Inhaler |
| HbsAg | Hepatitis B Surface Antigen |
| hCG | Human Chorionic Gonadotropin |
| HFA | Hydrofluoroalkane |
| HIV | Human Immunodeficiency Virus |
| HR | Heart Rate |
| IB | Investigators Brochure |
| ICF | Informed Consent Form |
| ICS | Inhaled Corticosteroid |
| ICMJE | International Committee of Medical Journal Editors |
| ie | Id Est, That Is |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| ISMPP | International Society for Medical Publications Professionals |
| IV | Intravenous |
| JRS | Japanese Respiratory Society |
| LABA | Long-acting β2 Agonist |
| LAMA | Long-acting Muscarinic Antagonist |
| $\lambda_z$ | Terminal Elimination Rate Constant |
| MDI | Metered Dose Inhaler |
| µg | Microgram |
| mL | Milliliter |
| mm | Millimeter |
| mmHg | Millimeter of Mercury |

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| msec (ms) | Millisecond |
| PK | Pharmacokinetics |
| QTcF | QT Corrected Using Fridericia's Formula |
| RAC($C_{max}$) | Accumulation ratio for $C_{max}$ |
| RAC($AUC_{0-12}$) | Accumulation ratio for $AUC_{0-12}$ |
| SABA | Short-acting β2-agonists |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| [redacted] | [redacted] |
| SOP | Standard Operating Procedure |
| $t_{½}$ | Apparent Terminal Elimination Half-life |
| [redacted] | [redacted] |
| TEAE | Treatment-emergent Adverse Event |
| $t_{max}$ | Time To Maximum Plasma Concentration |
| US | United States |
| Vd/F | Apparent Volume of Distribution |

# TRADEMARK INFORMATION

Trademarks not owned by Pearl Therapeutics, Inc. include:

Aerolizer

Aqua

Breezhaler

Cuvposa

Foradil

Oxis

Pulmicort

Respules

Rhinocort

Robinul

Robinul Forte

Spiriva

Symbicort

Turbuhaler

Ziploc

Vacutainer

# 1 INTRODUCTION AND STUDY RATIONALE

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

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are $\beta_2$-agonists, muscarinic antagonists, and methylxanthines which may be 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. Combining bronchodilators from different pharmacological classes may improve efficacy and decrease the risk of side effects compared with increasing the dose of a single bronchodilator [GOLD, 2014]. Long-acting $\beta_2$-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) reduce bronchoconstriction through different mechanisms, and there is a long history of combination therapy for COPD with short-acting agents in these classes.

Regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function, quality of life, and reduces the frequency of exacerbations in subjects with COPD and a forced expiratory volume in 1 second ($FEV_1$) value of <60% of predicted. Withdrawal from treatment with ICS may lead to exacerbations in some patients. When combined with a LABA, an ICS is more effective than the individual components in improving lung function, quality of life, and reducing exacerbations in subjects with moderate to very severe COPD. Furthermore, the addition of a LABA/ICS combination to the muscarinic antagonist tiotropium improves lung function and quality of life and may further reduce exacerbations, but more studies of triple therapy are needed [GOLD, 2014]. Pearl Therapeutics, Inc. (hereinafter referred to as Pearl) is developing the ICS/LAMA/LABA 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 COPD.

Glycopyrrolate (Robinul® and Robinul Forte®) is an antimuscarinic drug that is marketed in the United States (US) in both oral and parenteral formulations. Glycopyrrolate is a quaternary ammonium derivative, that when inhaled results in minimal mucosal absorption and systemic side effects. Glycopyrrolate is approved for respiratory inhalation in Japan for the treatment of COPD. In addition, tiotropium bromide (Spiriva® [Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA]) is approved worldwide as a powder for inhalation. It has been shown to reduce the rate of COPD exacerbations and to improve the effectiveness of pulmonary rehabilitation [Niewoehner, 2005; Casaburi, 2005].

Formoterol fumarate is a selective LABA approved in the US (eg., Foradil® Aerolizer®[ Merck Sharp & Dohme Corporation, a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA]) and worldwide (eg, Oxis® Turbuhaler®[Worldwide AstraZeneca Group of Companies; London, UK] Foradil) for use in asthma and COPD. Formoterol fumarate is also approved in the US and worldwide in combination with budesonide (eg., Symbicort® MDI, Symbicort® Turbuhaler® [AstraZeneca, LP, Wilmington Delaware]) 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.

Although formoterol fumarate is classified as a LABA, it has a rapid onset of action similar to short-acting $\beta_2$-agonists (SABAs). Formoterol fumarate is highly potent, displays high intrinsic activity, and can result in greater than 80% relaxation even under induced tone [Anderson, 1993]. Studies in subjects with COPD have demonstrated that the onset of action with formoterol fumarate is faster than with antimuscarinic agents or salmeterol, and similar to that of SABAs, such as albuterol, and that the duration of action is ≥12 hours [Berger, 2008]. Five large, placebo-controlled clinical studies of up to 12 months in duration in nearly 2500 patients demonstrated that formoterol fumarate is effective and well tolerated in patients with COPD [Dahl, 2001; Rossi, 2002; Albers R 2002;Campbell 2005; Campbell 2007].

Budesonide is a well-established corticosteroid approved worldwide in mono- and combination therapies for treatment of asthma and allergic rhinitis. It is available in both intranasal and inhaled formulations. Budesonide formulations currently approved and marketed in the US by AstraZeneca LP, Wilmington DE, USA, include: Rhinocort® Nasal Inhaler, Rhinocort Aqua® Nasal Spray, Pulmicort® Turbuhaler®, Pulmicort Respules®, and as the ICS component of Symbicort Inhalation Aerosol (Symbicort MDI). Inhaled budesonide as a mono therapy (Pulmicort) and in combination with formoterol fumarate dehydrate (ie, Symbicort) is approved for use in patients with COPD.

In clinical studies, Symbicort MDI 320/9 µg administered twice-daily (BID) demonstrated significant improvements in lung function compared with Budesonide MDI 320 µg BID, formoterol fumarate (Oxis Turbuhaler) 9 µg BID, or placebo in patients with COPD. In the clinical studies, improvements in secondary endpoints of morning and evening peak expiratory flow and reduction in rescue medication use were supportive of the efficacy of Symbicort MDI 320/9 µg [Symbicort Inhalation Aerosol Prescribing Information, 2012; Rennard, 2009; Tashkin, 2008]. The GOLD COPD guidelines acknowledge that combination therapy with an ICS and LABA is more effective than the individual components in improving lung function and health status, and reducing exacerbations in patients with moderate to very severe COPD [GOLD, 2014].

Pearl is developing BGF MDI using its porous particle technology platform. This technology is based on spray-dried porous particles comprised of distearoylphosphatidylcholine and calcium chloride that are co-suspended with micronized active pharmaceutical ingredients (APIs) in a hydrofluoroalkane (HFA) propellant to form stable suspension-based MDIs.

## 1.1 Study Rationale

BGF MDI is a proprietary, fixed-dose triple combination MDI product formulated with budesonide, glycopyrrolate, and formoterol fumarate for treatment of subjects with COPD. As described in the GOLD COPD guidelines, in some patients, the addition of a LABA/ICS to a LAMA improves lung function, quality of life, and may further reduce exacerbations. For patients with many symptoms and at high-risk of exacerbations (GOLD Category D [GOLD], 2014]), one treatment option is a combination of all three drug classes, which provides support to the use of a triple therapy (ICS/LAM/LABA).

The purpose of this study is to characterize the pharmacokinetics (PK) and safety and tolerability profile of two doses of BGF MDI (320/14.4/9.6 µg and 160/14.4/9.6 µg doses) following a single dose and after chronic dosing (7 days) , compared with Placebo MDI in healthy adult subjects of Japanese descent.

The safety/tolerability and efficacy of the individual components, budesonide, glycopyrronium, and formoterol fumarate are well characterized. Pearl has conducted an initial Phase I single-dose PK and safety study in healthy adult subjects (Study PT010001) with three doses of the triple combination product, BGF MDI compared with two doses of Symbicort® MDI and a single dose of the Pearl dual combination product Glycopyrronium and Formoterol Fumarate Metered Dose (GFF MDI; PT003).
The study demonstrated that formoterol and glycopyrronium plasma concentrations following administration of all BGF MDI doses were similar to those following GFF MDI administration. The budesonide plasma concentrations were comparable between BGF MDI and Symbicort MDI. All treatments were well tolerated with a low frequency of adverse events (AEs), and no untoward safety signals were observed. The results of Study PT010001 support the evaluation of BGF MDI 320/14.4/9.6 µg and lower doses in further clinical studies and suggest that the addition of budesonide to GFF MDI does not impact the systemic levels of either component. Based on these findings in Western subjects, Study PT010003 is being conducted to identify the appropriate dose(s) for evaluation in the Japanese population.

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective of this study is to assess the safety and tolerability of two doses of BGF MDI in healthy adult subjects of Japanese descent after single dosing and during chronic (7 days) dosing. The safety and tolerability profile of BGF MDI will be characterized by using physical examination assessments; adverse event (AE) reporting; vital sign measurements; clinical laboratory test values; and results from 12-lead electrocardiogram (ECG) procedures.

## 2.2 Secondary Objective

The secondary objective of the study is to describe the PK profile of two doses of BGF MDI healthy adult subjects of Japanese descent after single dosing and after chronic (7 days) dosing.

# 3 STUDY ENDPOINTS

## 3.1 Efficacy Endpoint

This study is being conducted to assess in healthy subjects. Therefore, efficacy will not be evaluated.

## 3.2 Safety Endpoint

The safety and tolerability of BGF MDI will be assessed from physical examination findings, AE reporting including serious AE (SAE) reporting, vital signs (blood pressure [BP], heart rate [HR], respiratory rate, and body temperature), clinical laboratory values (hematology, chemistry, and urinalysis), and findings from 12-lead safety electrocardiograms (ECGs).

## 3.3 Pharmacokinetic Endpoint

Pharmacokinetics of BGF MDI will be assessed and compared using plasma concentrations of budesonide, glycopyrronium, and formoterol. For the single dose administration, timepoints for PK blood sample collection will occur within a 60-minute window prior to dosing, and blood samples will be collected again post-dose at 2, 6, 20, and 40 minutes and at 1, 2, 4, 8, 10, 12, 16, and 24 hours. After 7 days of chronic dosing in each Treatment Period, timepoints for PK blood sample collection will occur within a 60-minute window prior to dosing, and blood samples will be collected again post-dose at 2, 6, 20, and 40 minutes and at 1, 2, 4, 8, 10, and 12 hours. Pharmacokinetic parameters calculated at the first day (Day 1) and last dose (Day 8) in each Treatment Period will include the following:

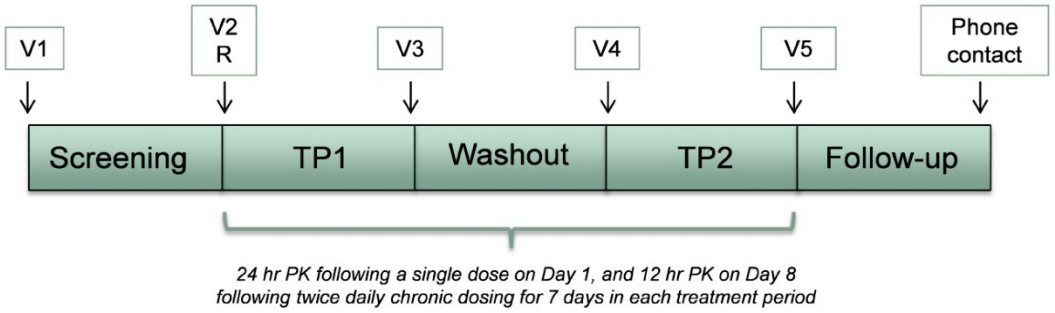
- Maximum plasma concentration ($C_{max}$)
- Area under the plasma concentration-time curve from 0 to 12 hours ($AUC_{0-12}$)
- Area under the plasma concentration-time curve from 0 to the time of the last measureable plasma concentration ($AUC_{0-t}$)
- Area under the plasma concentration-time curve from 0 extrapolated to infinity ($AUC_{0-\infty}$) (Calculated for Day 1 *only*)
- Time to maximum plasma concentration ($t_{max}$)
- Elimination half-life ($t_{½}$)
- Apparent total body clearance (CL/F)
- Apparent volume of distribution (Vd/F)
- Terminal elimination rate constant ($\lambda_z$)
- Accumulation ratio for $C_{max}$ (RAC [$C_{max}$])
- Accumulation ratio for $AUC_{0-12}$ (RAC [$AUC_{0-12}$])

# 4 INVESTIGATIONAL PLAN

## 4.1 Overall Study Design and Plan

This is a Phase I, single-center, randomized, double-blind, placebo-controlled, two-period, ascending dose, cross-over study to assess safety and PK of two doses of BGF MDI in healthy adult subjects of Japanese descent following a single dose and after chronic dosing for 7 days. The overall study design is summarized and illustrated in Figure 4-1.

**Figure 4-1. Study Design**




[1] Abbreviations: R=randomization; TP=Treatment Period

**Note**: All study drugs are administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7 of each Treatment Period, with a final single administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

Subjects who provide informed consent, undergo Screening procedures, and qualify for the study will be randomized to one of three treatment sequences, as shown in Table 4-1.

**Table 4-1. Treatment Sequences**

| Treatment Sequence | n | Treatment Period 1 | | Treatment Period 2 |
|---|---|---|---|---|
| 1 | 4 | Placebo MDI | **Wash-out** | BGF MDI 320/14.4/9.6 µg |
| 2 | 12 | BGF MDI 160/14.4/9.6 µg | | BGF MDI 320/14.4/9.6 µg |
| 3 | 4 | BGF MDI 160/14.4/9.6 µg | | Placebo MDI |

Abbreviations: BGF=budesonide, glycopyrrolate, and formoterol fumarate inhalation aerosol; MDI=metered dose inhaler

**Note**: All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7 of each Treatment Period, with a final single administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

Approximately 20 subjects are planned to be randomized, with four subjects in each of the two sequences that include a Placebo MDI treatment group, and 12 subjects in the BGF MDI (160/14.4/9.6 µg)/ BGF MDI (320/14.4/9.6 µg) treatment sequence.

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Subjects will be admitted as inpatients to the Clinical Research Unit (CRU; hereinafter referred to as "clinic") during the Treatment Periods. The inpatient Treatment Periods will be separated by a Washout Period of at least 7 calendar days and not exceeding 21 days between doses. For each Treatment Period, subjects will report to the clinic on Day-1 (the day prior to dosing), at which time, continuing eligibility will be assessed. If the subject continues to meet eligibility criteria, the subject will be admitted into the inpatient study unit.

Safety data will be closely monitored, and baseline and post-dosing serial blood draws (Section 7.9) for PK analysis (Refer to Table 8-2 and Table 8-3) will be obtained during each inpatient Treatment Period. After all scheduled assessments are completed and all available safety data have been reviewed by the Principal Investigator, subjects will be discharged from the clinic. Following the first Treatment Period, subjects will return to the clinic after their Washout Period of at least 7 calendar days between doses for their second inpatient Treatment Period. Other safety assessments will be obtained as listed in Table 8-2 and Table 8-3. A follow-up phone call will be conducted 5 days, but no later than 7 days, after completion of the last dose date on Treatment Period 2.

## 4.2 Study Duration and Dates

This study will include a Screening Period of up to 28 days and two Treatment Periods of 8 days each, separated by a minimum Washout Period of 7 days to a maximum of 21 days for added scheduling flexibility. A follow-up phone call will be conducted at least 5 days, but no longer than 7 days after completion of the last dose date on Treatment Period 2. Subject-participation duration is not expected to exceed 65 days. The study is anticipated to run for approximately 3 months and is not expected to exceed 6 months.

# 5 STUDY POPULATION SELECTION

Approximately 20 healthy male or female subjects will be randomized in this study. Subjects who withdraw from the study after receiving at least one single-dose treatment will not be replaced. Subjects who are randomized but did not receive treatment will be replaced. Subjects who are re-evaluated will maintain one screening number throughout the study.

## 5.1 Inclusion Criteria

Healthy subjects who meet all of the following inclusion criteria will be eligible for entry into this study:

1. Signed and dated Institutional Review Board (IRB)-approved Informed Consent Form (ICF) before any protocol specific screening procedures are performed.
2. Male and female first generation Japanese subjects ranging in age between18 to 55 years, inclusive:
3. First generation subjects who were born in Japan to two parents and four grandparents also born in Japan of full Japanese descent
4. Subjects must be an expatriate of Japan residing outside of Japan for less than five years
5. Subjects must have a valid Japanese passport
6. Subjects who have a body weight ≥50 kg (110 lbs.) at the Screening Visit and body mass index between 18.5 and 32 kg/$m^2$, inclusive
7. Be in good general health as determined by a thorough medical history and physical examination, ECG, vital signs, and clinical laboratory evaluation.
8. Willing and able to complete all study assessments and procedures.
9. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception from the Screening Period through the Final Telephone Follow-up: hormonal contraception, condom with spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, injectable contraceptive, or intra-uterine device. A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. Subjects must agree to practice the above birth control methods through the Final Telephone Follow-up as a safety precaution.
10. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months, do not require contraception during the study. Post-menopausal must be confirmed by a serum follicle-stimulating hormone (FSH) test at Screening.
11. Males with female partners of childbearing potential must agree to use a highly effective, medically acceptable form of contraception from the Screening Period through the Final Telephone Follow-up. Males with female partners of childbearing potential who themselves are surgically sterile (status post-vasectomy) must agree to use condoms with spermicide over the same period of time. Male subjects must agree to practice the above birth control methods through the Final Telephone Follow-up as a safety precaution.

12. Results of complete blood cell (CBC) count (including white blood cell count, hematocrit, hemoglobin, platelet count, differential), serum creatinine, electrolytes (Na+, K+), serum glucose, aspartate aminotransferase/alanine aminotransferase (AST/ALT), and total bilirubin must be within normal ranges or determined to be not clinically significant by the Investigator.

## 5.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible for entry into this study:

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 each of the two 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 with a history of ECG abnormalities including PR>220 msec; QRS complex >110 msec; QT Corrected Using Fridericia's Formula (QTcF) >450 ms in both males and females; or any significant morphological changes other than non-specific T-wave changes;
   - In addition, subjects who demonstrate any of these or any other significant 12-lead ECG abnormalities prior to the first Treatment Period (ie, 12-lead ECGs performed at Screening, baseline (pre-dose on Day 1 of the first Treatment Period [ECG obtained within 1 hour prior to dosing on Day 1 of Treatment Period 1]) will be excluded from participation in the study;
5. A history of additional risk factors for Torsades de Pointes (eg, heart failure, family history of Long QT Syndrome);
6. Subjects with the inability to coordinate the use of the Placebo MDI under supervision from site staff;
7. Subjects who have cancer that has not been in complete remission for at least 5 years;
8. Supine BP >140/90 mmHg or resting HR≥100 beats per minute at Screening (pre-dose on Day 1 of the first Treatment Period);
9. Male subjects with symptomatic prostatic hypertrophy that is clinically significant in the opinion of the Investigator;
10. Male subjects with a trans-urethral resection of the prostate or full resection of the prostate within 6 months prior to Screening;
11. Subjects with bladder neck obstruction or urinary retention that is clinically significant in the opinion of the Investigator;
12. Subjects with a diagnosis of glaucoma that in the opinion of the Investigator has not been adequately treated;
    - All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective β-blockers such as betaxolol, carteolol, levobunolol, metipranolol, prostaglandin analogues, and timolol;

13. History of substance-related disorders (with the exception of caffeine-related and nicotine-related disorders) as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM), fourth edition, text revision within 1 year of Screening;
14. History of smoking or the use of nicotine containing products or electronic cigarettes within 3 months of Screening by self-reporting;
15. A positive alcohol breathalyzer or urine drug screen for drugs of abuse at the Screening Visit or at the beginning of each inpatient period;
16. Treatment with an investigational drug within 30 days or five half-lives (whichever is longer) prior to the beginning of the Screening Period;
17. Treatment with any prescription or non-prescription drugs (including vitamins, herbal, and dietary supplements) within 30 days or five half-lives (whichever is longer) prior to Visit 2 (Day 1);
    - Acetaminophen will be permitted at doses of ≤2 grams/day. In females, oral and/or implanted contraceptive medication is permitted;
18. Subjects with a history of an allergic reaction or hypersensitivity to any drug or who develop allergic reaction or hypersensitivity to any component of the formulation(s) used in this study;
19. Blood collection of greater than 500 mL within 56 days prior to Screening;
20. Subjects with pre-existing blood conditions, as described:
    a. Subjects with anemia at Screening: defined as hemoglobin < 13.8 and < 11.3 for males and females, respectively, ***or***
    b. Hematocrit < 40.2 % and < 34.4 % for males and females, respectively;
21. Seropositivity for human immunodeficiency virus (HIV) at Screening;
22. Positive for hepatitis B surface antigen (HbsAg) or positive hepatitis C antibody at Screening;
23. Subjects with a chronic medical condition that requires ongoing treatment with medication;
24. Subjects with a history of major surgery within 4 weeks or minor surgery within 2 weeks of drug administration;
25. 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;
26. Any other condition and/or situation that causes the Investigator to deem a subject unsuitable for the study (eg, due to expected study drug non-compliance, inability to medically tolerate the study procedures, or a subject's unwillingness to comply with study-related procedures);
27. Subjects with abnormal-glomerular filtration rate (GFR; estimated GFR <90 mL/min) using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI);
28. Subjects who have participated in a previous Pearl study involving BGF or its individual components budesonide, glycopyrronium, or formoterol fumarate.

## 5.3 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.

## 5.4 Prior, Concomitant, and Prohibited Medications

Investigational therapies are not permitted within 30 days or five half-lives (whichever is longer) prior to beginning the Screening Period.

All medications approved for control of intraocular pressure are allowed including topical ophthalmic non-selective β-blockers such as betaxolol, carteolol, levobunolol, metipranolol, prostaglandin analogues (eg, bimatoprost), and timolol). Otherwise, the use of prescription or over-the counter medications within 30 days or five half-lives (whichever is longer) prior to Visit 2 (Day 1) is not permitted. Acetaminophen will be permitted at doses of ≤2 grams/day as determined to be necessary by the Investigator. With the exception of treatments for control of intraocular pressure and contraceptives in female subjects, ongoing treatment for chronic conditions will not be allowed.

Any medications that were being taken prior to signing the ICF will be documented as prior study drugs and must be stopped prior to entry.

## 5.5 Other Study Restrictions

### 5.5.1 Surgical Procedure/Intervention Restrictions

Major surgical interventions are not permitted within 4 weeks of study drug administration and minor surgical interventions are not allowed within 2 weeks of study drug administration.

### 5.5.2 Dietary Restrictions

For scheduled clinical laboratory assessment blood draws, subjects will be fasting for at least 4 hours. Meals during the dosing day of each Treatment Period will be standardized after the 4-hour post-dose clinical laboratory draw. There are no restrictions regarding clear fluid intake.

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

### 5.5.3 Illicit Drugs and/or Drugs of Abuse Restriction

Illicit drugs and/or drugs of abuse will not be allowed from within 1 year of Screening to whenever the subject discontinues the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented. Refer to Exclusion Criterion 13 and 26 in Section 5.2)

### 5.5.4 Smoking Restrictions

Smoking is prohibited duration of the study and 3 months prior to screening. Electronic cigarettes will be treated the same way as smoking is considered in the protocol.

## 5.6 Removal of Subjects from the Study or Study Drug

The Investigator may withdraw a subject at the occurrence of any or all of the following:

- Protocol deviation
- AE
- Clinically significant change in a laboratory parameter(s)
- Termination of the study by the Sponsor or Investigator
- Request by the subject to be discontinued from the study
- Investigator's discretion

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

## 6.1 Subject Information

Clinical supplies will be packaged to support enrollment of the study. All treatment arms will be blinded. The characteristics of the BGF MDI and Placebo MDI doses that will be administered during the study are presented in Table 6-2.

An unblinded pharmacist at the site will be provided with a written randomization scheme for allocation of subjects to one of three treatment sequences and to manage the distribution of clinical supplies. The three treatment sequences are listed in the following table (Table 6-1):

**Table 6-1. Treatment Sequences**

| Treatment Sequence | Number/Subjects | Treatment Period 1 (7 Days) | Washout Prior to Crossover | Treatment Period 2 (7 Days) |
|---|---|---|---|---|
| Sequence 1 | 4 Subjects | Placebo MDI (Matching) | Approximate 7-21 Day Duration | BGF MDI 320/14.4/9.6 µg |
| Sequence 2 | 12 Subjects | BGF MDI 160/14.4/9.6 µg | | BGF MDI 320/14.4/9.6 µg |
| Sequence 3 | 4 Subjects | BGF MDI 160/14.4/9.6 µg | | Placebo MDI (Matching) |

Abbreviations: BGF=budesonide, glycopyrronium, and formoterol fumarate inhalation aerosol; MDI=metered dose inhaler; µg=microgram.

**Note:** All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7 of each Treatment Period, with a final single administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

For each subject, single dose administration (Day 1),BID dosing (Day 2 through Day 7), and single-morning dose (Day 8) administration of study drug for chronic dosing of 7 days during each of the two Treatment Periods should occur at approximately the same time of day.

## 6.2 Dispensing Study Drug

All subjects will receive BGF MDI (320/14.4/9.6 µg), BGF MDI (160/14.4/9.6 µg), or Placebo MDI by random assignment to one of three predetermined treatment sequences (Refer to Section 6.1). At Screening, subjects will be instructed on the proper use of an MDI using a bulk-supplied Placebo MDI and, at that time, must demonstrate the ability to coordinate use of the MDI.

On Day 1 of each Treatment Period, prior to the first MDI administration, the MDI device will be primed in the study site pharmacy by the pharmacist and delivered to the inpatient clinic. Just prior to dosing, subjects will again be given detailed instruction regarding the proper use of the MDI device to ensure comprehension of its use. At the time of all study drug-dosing, a healthcare provider will be present to ensure that the subject properly administers the required number of activations of the MDI device.

## 6.3 Study Drug Product Descriptions

The BGF MDI active drug substances are budesonide, glycopyrronium, and formoterol fumarate dihydrate. Investigational materials will be provided by Pearl as summarized in the following table (Table 6-2):

### Table 6-2. Product Descriptions

| Product Name & Dose | Product Strength | Dosage Form | Administration |
|---|---|---|---|
| BGF MDI 320/14.4/9.6 µg ex-actuator | 160/7.2/4.8 µg/actuation | MDI | Taken as 2 inhalations |
| BGF MDI 160/14.4/9.6 µg ex-actuator | 80/7.2/4.8 µg/actuation | MDI | Taken as 2 inhalations |
| Matching Placebo MDI | Formulation does not contain active ingredient | MDI | Taken as 2 inhalations |

Abbreviations: BGF MDI = budesonide, glycopyrrolate, and formoterol fumarate inhalation aerosol; MDI=metered dose inhaler.
**Note**: All study drugs will be administered by oral inhalation. Placebo is formulated by Pearl in the image of the active test product(s) (ie, matching).

Following Screening and determination of eligibility, dosing will span two Treatment Periods based on three treatment sequences. The treatment and study visit schedule is illustrated in Table 4-1.

## 6.4 Study Drug Packaging and Box Labeling Information

Study drug will be provided as packaged supplies. Each subject will be randomized to one of three treatment sequences.

**BGF MDI and Placebo MDI:** Each of the formulations (approximately 10.8 grams) is contained within a coated aluminum canister fitted with a metering valve and plastic actuator. The products are foil overwrapped with desiccant. The products are formulated with sufficient suspension to ensure delivery of 120 inhalations from the nominal 50 µL valve over the shelf-life of the product.

## 6.5 Unblinding Procedures

The Sponsor will provide disclosure cards with the clinical supplies for the purpose of unblinding. The Investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject.

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

## 6.6 Study Drug Storage Requirements

**BGF MDI and Placebo MDI:** Prior to dispensing, BGF MDI and Placebo MDI should be stored according to the product label.

Clinical supplies for this study will be provided to the study site pharmacy by [redacted].
The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this protocol or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained.

## 6.7 Preparation of Study Products for Dispensing and Administration

Instructions regarding the administration of study drug are provided in Appendix 1.

## 6.8 Study Drug Accountability/Return of Clinical Supplies

**NOTE: 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 assistants have access. Storage conditions for the clinical supplies should be observed, monitored, and documented. Clinical supplies are to be dispensed only in accordance with the protocol. The Investigator is responsible for keeping accurate records of the clinical supplies received from [redacted], 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 Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned to [redacted].

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

For each subject, all used study drug materials will be collected and placed in a plastic bag (Ziploc® or similar type bag) and labeled with the subject number. Used subject supplies will be kept at 20°C to 25°C (68°F to 77°F) in a secure and locked cabinet until returned to [redacted].

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

# 7 STUDY PROCEDURES

## 7.1 Informed Consent

The informed consent form (ICF) must be executed *prior* to performing any and all study-related activities. The ICF must be approved by the Independent Ethics Committee (IEC)/IRB that is reviewing the study documents. 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 Eligibility of Subjects

Eligibility screening of healthy subjects will be completed within 28 days prior to administration of the first study drug and will be documented on the eCRF. Confirmation of eligibility will be performed at clinic admission (Day -1), Day 1, and Day 8 for each of the two Treatment Periods. Screening failures and the reason for screen-failure will be documented in the study site source documents.

## 7.3 Medical History

Relevant medical history, based on the opinion of the Investigator, will be obtained from the subject at Screening, on the day of each clinic admission (Day -1), and during the Follow-up telephone call, 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 Use of Concomitant Medications

The Investigator or designated qualified personnel will assess subject-use of concomitant medications at the Screening Visit, on the day of each clinic admission (Day -1), on Day 1 and Day 8 of each Treatment Period, and during the Final Telephone Follow-up. Concomitant medication use will be recorded on the eCRF. Specific information regarding use of concomitant medication and/or prior therapies is provided in Section 5.4.

## 7.5 Physical Examination

A complete physical examination including height and weight will be performed at the time of Screening and on the day of each clinic admission (Day -1). The findings of each examination will be recorded on the source documents and clinically significant abnormalities will be recorded on the eCRF.

The physical examination will include:

- Documentation of height (Screening only)
- Documentation of weight (Screening only)
- General appearance
- Head, eyes, ears, nose, and throat
- Respiratory
- Cardiovascular
- Musculoskeletal
- Gastrointestinal
- Neurologic
- Extremities
- Dermatologic
- Lymphatic

## 7.6 Vital Signs

Vital sign determinations, including BP, HR, respiratory rate, and body temperature will be performed after the subject has been supine for a 5-minute period at the Screening Visit, on the day of each clinic admission (Day -1), and on Day 1 and Day 8 of each Treatment Period, within 1 hour prior to administration of study drug and 30 minutes, 2 hours, 12 hours, and 24 hours (Day 1 only) post administration of study drug (Refer to Table 8-2 and Table 8-3).

## 7.7 Electrocardiography

Twelve-lead ECGs will be recorded at Screening and on the day of each clinic admission (Day -1) (baseline represents pre-dose on Day 1 of the first Treatment Period). On each treatment day (Day 1 and Day 8), 12-lead ECGs will be obtained within 1 hour prior to dosing and at 30 minutes and 2, 12, and 24 (Day 1 only) hours post-dosing (Refer to Table 8-2 and Table 8-3). Subjects should be supine and resting for at least 5 minutes before and during the ECG recording procedure. Subjects with any ECG abnormalities should be evaluated by the Investigator to determine if each abnormality is clinically

significant. All clinically significant abnormalities will be reported as AEs and followed closely by the Investigator in order to assure the safety of the study subject.

## 7.8 Clinical Laboratory Tests

### 7.8.1 Laboratory Parameters

**Note:** Subjects must be **fasting for at least 4 hours prior** to any scheduled clinical laboratory assessment blood draw.

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 7-1 will be collected at Screening and on the day of each clinic admission (Day -1 of each Treatment Period).

At 12 hours post administration of study drug on Day 1 and Day 8 during each of the two Treatment Periods, chemistry and hematology samples will be collected.

Additionally, blood samples will be drawn for assessments of glucose and potassium level determination within 60 minutes *prior* to dosing and at 30 minutes and 2 and 4 hours *post*-administration of study drug on Day 1 and Day 8 (Refer to Table 8-2 and Table 8-3).

Meals during the dosing day of each Treatment Period (Day 1 and Day 8) will be standardized after the 4-hour post-dose clinical laboratory draw.

There are no restrictions regarding clear fluid intake.

## Table 7-1. Laboratory Tests

| Hematology | Chemistry | |
|---|---|---|
| Hematocrit [a]<br>Hemoglobin<br>Platelet count<br>Red blood cell (RBC) count<br>White blood cell (WBC) count<br>WBC differential<br>Mean corpuscular volume (MCV)<br>Mean cell hemoglobin (MCH)<br>MCH concentration (MCHC) | Creatinine [b]<br>Potassium (K+) [c]<br>Sodium (Na+)<br>Chloride (Cl-)<br>Magnesium (Mg++)<br>Serum Iron<br>Ferritin<br>Calcium<br>Inorganic phosphate<br>Glucose [c]<br>Urea<br>Bilirubin (Total) | Bilirubin (direct)<br>Alanine aminotransferase (ALT)<br>Aspartate aminotransferase (AST)<br>Gamma-glutamyltransferase (GGT)<br>Alkaline phosphatase<br>Total Protein<br>Albumin |
| **Urinalysis:** 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. | | |
| **Urine drug screen:** A urine sample will be collected and analyzed (positive or negative) for drugs of abuse including amphetamine, opiate, cocaine, barbiturates, benzodiazepines, and marijuana [tetrahydrocannabinol]. | | |
| **Breathalyzer Test:** A breathalyzer test will be performed for the presence of alcohol (positive or negative). | | |
| **Serology:** 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. | | |
| **For females who are not post-menopausal:** A serum hCG test at Screening and urine hCG test at admission for each of the two Treatment Periods. | | |
| **For females of non-childbearing potential:** A serum hCG test at Screening and urine hCG test at admission for each of the two Treatment Periods. In addition, a serum FSH test for confirmation of non-childbearing status will be performed at Screening only. | | |

Abbreviations: CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration Equation; eGFR=estimated glomerular filtration rate; HbsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; FSH=follicle-stimulating hormone.

a Packed cell volume
b Serum creatinine value will be used to calculate eGFR using CKD-EPI.
c Additionally, within 60 minutes prior to dosing and at 30 minutes, 2 hours, and 4 hours post-dose of each Treatment Period

### 7.8.2 Laboratory Sample Collection, Storage and Shipping

Detailed instructions for laboratory sample collection, processing, and shipping instructions will be provided in the [redacted] laboratory manual. Approximately 500 mL of blood will be collected per subject during the study.

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.

## 7.9 Pharmacokinetic Assessments

**Note:** Pharmacokinetic sampling will occur in conjunction with Treatment Periods 1 and 2. Sample collections will be scheduled for the nominal timepoint and actual collection times will be recorded in the source documents (Refer to Table 8-2and Table 8-3).

### 7.9.1 Blood Sample Collection Schedule

***PRE-Dose Administration Sample Collection-On Day 1 AND Day 8:***

Approximately 10 mL of whole blood will be collected within 1 hour *prior* to administration of study drug.

***POST-Dose Administration –On Day 1 ONLY:***

Approximately 10 mL of whole blood will be collected at 2, 6, 20, and 40 minutes, and at Hour(s) 1, 2, 4, 8, 10, 12, 16 , and 24.

***POST-Dose Administration Sample Collection –On Day 8 ONLY:***

Approximately 10 mL of whole blood will be collected at 2, 6, 20, and 40 minutes, and at Hour(s) 1, 2, 4, 8, 10, and 12.

### 7.9.2 Procedure for Sample Collection

Samples will be collected via an indwelling intravenous (IV) cannula (per the study site's Standard Operating Procedure [SOP]) or, if necessary, by direct venipuncture into vacuum collection tubes (for example Vacutainer™ [redacted] plasma collection tube) containing thylenediaminetetraacetic acid (EDTA) tripotassium. After processing, the plasma for each sample will be harvested, divided into two approximately equal aliquots, and transferred into cryotubes appropriate for plasma. Aliquots are to be frozen at≤-60°C. Refer to Appendix 2 for plasma collection, processing, and handling.

### 7.9.3 Procedure for Shipping Samples

Samples are to be shipped frozen by overnight courier to the bioanalytical laboratory [redacted] for analysis. Plasma levels of budesonide, glycopyrronium, and formoterol will be determined using validated High Performance Liquid Chromatography tandem Mass Spectrometry methodology. Instructions for sample handling, storage, and shipping will be provided in the [redacted] laboratory manual.

## 7.10 Safety Assessments

### 7.10.1 Adverse Events Assessments

#### 7.10.1.1 Performing Adverse Events Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's case report form and on the AE Reporting Form. If the AE is "alarming," the Investigator must report the AE immediately to Pearl Therapeutics. In addition, certain AEs (as described in Section 7.10.1.2) are classified as "serious" and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as a serious AE (SAE) to Pearl Therapeutics or its designee.

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

#### 7.10.1.2 Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonization, the U.S. 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:

- 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.

Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, blood transfusion) are not considered AEs, the condition that results in the procedure is considered an AE (eg, bleeding esophageal varices, dental caries).

An AE does **not** include:

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

#### 7.10.1.3 Pre-Randomization Adverse Events

Adverse events that occur between the time subject signs the ICF for the study and the time when that subject is randomized will be summarized as medical history and not as a treatment-emergent adverse event (TEAE) unless the event meets the definition of an SAE as defined in Section 7.10.1.8

#### 7.10.1.4 Treatment Emergent Adverse Events

All AEs that occur at the time of and following the first administration of study drug through the Final Telephone Follow-up will be considered as being TEAEs.

#### 7.10.1.5 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.

#### 7.10.1.6 Relationship

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

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

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

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

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

#### 7.10.1.7 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 BUN and creatinine in the setting of an AE of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). In such cases, the laboratory abnormality itself (eg, elevated creatinine in a setting of renal failure) does not need to be recorded as an AE. However, isolated laboratory abnormalities should be reported as AEs if they are considered to be clinically significant by the Investigator.

Criteria for a "clinically significant" laboratory abnormality are:

- A laboratory abnormality that leads to a dose-limiting toxicity (eg, an abnormality that results in study drug dose reduction, suspension, or discontinuation)
- A laboratory abnormality that results in any therapeutic intervention (ie, concomitant medication or therapy)
- Other laboratory abnormality judged by the Investigator to be of any particular clinical concern (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.

### 7.10.1.8 Serious Adverse Events

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

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

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

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

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

An unexpected AE means any AE in which the specificity or severity is not consistent with the current Investigator's Brochure (IB).

#### 7.10.1.8.1 Reporting Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for AE identification, documentation, grading, assignment of causality, and prompt notification of SAEs to Pearl Therapeutics' Medical Monitor or designee. All SAEs must be reported to Pearl Therapeutics no later than 24 hours after the Investigator recognizes/classifies the event as a SAE. At a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report using the appropriate form (eg, SAE Report Form). After the initial report, as necessary, the Investigator must provide any additional information regarding the SAE to the Medical Monitor within two working days after he/she receives that information. This follow-up information will be a detailed written report that may include copies of hospital records, case reports, and autopsy reports, and other pertinent documents.

Post-study SAEs following the last dose of study drug must be reported to Pearl Therapeutics as described in Section 7.10.1.11.

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

#### 7.10.1.9 Supplemental Investigations of SAEs

The Investigator and supporting personnel responsible for subject care should discuss with the Medical Monitor any need for supplemental investigations of SAEs. The results of these additional assessments conducted must be reported to Pearl Therapeutics.

If a subject dies during participation in the study and a post-mortem examination is performed, a copy of the autopsy report must be submitted to Pearl Therapeutics.

#### 7.10.1.10 Post-Study Follow-Up of Adverse Events

All AEs, including a worsening of clinically significant laboratory values or physical examination findings compared with baseline values, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost-to-follow-up.

Adverse events ongoing at the Follow-up/Final Visit will be followed for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes or resolves. If resolved, a resolution date should be documented on the case report form or reported to Pearl Therapeutics if the case report forms have been locked.

The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. Activities at Follow-up may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals as is practical.

#### 7.10.1.11 Notification of Post-Study Serious Adverse Events

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

#### 7.10.1.12 International Review Board/Independent Ethics Committee Notification of Serious Adverse Events

The Investigator is responsible for promptly notifying her/his investigational research board/independent ethics committee (IRB/IEC) of all SAEs, including any follow-up information, occurring at her/his site and any SAE regulatory report, including any follow-up reports that he/she receives from Pearl Therapeutics. Documentation of the submission to the

IRB/IEC must be retained for each safety report. The Investigator is also responsible for notifying Pearl Therapeutics if their IRB/IEC requires revisions to the informed consent form or other measures based on its review of an SAE report.

#### 7.10.1.13 Health Authority Safety Reports

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

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

### 7.10.2 Overdose

An overdose is defined as a dose greater than the high dose level evaluated in this study as described in Section 6.3 (Product Descriptions) that results in clinical signs and symptoms. In the event of an overdose of study medication, the Investigator should use clinical judgment in treating the overdose and contact the study Medical Monitor. The Investigator should refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drug(s) being used in this study. Such document may include, but not be limited to, the Investigator's brochure for BGF MDI.

### 7.10.3 Pregnancy

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

## 7.11 Termination of the Study

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

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

# 8 STUDY ACTIVITIES

A time and events schedule is provided in Table 8-1 schedules of inpatient assessments on Day 1 and Day 8 are provided in Table 8-2 and Table 8-3, respectively.

## Table 8-1 Schedule of Events for Screening, Treatment Sequences, and Follow-up

| Procedure | Screening | Inpatient Treatment Sequence 1 | | | | Inpatient Treatment Sequence 2 | | | Follow up |
|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 | Clinic Admission Day -1 | Visit 2 Day 1 | Visit 3 Day 8 | Washout | Clinic Admission Day -1 | Visit 4 Day 1 | Visit 5 Day 8 | Telephone Follow up |
| **Study Day** | **-28 to -2** | **-1** | **1** | **8** | **7 (+14 days)** | **-1** | **1** | **8** | **5 to7 days** |
| **Informed Consent** | X | | | | | | | | |
| **Medical History** | X | X | | | | X | | | X |
| **Demographics** | X | | | | | | | | |
| **Physical Examination** | X | X | | | | X | | | |
| **Vital Signs (BP, Temperature, HR, Respiratory Rate)** | X | X | X | X | | X | X | X | |
| **Eligibility Review** | X | X | X | X | | X | X | X | |
| **Placebo MDI Usage Demonstration/Practice** [a] | X | | X | X | | | X | X | |
| **12-lead ECG** | X | X | X | X | | X | X | X | |
| **Clinical Laboratory Testing** | X | X | X | X | | X | X | X | |
| **Adverse Events** | | X | X | X | | X | X | X | X |
| **Concomitant Medications** | X | X | X | X | | X | X | X | X |
| **Urine Drug Screen** | X | X | | | | X | X | X | |
| **Alcohol Breathalyzer** | X | X | | | | X | X | X | |
| **Pregnancy Test (women only)** [b] | X [c] | X | | | | X | X | X | |
| **Serology: (HIV, HBsAg, HepC)** | X | | | | | | | | |

| Procedure | Screening | Inpatient Treatment Sequence 1 | | | | Inpatient Treatment Sequence 2 | | | Follow up |
|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 | Clinic Admission Day -1 | Visit 2 Day 1 | Visit 3 Day 8 | Washout | Clinic Admission Day -1 | Visit 4 Day 1 | Visit 5 Day 8 | Telephone Follow up |
| **Study Day** | **-28 to -2** | **-1** | **1** | **8** | **7 (+14 days)** | **-1** | **1** | **8** | **5 to7 days** |
| **PK Assessment** | | | X | X | | | X | X | |
| **Study Drug Administration** | | | X [d] | X [d] | | | X [d] | X [d] | |
| **Inpatient Admission** | | X | | | | X | | | |
| **Inpatient Discharge** | | | | X | | | | X | |

Abbreviations: BP=blood pressure; ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; Hep C=hepatitis C; HIV=human immunodeficiency virus; HR=heart rate; MDI=metered dose inhaler; PK=pharmacokinetic(s).

[a] Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.

[b] For all women (childbearing potential and non-childbearing potential) (serum at Screening and urine thereafter).

[c] Follicle-stimulating hormone test for women of non-childbearing potential at Screening only.

[d] See the Schedule of Inpatient Period Assessments (Table 8-2; Table 8-3) for details regarding times and events for the Screening and baseline 12-lead ECG, vital signs, drug administration, and PK assessments during Treatment Periods 1 and 2. All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7, with a final single-dose administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

## Table 8-2 Schedule of Assessments on Day 1 of Each Inpatient Treatment Period (Visits 2 and 4)

| Procedure | Time Relative to Drug Administration | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **-60 min** | **0 hr** | **2 min** | **6 min** | **20 min** | **30 min** | **40 min** | **1 hr** | **2 hrs** | **4 hrs** | **8 hrs** | **10 hrs** | **12 hrs** | **16 hrs** | **24 hrs** |
| **PK Blood Draw** | X[a] | | X | X | X | | X | X | X | X | X | X | X | X | X |
| **Administration of Study Medication** [b] | | X | | | | | | | | | | | | | |
| **12-lead Safety ECG** [c] | X[a] | | | | | X | | | X | | | | X | | X |
| **Clinical Laboratory Tests**[e] | X[e] | | | | | X[d] | | | X[d] | X[d] | | | X[e] | | |
| **Vital Signs** | X[a] | | | | | X | | | X | | | | X | | X |
| **Adverse Events** | | X | X | 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 | X | X |

Abbreviations: ECG=electrocardiogram; PK=pharmacokinetic

[a] Within 1 hour of dosing

[b] All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7, with a final single-dose administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

[c] Twelve-lead safety ECGs will be recorded at the Screening Visit, on Day -1 to confirm eligibility, within 1 hour prior to dosing, and as scheduled above.

[d] Glucose and potassium only

[e] Complete clinical laboratory testing - chemistry and hematology

[f] For additional details, refer to Table 8-2. and Table 8-3.

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

## Table 8-3. Schedule of Assessments on Day 8 of Each Inpatient Treatment Period (Visits 3 and 5)

| Procedure | Time Relative to Drug Administration | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **-60 min** | **0 hr** | **2 min** | **6 min** | **20 min** | **30 min** | **40 min** | **1 hr** | **2 hrs** | **4 hrs** | **8 hrs** | **10 hrs** | **12 hrs** |
| **PK Blood Draw** | X[a] | | X | X | X | | X | X | X | X | X | X | X |
| **Administration of Study Medication** [b] | | X | | | | | | | | | | | |
| **12-lead Safety ECG** | X[a] | | | | | X[c] | | | X[c] | | | | X[c] |
| **Clinical Laboratory Tests** | X[e] | | | | | X[d] | | | X[d] | X[d] | | | X[e] |
| **Vital Signs** | X[a] | | | | | X | | | X | | | | 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: ECG=electrocardiogram; PK=pharmacokinetic

[a] Within 1 hour of dosing

[b] All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7, with a final single-dose administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

[c] Twelve-lead safety ECGs will be recorded at the Screening Visit, on Day -1 to confirm eligibility, within 1 hour prior to dosing, and as scheduled above.

[d] Glucose and potassium only

[e] Complete clinical laboratory testing - chemistry and hematology

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

## 8.1 Screening Visit 1 (Days -28 to Day -2, Prior to Randomization)

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

After obtaining written and signed informed consent, the following procedures and assessments will be performed during the Screening period, prior to randomization, and results will be documented in the eCRF and/or source documents:

- Informed consent (obtain first, prior to other study procedures)
- Demographics and relevant medical history
- Physical examination
- Vital signs
- Review of eligibility criteria
- Placebo MDI usage demonstration and practice
- 12-lead ECG
- Clinical laboratory evaluations (including urinalysis)
- Urine drug testing
- Alcohol breathalyzer test
- Serum pregnancy test (women only; for all women of childbearing potential and non-childbearing potential)
- Follicle-stimulating hormone test for women of non-childbearing potential
- Serology (HIV, HBsAg, and hepatitis C)
- Document concomitant medications

## 8.2 Admission to Clinic (Day -1 of Treatment Period 1)

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

After the subject is admitted to the study center, the following procedures will be obtained and/or performed:

- Medical history
- Physical examination

- Vital signs
- Review of eligibility criteria
- 12-lead ECG
- Clinical laboratory evaluations (including urinalysis)
- Placebo MDI usage demonstration and practice
- Documentation of AEs
- Documentation of concomitant medications
- Urine drug screen
- Alcohol breathalyzer test
- Urine pregnancy test for all women (of childbearing *and* non-childbearing potential)

## 8.3 Visit 2 (Day 1 of Treatment Period 1)

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

The following study activities and assessments will be performed on Day 1 in conjunction with the first Treatment Period and results will be documented in the eCRF and/or source documents:

- Review of eligibility criteria
- Randomization and treatment assignment
- Placebo MDI usage demonstration and practice
- Pre- and post-dose documentation of vital signs per Table 8-2
- Administration of study drug; a single dose of study drug will be administered by oral inhalation. (Refer to Appendix 1 for details regarding study drug dispensing and administration).
  - **Note:** Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.
- Collect pre- and post-dose PK samples per Table 8-2
- Collect blood samples for clinical laboratory testing per Table 8-2
- Perform 12-lead ECG per Table 8-2
- Documentation of 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 7.10.1.8)
- Documentation of concomitant medications

After all scheduled assessments are complete and all available safety data has been reviewed by the Investigator, schedule next visit. Subjects will remain in the clinic until completion of Treatment Period 1.

## 8.4 Visit 5 (Day 2 of Treatment Period 1)

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

- Administration of study drug; study drug will be administered BID by oral inhalation. (Refer to Appendix 1 for details regarding study drug dispensing and administration).
  - It is recommended that the timing of study drug administration is anchored to the timing of the first dose, such that the volunteer is dosed every 12 hours: between 8 to 10 am for the morning dose; and between 8 to 10 PM for the evening dose.
    - **Note**: Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.
- Documentation of 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 7.10.1.8)

## 8.5 Days 3–7 of Treatment Period 1

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

- Administration of study drug; study drug will be administered BID by oral inhalation. (Refer to Appendix 1 for details regarding study drug dispensing and administration).
    - **Note:** Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.
- Documentation of 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 7.10.1.8)

## 8.6 Day 8 of Treatment Period 1

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

The following study activities and assessments will be performed on Day 8 in conjunction with the first Treatment Period and results will be documented in the eCRF and/or source documents:

- Placebo MDI usage demonstration and practice
- Pre- and post-dose documentation of vital signs per Table 8-3
- Administration of study drug; only a single morning dose of study drug will be administered by oral inhalation. (Refer to Appendix 1 for details regarding study drug dispensing and administration)
    - **Note:** Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.
- Collect pre- and post-dose PK samples per Table 8-3
- Collect blood samples for clinical laboratory testing per Table 8-3
- Perform 12-lead ECG per Table 8-3
- Documentation of AEs
- Documentation of concomitant medications

After all scheduled assessments are complete and all available safety data has been reviewed by the Investigator, discharge from the clinic upon completion of all protocol-specified procedures and complete a Washout Period of at least 7 calendar days, and not exceeding 21 days between doses. Prior to discharge from the clinic for Treatment Period 1, schedule the clinic admission for Treatment Period 2.

## 8.7 Visit 5 (Day 8 of Treatment Period 2)

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

The following study activities and assessments will be performed on Day 8 in conjunction with the second Treatment Period and results will be documented in the eCRF and/or source documents:

- Placebo MDI usage demonstration and practice
- Pre- and post-dose documentation of vital signs per Table 8-3
- Administration of study drug (Refer to Appendix 1 for details regarding study drug dispensing and administration)
    - **Note:** Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.
- Collect pre- and post-dose PK samples per Table 8-3

- Collect blood samples for clinical laboratory testing per Table 8-3
- Perform 12-lead ECG per Table 8-3
- Documentation of AEs
- Documentation of concomitant medications

After all scheduled assessments are complete and all available safety data has been reviewed by the Investigator, and discharge from the clinic upon completion of all protocol-specified procedures.

## 8.8 Follow-Up Telephone Call

**Note Regarding Cross-over Period (Treatment Period 2):** With the exception of Randomization and treatment assignment at Visit 2 (Day 1 of Treatment Period 1), the procedures and timings for Treatment Period 2 mirror those performed for Treatment Period 1.

Upon completion of the study, a follow-up phone call with each subject will be completed at least 5 days but no longer than 7 days from the last dose date. Subjects will be asked about any new or outstanding AEs, any new concomitant medication, and any changes to birth control method. This will be documented appropriately in the subject source documents and eCRFs.

- Review of medical history
- Documentation of AEs and concomitant medications
- Documentation of changes to birth control

# 9 PLANNED STATISTICAL METHODS

## 9.1 General Considerations

A detailed Statistical Analysis Plan (SAP) will be finalized prior to database lock and unblinding.

## 9.2 Analysis Populations

Two subject populations will be evaluated during this study and are defined as follows:

- **Safety Population:** All subjects who receive at least one dose of any study drug.
- **PK Population:** All subjects in the Safety Population who have sufficient data to reliably calculate at least one PK parameter at either dose level of BGF MDI and do not have major protocol deviations (to be determined prior to unblinding).

Safety and tolerability analyses will be performed on data from all subjects in the Safety Population.

Pharmacokinetic analysis will be performed using the PK population.

## 9.3 Demographics and Baseline Characteristics

Demographic information will include date of birth, 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.

## 9.4 Analysis of Pharmacokinetic Variables

Pharmacokinetic analysis will be performed using the PK population.

Pharmacokinetic parameters at both doses will include $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{0-12}$, $AUC_{0-t}$, $AUC_{0-\infty}$, CL/F, Vd/F, $\lambda_z$, RAC ($C_{max}$), and RAC ($AUC_{0-12}$). Other PK parameters may be calculated, as appropriate.

The initial calculation of PK parameters will be performed using non-compartmental analysis. Model-based parameter estimation may be performed following examination of the data. Summary statistics will be used to describe the plasma concentrations and PK parameters for budesonide, glycopyrronium, and formoterol by treatment.

## 9.5 Safety Analyses

No formal statistical analysis of safety data is planned. Safety data will be summarized by treatment and listed. The safety of BGF MDI will be assessed from physical examination

findings, AE reporting including SAE reporting, vital signs (BP, HR, respiratory rate, and body temperature), clinical laboratory values (hematology, chemistry, and urinalysis), and findings from 12-lead ECGs. The incidence of AEs and SAEs will be tabulated by treatment. Summary statistics of assessed laboratory values will be tabulated by treatment.

## 9.6 Interim Analysis

No interim analysis is planned for the study.

## 9.7 Randomization

Following determination of study eligibility, subjects will be randomized to one of three treatment sequences shown below in a 1:3:1 ratio where A, B, and C each represent Placebo MDI, BGF 160/14.4/9.6 µg, and BGF 320/14.4/9.6 µg, respectively.

**AC BC BA**

The design allows the lower dose of BGF MDI to be examined in the first period prior to administering the higher dose in the second period.

## 9.8 Determination of Sample Size

The anticipated sample size of approximately 20 randomized subjects was selected to provide approximately 16 completers. No formal criteria for the evaluation of PK were used to determine the sample size, but the chosen size is expected to provide reasonable estimates of the PK parameters in healthy adult subjects of Japanese descent.

## 9.9 Analysis Plan

All analyses will be specified in a detailed statistical analysis plan (SAP) that will be accompanied by table and data listing shells with mock graphical representations. The SAP will be approved by signature before database lock and prior to unblinding.

# 10 ADMINISTRATIVE CONSIDERATIONS

## 10.1 Regulatory Authority Approval

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

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

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

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

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

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

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

## 10.4 Laboratory Accreditation

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

## 10.5 Confidentiality

### 10.5.1 Confidentiality of Data

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

### 10.5.2 Confidentiality of Subject/Patient Records

By signing this protocol, the Investigator agrees that Pearl Therapeutics (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 Pearl Therapeutics. In addition, the Investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable laws (ie, Health Insurance Portability and Accountability Act), rules and regulations.

## 10.6 Quality Control and Assurance

Pearl Therapeutics is responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

## 10.7 Data Management

Data management procedures and information for this protocol will be provided by Pearl Therapeutics or their designee.

## 10.8 Study Monitoring

In accordance with applicable regulations, GCP, and Pearl Therapeutics 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 issues.

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

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

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

## 10.9 Retention of Data

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

## 10.10 Financial Disclosure

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

## 10.12 Publication Policy

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

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

1. **Responsibility:** Each principal Investigator is responsible for the accuracy and completeness of all data from their site. Pearl Therapeutics (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.
2. **Authorship and Publication Committee:** Pearl Therapeutics, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE. It is anticipated that a publication committee will be formed to assume oversight of these activities.
   All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
3. **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted at least 30 days prior to submission for publication or presentation to Pearl Therapeutics for review, approval, and to ensure consistency with the policy in this protocol. Pearl Therapeutics will have the right to request appropriate modification to correct facts and to represent its opinions, or the opinions of the publication committee, if these differ with the proposed publication.
4. **Confidentiality:** Investigators will conduct all interactions with Pearl Therapeutics and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of nonclinical studies, or chemical formulae) may still need to remain confidential.
5. **Medical Journal Review:** Consistent with the intention of Pearl Therapeutics to publish the study in a fair and accurate manner, Pearl Therapeutics 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 Pearl Therapeutics will make suitable arrangements to ensure that the identity of journal reviewers is kept confidential. Records will be maintained of reviewers and the respective documents and datasets that were reviewed by each of them.
6. **Reporting of Clinical Trials Results:** To provide transparency in the conduct and reporting of randomized clinical trials, Pearl reports clinical findings based on the guidance of The CONSORT (CONsolidated Standards of Reporting Trials) Statement [CONSORT, 2010] and a 25-item checklist which is intended to improve the reporting of a randomized controlled 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, Pearl Therapeutics will make available appropriate information regarding the

study via the internet. This will include registration and listing of the study on www.clinicaltrials.gov, the US National Institutes of Health listing of clinical trials, and other clinical trial listings as appropriate.

# 11 REFERENCE LIST

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# Appendix 1 Administration of Study Drug

All subjects will receive two treatments by random assignment to one of three predetermined treatment sequences as listed in Section 6.1of this protocol. This is a double-blind study. The Pearl products (BGF MDI and Placebo MDI) are identical in form and function and indistinguishable from each other.

At the Screening Visit, subjects will be instructed in the proper use of the MDI and, at that time, must demonstrate the ability to coordinate use of the MDI using a bulk-supplied Placebo MDI.

**BGF MDI and Placebo MDI Administration:** For specific guidance for the Handling and Instructions for Use of BGF MDI and BFF MDI, please refer to Section 3.3 of the Investigator Brochure (IB). On Day 1 of each Treatment Period, prior to the first MDI administration, the MDI device will be primed in the study site pharmacy by the pharmacist and delivered to the inpatient clinic. . Just prior to dosing, subjects will again be given detailed instruction regarding the proper use of the MDI device to ensure comprehension of its use. At the time of dosing, a healthcare provider will be present to ensure that the two activations of the MDI device are properly administered by the subject. The dosing time must be documented on the eCRF. The three MDI treatments are:

- BGF MDI 320/14.4/9.6 µg
- BGF MDI 160/14.4/9.6 µg
- Placebo MDI

The dose delivery specifications for the three treatments are provided in the following table:

## Table A1-1. Dose Delivery Specifications

| Product Name & Dose | Product Strength | Dosage Form | Administration |
|---|---|---|---|
| BGF MDI 320/14.4/9.6 µg ex-actuator | 160/7.2/4.8 µg/actuation | MDI | Taken as 2 inhalations |
| BGF MDI 160/14.4/9.6 µg ex-actuator | 80/7.2/4.8 µg/actuation | MDI | Taken as 2 inhalations |
| Placebo MDI | Formulation does not contain active ingredient | MDI | Taken as 2 inhalations |

[2] Abbreviations: BGF MDI=budesonide, glycopyrrolate, and formoterol fumarate inhalation aerosol; MDI=metered dose inhaler
**Note:** All study drugs are administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7 of each Treatment Period, with a final single administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

# Appendix 2 Plasma Collection, Processing, and Handling (PK Samples)

- Collect approximately 10 mL of blood into a 2 tubes containing EDTA tripotassium ($4 \times 10^{3}$M in phosphate buffered saline). Care should be taken to minimize hemolysis during sample collection.
- Place all tubes on wet ice immediately after collection.
- Centrifuge the blood within 30 minutes of collection at >1000 x g (~2500 rpm) for 10 to 15 minutes.
- Transfer approximately equal aliquots (Aliquot A and Aliquot B) of plasma into duplicate labeled polypropylene test tubes with a snap or screw cap. Care should be taken to minimize contamination with red blood cells during transfer of plasma.
- Securely cap the labeled tubes. Please ensure the following when labeling the plasma aliquots:
  - Sample vials must be clearly and accurately labeled using a solvent resistant ink (do not use ballpoint pen) or using supplied labels.
  - The information on the labels should correspond to the information recorded on the PK Sample Log worksheet for each subject.
  - The actual date and clock time (24-hour clock) of sample collection should be entered on the PK Sample Log worksheet.
  - The plasma samples should then be placed in a freezer capable of maintaining a temperature of at least -60°C as soon as possible after aliquoting for storage. Store Aliquot A samples separate from Aliquot B samples as these will be shipped separately.
- Ship frozen plasma samples within dry ice using a supplied cooler and labeling according to the procedure provided by the courier service.
- Ship samples only on a Monday, Tuesday, or Wednesday or at least 3 days prior to a holiday via priority overnight delivery.
- Ship Aliquot A samples first.
- Aliquot B samples should be retained frozen until receipt of Aliquot A samples is confirmed and then shipped according to instruction.

**Shipping Address:**

[redacted]

**ATTENTION: Sample Management**

Phone: [redacted]
E-mail: [redacted]

## Appendix 3 Sponsor Signatory

**Study Title:** A Phase I, Randomized, Double-Blind, Placebo-Controlled, Two-Period, Ascending Dose, Crossover Study to Assess the Safety and Pharmacokinetics of Two Doses of PT010 in in Healthy Adult Subjects of Japanese Descent Following a Single Dose and After Chronic Dosing for 7 Days

**Study Number:** PT010003-01

**Final Date:** [redacted]

**Signature:** [redacted] Date: [redacted]

**Name:** [redacted]

**Title:** [redacted] Pearl Therapeutics, Inc.

## Appendix 4 Investigator's Agreement and Signature Page

**Study Title:** A Phase I, Randomized, Double-Blind, Placebo-Controlled, Two-Period, Ascending Dose, Crossover Study to Assess the Safety and Pharmacokinetics of Two Doses of PT010 in in Healthy Adult Subjects of Japanese Descent Following a Single Dose and After Chronic Dosing for 7 Days

**Study Number:** PT010003-01

**Final Date:** [redacted]

**I agree:**

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

Signature: [redacted] Date: [redacted]

Name: [redacted]

Affiliation: [redacted]