Revised Clinical Study Protocol

Study Code	PT010010
NCT #	NCT03075267
Version	Ver. 4.0 Amendment 3
Date	12 May 2017

A Phase I, Randomized, Double-Blind, Parallel-Group Study to Assess the Pharmacokinetics and Safety of Two Doses of PT010 and a Single Dose of PT003 in Healthy Chinese Adult Subjects Following A Single Administration and After Chronic Administration for 7 Days

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

Amendment No.	Date of Amendment
Version 1.0	07 May 2015
Version 2.0	20 October 2016
Version 2.1	15 November 2016
Version 3.0	25 January 2017
Version 4.0	12 May 2017

Clinical Trial Protocol: PT010010-03

Title:	A Phase I, Randomized, Double-Blind, Parallel-Group Study to Assess the Pharmacokinetics and Safety of Two Doses of PT010 and a Single Dose of PT003 in Healthy Chinese Adult Subjects Following A Single Administration and After Chronic Administration for 7 Days
Study Number:	PT010010-03 (AZ code: D5980C00005)
Study Phase:	Phase I
Product Name:	Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler; (BGF MDI-(PT010)) Glycopyrronium and Formoterol Fumarate Inhalation Aerosol, PT003; Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler (GFF MDI)
Investigator:	[redacted]
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]

	Version Number	Date
Original Protocol:	Version 1.0	07 May 2015
Revised Protocol	Version 2.0	20 October 2016
Revised Protocol	Version 2.1	15 November 2016
Revised Protocol	Version 3.0	25 January 2017
Revised Protocol	Version 4.0	12 May 2017

SUMMARY OF CHANGES INCLUDED IN THIS PROTOCOL AMENDMENT VERSION 4.0

Description of Change	Rationale
Revised ECG and vital signs assessment time window from within 60 minutes pre-dose to within 120 minutes pre-dose to allow adequate time to complete all pre-dose study procedures.	Minor change to ECG and vital signs assessment due to operational complexity in timing requirements for original procedures
Other administrative changes to correct and/or clarify protocol language were also addressed. These changes included edits for consistency, grammar, and typographical errors, which are not summarized in this table	

SUMMARY OF CHANGES INCLUDED IN PROTOCOL AMENDMENT VERSION 3.0

Description of Change	Rationale
Revised total blood volume throughout the protocol (Synopsis and Section 7.4.5) to reflect new total volume from approximately 187 to 194mls	Minor change to total blood volume due to local laboratory requirements for serology and hematology
Other administrative changes to correct and/or clarify protocol language were also addressed. These changes included edits for consistency, grammar, and typographical errors, which are not summarized in this table	

SUMMARY OF CHANGES INCLUDED IN PROTOCOL AMENDMENT VERSION 2.1

The amended study protocol, PT010010-01 (Version 2.1), includes the following revisions to align with protocol and other requirements:

Description of Change	Rationale
Changed title page to include Investigator information	Revised to reflect single center details
Section 5.5.3 revised reference to Exclusion Criterion	Revised from Exclusion criteria “14” to “16”
Section 6.2 revised to clarify process at the site	Revised delivery study medication from “inpatient clinic” to” delegated

Description of Change	Rationale
	staff"
Section 7.4.5 for Clinical Laboratory Tests section revised for consistency	Clarified visit details for respective procedures and fasting requirement and removed details that no longer applied
Section 7.5.8.1and 7.5.8.2 revised to include Pearl Pharmacovigilance role	Clarified these sections to reflect Pearl Pharmacovigilance role versus Medical monitor role for safety reporting and investigations
Section 8 (various sub-sections), Tables 8-1, 8-2 and 8-3 revised to include consistency and clarity and included physical exam at Visit 4 and removed follow-up telephone call review of medical history and documentation of birth control changes	Clarified visit details in respective Tables and procedure sections including table footnote reference (s) and language in alignment with related protocol sections and included an additional physical exam
Other administrative changes to correct and/or clarify protocol language were also addressed. These changes included edits for consistency, grammar, and typographical errors, which are not summarized in this table	

SUMMARY OF CHANGES INCLUDED IN THIS PROTOCOL AMENDMENT VERSION 2.0

The amended study protocol, PT010010-01 (Version 2.0), includes the following revisions:

Description of Change	Rationale
Changed Sponsor Contact on title and sponsor signature page	Revised to reflect named Clinical Program Head
Title Page, AZ Study number included	(AZ code:D5980C00005) added per internal input
Deleted 'Cohorts" and revised anticipated study run time (*Global Change)	Cohorts do not apply to the current study design and run time removed to allow flexibility
Revised Secondary Objective in Synopsis and Section 2.0	Revised this objective for consistency throughout the protocol
Pharmacokinetic assessments revised in the Synopsis, and Blood sample collection Section 7.3.1and Laboratory Sample Collection, Storage and Shipping Section 7.4.5.1	Post dose PK blood draw volume reduced and a time-point at 16 hrs removed to minimize subject discomfort and multiple blood draws
Product approvals revised for China in Section 1.0	FF approval in China is for COPD only
Revised heart rate to pulse rate for vital signs in Secondary Endpoint Section 3.2, Vital Signs Section 7.4.3, and Safety Analyses Section 9.5	Revised "heart rate" with "pulse rate" to reflect proper procedure at the study site in China.
Duration revised in Synopsis and Study Duration and Dates in Section 4.2	Revised the study duration to 43 days to reflect 28 days of screening, 8 treatment days and 5-7 days for follow-up
Inclusion Criteria for gender revised and criteria for the requirement for normal chest X-ray and abdominal ultrasound added in Section 5.1	As this study will be conducted in China only, the generation details for origin and descent was removed and the other diagnostic criteria added to ensure the subject was healthy
Exclusion Criteria Section 5.2 and Prior, Concomitant and Prohibited Medications Section 5.4 and Table 7-3 Laboratory Tests revised	China specific local requirements included for Blood collection, donation and transfusion; after confirming HIV positivity further CDC testing included, Syphilis exclusion and calculation for GFR

Description of Change	Rationale
	added (Table 7-3), criteria for glaucoma clarified as a complete exclusion so as to include a healthy volunteer population that does not require the use of concomitant medications (Section 5.4) to treat such a condition
Fasting time period increased from 4 to 8 hrs prior to blood draw in Section 5.5.2, Section 7.4.5	Revised to match the standard site requirements
Study Clinical Supplies Section 6.1, Section 6.5 and Section 6.8	This section revised to include envelope based randomization scheme.
Study Procedures Section 7.0 through Section 7.4 and Section 8.0	Study procedure time points, visit frequency, local laboratory testing, clarified and aligned based on input from study site for local requirements
Adverse Events Section 7.5	This section revised to reflect current eCRF collection requirements.
Sample Size in the Synopsis and Section 9.7	This section was updated to include the description of inter-subject variability of glycopyrronium after single-dose administration
Other administrative changes to correct and/or clarify protocol language were also addressed. These changes included edits for consistency, grammar, and typographical errors, which are not summarized in this table *when change affects the Protocol in more than 3 Sections	

SYNOPSIS

Sponsor: Pearl Therapeutics, Inc. ("Pearl") [redacted]
Names of Finished Products: Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (PT010, BGF metered dose inhaler [MDI]) Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (PT003, GFF MDI)
Name of Active Ingredients: Budesonide, Glycopyrronium, and Formoterol Fumarate Glycopyrronium and Formoterol Fumarate
Study Title: A Phase I, Randomized, Double-Blind, Parallel-Group Study to Assess the Pharmacokinetics and Safety of Two Doses of PT010 and a Single Dose of PT003 in Healthy Chinese Adult Subjects Following A Single Administration and After Chronic Administration for 7 Days
Study Number: PT010010-03
Study Phase: I
Primary Objective: • To assess the Pharmacokinetic (PK) profile of two doses of BGF MDI and single dose of GFF MDI in healthy Chinese adult subjects after single administration and after chronic administration for 7 days.
Secondary Objective: • To assess the safety and tolerability of two doses of BGF MDI and a single dose of GFF MDI in healthy Chinese adult subjects after single administration and after chronic administration for 7 days

Study Design:

This is a Phase I, randomized, double-blind, parallel-group study to assess the pharmacokinetics and safety of two doses of BGF MDI and a single dose of GFF MDI in healthy Chinese adult subjects. Pharmacokinetics will be assessed following a single administration and after chronic administration for 7 days. Safety will be assessed during the 8-day treatment period and throughout the entire study until subjects are released from participation. All study drugs will be administered by oral inhalation. It is planned that the study will enroll and randomize an estimated 96 eligible subjects to one of 3 treatment groups in a 1:1:1 ratio to have approximately 90 completed subjects. Subjects will receive one of the three following treatments:

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

This study includes a Screening Period of up to 28 days and a single Treatment Period of 8 days, A follow-up phone call will be conducted at least 5 days, but no longer than 7 days after completion of the last dose. The maximum participation in the study for each subject is not expected to exceed approximately 42 days.

Study Population:

The planned study population includes a total of approximately 96 male and female adult healthy Chinese subjects. Subjects will be enrolled and randomized in the study to provide approximately 90 subject completers.

Test Product, Dose, and Mode of Administration:

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

Product Name & Dose	Product Strength	Dosage Form/ Fill Count	Administration
BGF MDI 320/14.4/9.6 µg ex-actuator	160/7.2/4.8 µg/actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
BGF MDI 160/14.4/9.6 µg ex-actuator	80/7.2/4.8 µg/actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
GFF MDI 14.4/9.6 µg ex-actuator	7.2/4.8 µg /actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
Placebo			
Placebo MDI[a]	Formulation does not contain active ingredient	MDI 120 inhalations	Subjects will use the placebo MDI for training purpose only to demonstrate proper use of the MDI on Day -1, Day 1 and Day 8 (and on other treatment days as needed per site discretion)

Abbreviations: BID=twice daily; BGF MDI = budesonide, glycopyrronium , and formoterol fumarate ; MDI=metered dose inhaler. GFF=Glycopyrronium and Formoterol Fumarate; HFA=hydrofluoroalkane;

[a]Placebo MDI will be used for training purposes. All placebos are created by Pearl in the image of the active test product, with no active moieties.

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.

Duration of Treatment:

It is planned that each subject will receive study treatment for 8 days

Duration of Study:

The entire study period is scheduled to take approximately 5 weeks (expected range between 2 to 6 weeks) for each individual subject.

Pharmacokinetic Assessments:

Pharmacokinetics of BGF MDI and GFF MDI will be assessed and compared using plasma concentrations of budesonide, glycopyrrolate and formoterol. For the single dose administration, time points for pharmacokinetic (PK) blood sample collection will be pre-dose within 60 minutes and post-dose at 2, 6, 20, and 40 minutes and at 1, 2, 4, 8, 10, 12, and 24 hours. Following 7 days of chronic dosing BID, time points for PK blood sample collection will be pre-dose within 60 minutes and post-dose at 2, 6, 20, and 40 minutes and at 1, 2, 4, 8, 10, 12 and 24 hours starting on the morning of the 8th day.

Pharmacokinetic parameters calculated after single-dose administration (Day 1) and chronic administration (Day 8) will include maximum plasma concentration (C_{max}), apparent total body clearance (CL/F), area under the plasma concentration-time curve from 0 to 12 hours

(AUC_{0-12}), and time to maximum plasma concentration (t_{max}). Pharmacokinetic parameters calculated after single-dose administration (Day 1) will include 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 ($AUC_{0-\infty}$); elimination half-life ($t_{½}$); apparent volume of distribution (Vd/F) and the terminal elimination rate constant (λ_z). The accumulation ratio for C_{max} (RAC [C_{max}]); accumulation ratio for AUC_{0-12} (RAC [AUC_{0-12}]) and the ratio (AUC_{0-12} / $AUC_{0-\infty}$) will be derived by taking subject level ratios of Day 8 values to Day 1 values.

Other PK parameters may be calculated, as appropriate.

Safety Assessments:

The safety and tolerability profile of two doses of BGF MDI and a single dose GFF 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 blinded study drug.

PK Population: All subjects in the Safety Population who have sufficient data to reliably calculate at least one PK parameter 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: Descriptive statistics without model adjustment will be used to describe the budesonide, glycopyrrolate and formoterol PK parameters after treatment with two doses of BGF MDI and single dose of GFF MDI.

Sample Size:

Previous studies with BGF MDI suggest that the inter-subject variability of glycopyrronium after single-dose administration may be as high a [redacted]

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ABBREVIATIONS AND DEFINITIONS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
API	Active Pharmaceutical Ingredients
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, Glycopyrronium, 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
CFDA	China Food and Drug Administration
FF MDI	Formoterol Fumarate Metered Dose Inhaler
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GFF MDI	Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler
GFR	Glomerular Filtration Rate

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP MDI	Glycopyrronium Metered Dose Inhaler
HbsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HFA	Hydrofluoroalkane
HIV	Human Immunodeficiency Virus
IB	Investigators Brochure
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
ie	Id Est, That Is
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
LABA	Long-acting β_2 Agonist
LAMA	Long-acting Muscarinic Antagonist
λ_z	Terminal Elimination Rate Constant
MDI	Metered Dose Inhaler
µg	Microgram
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of Mercury
msec (ms)	Millisecond
PK	Pharmacokinetics
PR	Pulse Rate
PT003	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol
PT010	Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol
QTcF	QT Corrected Using Fridericia's Formula
RAC(C_{max})	Accumulation ratio for C_{max}

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

RAC(AUC_{0-12})	Accumulation ratio for AUC_{0-12}
SABA	Short-acting β_2-agonists
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
$t_{½}$	Apparent Terminal Elimination Half-life
TEAE	Treatment-emergent Adverse Event
t_{max}	Time To Maximum Plasma Concentration
Vd/F	Apparent Volume of Distribution

TRADEMARK INFORMATION

Trademarks not owned by Pearl Therapeutics, Inc. include:

Oxis

Pulmicort

Respules

Spiriva

Symbicort

Turbuhaler

Vacutainer

Ziploc

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

Glycopyrronium is a quaternary ammonium derivative, that when inhaled results in minimal mucosal absorption and systemic side effects. Glycopyrronium is not approved for respiratory inhalation in China for the treatment of COPD, although it is approved in other

countries for treatment of COPD. In addition, tiotropium bromide ([redacted]) 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 [redacted]

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

Although formoterol fumarate is classified as a LABA, it has a rapid onset of action similar to short-acting β_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 China by [redacted], include: Pulmicort® Turbuhaler® and Pulmicort Respules®. Inhaled budesonide as a mono therapy (Pulmicort) and in combination with formoterol fumarate di hydrate (i.e., Symbicort) is approved for use in patients with COPD.

Pearl is developing BGF MDI and GFF 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, glycopyrronium, and formoterol fumarate for treatment of subjects with COPD. As described in the GOLD COPD guidelines, in some patients, the addition of a LABA/ICS to a LAMA improves lung function, quality of life, and may further reduce exacerbations. For patients 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 safety/tolerability and efficacy of the individual components, budesonide, glycopyrronium, and formoterol fumarate are well characterized.

The doses of the glycopyrronium and formoterol fumarate components of BGF MDI match the doses utilized in the GFF MDI development program. The GFF MDI clinical program consisted of 12 clinical studies to support the dose selection of glycopyrronium and formoterol fumarate for the dual combination GFF MDI, as well as its components GP MDI and FF MDI, in subjects with moderate to very severe COPD. Based on the data obtained through this Phase II program, doses of glycopyrronium and formoterol fumarate of 14.4 and 9.6 μg BID, respectively, were selected for progression into Phase III. Two Phase III pivotal efficacy and safety studies, and one long-term extension study, have recently completed which evaluated the efficacy and safety of GFF MDI, GP MDI, and FF MDI as bronchodilator treatments in subjects with moderate to very severe COPD. In addition a Phase I study (Study PT003010) was recently completed that characterized the pharmacokinetic (PK) and safety profile of GFF MDI and GP MDI in adult Japanese healthy subjects which demonstrated similar glycopyrronium and formoterol plasma concentrations following single-dose administration of GFF MDI and GP MDI with a favorable safety profile.

In order to select the appropriate budesonide dose for Phase III, Pearl has conducted two Phase I single-dose PK and safety studies in healthy adult Western subjects (Studies PT010001 and PT010002) comparing BGF MDI to GFF MDI, Symbicort® MDI, or Symbicort Turbuhaler, and (Study PT010003) with two doses of the triple product, BGF MDI compared with Placebo MDI in adult healthy Japanese subjects.

Study PT010001 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.

Study PT010002 was conducted to investigate the PK comparability of BGF MDI and BFF MDI to Symbicort Turbuhaler. The budesonide component of BGF MDI was nearly identical on C_{max} with a GMR of 1.02 and 90% CI of (0.81, 1.30), but AUC_{0-12} was approximately 25% higher than Symbicort TBH. Similar results were obtained for the comparison of BFF MDI to Symbicort TBH. Study PT010002 also investigated the potential for a DDI by comparing the budesonide and formoterol 12-hour PK profiles following a single dose of BGF MDI or BFF MDI. No DDI was observed as both budesonide and formoterol C_{max} and AUC_{0-12}were similar following administration of either BGF MDI or BFF MDI.

Study PT010003 demonstrated that administration of single and multiple doses of BGF MDI 160/14.4/9.6 µg and BGF MDI 320/14.4/9.6 µg to Japanese subjects were safe and well tolerated in this study. Formoterol and glycopyrronium plasma concentrations following administration of BGF MDI 160/14.4/9.6 µg and BGF MDI 320/14.4/9.6 µg were similar following single and chronic administrations. The budesonide plasma concentrations were proportionally higher from BGF MDI 320/14.4/9.6 µg compared to BGF MDI 160/14.4/9.6 µg following single and chronic administrations. All treatments were well tolerated with a low frequency of adverse events (AEs), TEAEs were mild to moderate in severity and no unexpected safety signals were observed.

Based on these findings in Western and Japanese subjects, Study PT010010 is being conducted to confirm the appropriate dose(s) for evaluation in the Chinese population.

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) and a single dose of GFF MDI (14.4/9.6 µg dose) in healthy Chinese adult subjects after single administration and after chronic administration for 7 days.

2 STUDY OBJECTIVES

2.1 Primary Objective

- The primary objective of the study is to assess the Pharmacokinetic (PK) profile of two doses of BGF MDI and a single dose of GFF MDI in healthy Chinese adult subjects after single administration and after chronic administration for 7 days.

2.2 Secondary Objective

- The secondary objective of this study is to assess the safety and tolerability of two doses of BGF MDI and a single dose of GFF MDI in healthy Chinese adult subjects after single administration and after chronic administration for 7 days.

3 STUDY ENDPOINTS

3.1 Pharmacokinetic Endpoint

Pharmacokinetics of BGF MDI and GFF MDI will be assessed and compared using plasma concentrations of budesonide, glycopyrronium, and formoterol. For the single dose administration, time points for PK blood sample collection will be pre-dose within 60 minutes and post-dose at 2, 6, 20, and 40 minutes and at 1, 2, 4, 8, 10, 12, and 24 hours. Following 7 days of chronic dosing BID, time points for PK blood sample collection will be pre-dose within 60 minutes and post-dose at 2, 6, 20, and 40 minutes and at 1, 2, 4, 8, 10, 12 and 24 hours.

Pharmacokinetic parameters calculated at the first day (Day 1) and last dose (Day 8) during the 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})
- Time to maximum plasma concentration (t_{max})
- Apparent total body clearance (CL/F)

The following PK parameters will be calculated at Day 1 only:

- 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 ($AUC_{0-\infty}$)
- Elimination half-life ($t_{½}$)
- Apparent total body clearance (CL/F)
- Apparent volume of distribution (Vd/F)
- Terminal elimination rate constant (λ_z)

The following will be derived by taking subject level ratios of Day 8 values to Day 1 values:

- Accumulation ratio for C_{max} (RAC [C_{max}])
- Accumulation ratio for AUC_{0-12} (RAC [AUC_{0-12}]) and the ratio (AUC_{0-12} / $AUC_{0-\infty}$)

3.2 Secondary Endpoint

The safety and tolerability of BGF MDI and GFF MDI will be assessed from physical examination findings, AE reporting including serious AE (SAE) reporting, vital signs (blood

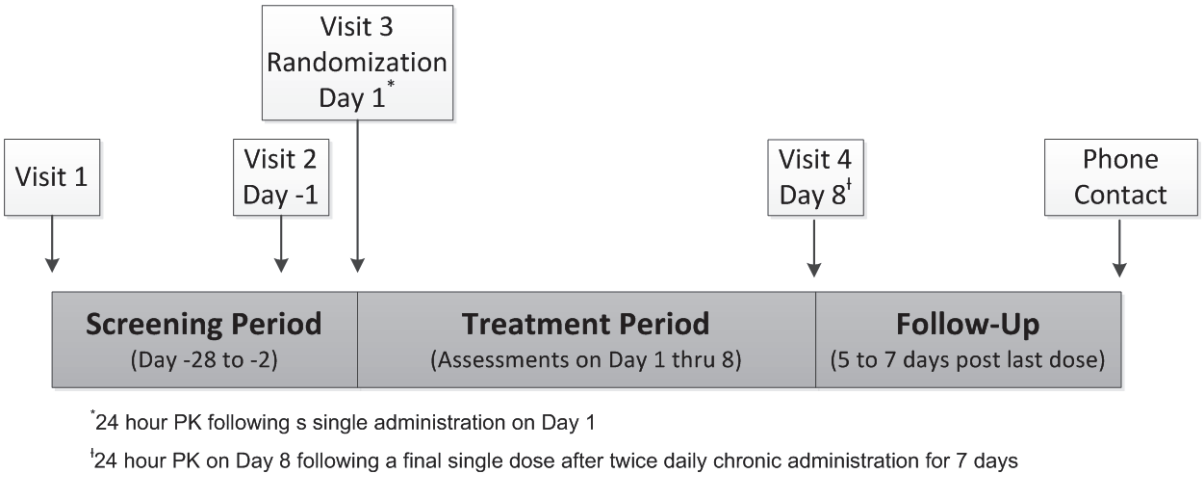
pressure [BP], pulse rate [PR], respiratory rate, and body temperature), clinical laboratory values (hematology, chemistry, and urinalysis), and findings from 12-lead safety electrocardiograms (ECGs).

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This a Phase I, single-center, randomized, double-blind, parallel-group study to assess the pharmacokinetics and safety and tolerability of two doses of BGF MDI and a single dose of GFF MDI in healthy Chinese adult subjects. The overall study design is summarized and illustrated in Figure 4-1.

Figure 4-1. Study Design



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 the 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 in a 1:1:1 ratio to one of three treatments: BGF MDI (320/14.4/9.6 µg), BGF MDI (160/14.4/9.6 µg), and GFF MDI (14.4/9.6 µg). Approximately 32 subjects will be randomized to each treatment arm.

Subjects will be admitted as inpatients to the Clinical Research Unit (hereinafter referred to as "clinic") during the Treatment Period. For the Treatment Period, subjects will be admitted to the clinic on Visit 2 (the day prior to dosing), at which time, continuing eligibility will be assessed. At in-clinic Visit 3 (Day 1 of Treatment), if the subject continues to meet eligibility criteria, the subject will be randomized into the study, admitted into the inpatient study unit and administered their first single dose of study drug.

During the inpatient treatment period study, study specified procedures include safety assessments and baseline and pre-, post-dose serial blood draws as defined in Section 7.3 and Table 8—1, Table 8—2, and Table 8—3. After all protocol specified assessments are completed and safety data has been reviewed by the Principal Investigator (Investigator) or designated staff, the subjects will be discharged from the clinic on Day 9. A follow-up phone call will be conducted at least 5 days, but no later than 7 days, after last dose on Day 8.

4.2 Study Duration

This study will include a Screening Period of up to 28 days and a single Treatment Period of 8 days. 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 Day 8. The entire study period is scheduled to take approximately 5 weeks (expected range between 2 to 6 weeks) for each individual subject.

5 STUDY POPULATION SELECTION

Approximately 96 healthy male or female subjects will be randomized in this study. Subjects who withdraw from the study after receiving at least one dose of blinded 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, dated, an Independent Ethics Committee (IEC)-approved Informed Consent Form (ICF) before any protocol specific screening procedures are performed.
2. Male and female Chinese subjects ranging in age between18 to 45 years:
3. Subjects who have a body weight ≥50 kg (110 lbs) at the Screening Visit and body mass index between 19 and 24 kg/m^2, inclusive
4. Be in good general health as determined by a thorough medical history and physical examination, electrocardiogram (ECG), vital signs, and clinical laboratory evaluation.
5. Willing and able to complete all study assessments and procedures.
6. Females of childbearing potential must agree to be abstinent or else use one 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.
7. Females of non-childbearing potential, are defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 24 months. Post-menopausal status must be confirmed by a serum follicle-stimulating hormone (FSH) test at Screening.
8. Males with female partners of childbearing potential must agree to use a highly effective, medically acceptable form of contraception (see Inclusion criterion #6 above) 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.
9. 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 or medically qualified designee. If the subject's

Hb is slightly abnormal as compared to the reference value, it will be the judgement of the Investigator or medically qualified designee whether the subject remains eligible for the study, based on good clinical practices.

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 prior to initiating treatment.
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 initiating treatment (i.e., 12-lead ECGs performed at Screening, Day-1, baseline (pre-dose on Day 1 [ECG obtained within 1 hour prior to dosing on Day 1]) will be excluded from participation in the study.
5. A history of additional risk factors for Torsades de Pointes (e.g., heart failure, family history of Long QT Syndrome).
6. Subjects who have cancer that has not been in complete remission for at least 5 years.
7. Supine BP >140/90 mmHg or resting PR≥100 beats per minute at Screening, Day-1 and Day 1 pre-dose.
8. Male subjects with symptomatic prostatic hypertrophy that is clinically significant in the opinion of the Investigator or medically qualified designee.
9. Male subjects with a trans-urethral resection of the prostate or full resection of the prostate within 6 months prior to Screening.
10. Subjects with bladder neck obstruction or urinary retention that is clinically significant in the opinion of the Investigator or medically qualified designee.
11. Subjects with a diagnosis of glaucoma.
12. History of substance-related e.g. drug or alcohol abuse disorders (with the exception of caffeine-related and nicotine-related disorders).
13. An abnormal clinically significant chest X-ray during Screening (Day -28 to Day-1) or within 6 months prior to screening. If the subject is able to provide a report of a chest X-ray or CT within 6 months prior to Screening to assess this criteria, a chest X-ray at Screening will not be required.
14. An abnormal clinically significant abdominal ultra-sound examination during Screening (Day -28 to Day -1) or within 3 months prior to screening. If the subject is able to provide

a report of an abdominal ultrasound within 3 months prior to Screening to assess this criteria, the abdominal ultra-sound at Screening will not be required.

15. History of smoking or the use of nicotine containing products or electronic cigarettes within 3 months of Screening by self-reporting.
16. A positive alcohol breathalyzer or urine drug screen for drugs of abuse at the Screening Visit or at the beginning of the inpatient period.
17. Treatment with an investigational drug within 30 days or five half-lives (whichever is longer) prior to screening.
18. 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 3 (Day 1):
    - Acetaminophen will be permitted at doses of ≤2 grams/day. In females, oral and/or implanted contraceptive medication is permitted.
19. 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.
20. Blood collection/donation/transfusion:
    - Blood donation (include element donation) or blood loss greater than 400 ml within 90 days; or greater than 200 ml within 30 days prior to screening.
    - Blood transfusion within 90 days prior to screening.
21. Positive for human immunodeficiency virus (HIV) antibody at Screening.
22. Positive for hepatitis B surface antigen (HbsAg) or positive hepatitis C antibody at Screening.
23. Positive for Syphilis Ab (using TRUST to check for the Syphilis antibody currently).
24. Subjects with a chronic medical condition that requires ongoing treatment with medication.
25. Subjects using any herbal tea, herbal supplement, herbal oral medications, or herbal inhalation and nebulizer products within 2 weeks prior to Visit 1 (Screening) and do not agree to stop using them during the study drug treatment.
26. Subjects with a history of major surgery within 4 weeks or minor surgery within 2 weeks of drug administration (Visit 3).
27. 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 (Visit 3).
28. Any other condition and/or situation that causes the Investigator or medically qualified designee to deem a subject unsuitable for the study (e.g., 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).
29. Subjects with abnormal-glomerular filtration rate (GFR); estimated GFR <60 mL/min using the C-MDRD (modified for Chinese) equation in Section 7.4.5.

30. Previous Participation: Subjects who were previously enrolled in any PT003 or PT010 study conducted or sponsored by Pearl Therapeutics, Inc.

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 on Day 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.

The use of prescription or over-the counter medications within 30 days or five half-lives (whichever is longer) prior to Visit 3 (Day 1) is not permitted.

Acetaminophen will be permitted at doses of ≤2 grams/day as determined to be necessary by the Investigator or medically qualified designee.

With the exception of, contraceptives in female subjects, or need for medication during an emergency 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 (Visit 3) and minor surgical interventions are not allowed within 2 weeks of study drug administration (Visit 3).

5.5.2 Dietary Restrictions

Fasting (at least 8 hours) is required for scheduled complete clinical laboratory testing – chemistry and hematology (including glucose and potassium), at Screening Visit 1, Visit 2 (Day -1) and for 24 hours post-dose sample collection on Day 8.

Fasting is not required for glucose and potassium only blood sample collections on Visit 3 (Day 1) at 30min and at 2 hours post-dose and on Visit 4 (Day 8) at 30min, 2 hours and 12 hours post-dose.

Standardized meals will be administered at specified times after observation of fasting time for blood draws. 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, beverages or medications for at least 6 hours prior to each study visit and for the duration of each study visit. Examples of such products include coffee, tea, chocolate, and cola. Decaffeinated beverages are acceptable.

5.5.3 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 or completes 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 16 in Section 5.2.

5.5.4 Smoking Restrictions

Smoking is prohibited throughout the duration of the study and 3 months prior to screening. Electronic cigarettes and nicotine supplements 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 or medically qualified designee may withdraw a subject at the occurrence of any or all of the following:

- Protocol deviation
- AE
- Subject becomes pregnant
- 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 groups will be blinded. The characteristics of BGF MDI and GFF MDI that will be administered during the study are presented in Table 6—1

An envelope-based randomization system will be used to assign blinded study medication to subjects. The site will receive a large portfolio envelope containing subject randomization envelopes for subjects. Each large portfolio envelope contains a series of subject randomization envelopes, identified by a unique randomization number and organized in sequential order. Only subjects eligible for randomization will be assigned the next-in-sequence randomization envelope. Each envelope will contain a form which provides the blinded component IDs to be assigned to the subject.

For each subject, treatment will comprise of 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. Dosing 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 GFF MDI (14.4/9.6 µg) random assignment to one of three predetermined parallel treatment groups (Refer to Section 6.1). At Screening, Day -1, and before study medication dosing on Day 1 and Day 8 subjects will be instructed on the proper use of an MDI using a bulk-supplied MDI (placebo) and, at that time, must demonstrate the ability to coordinate use of the MDI.

On Day 1 of the 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 delegated staff. 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 and GFF MDI active drug substances are budesonide, glycopyrronium, and formoterol fumarate dihydrate; and glycopyrronium and formoterol fumarate dihydrate, respectively. Investigational materials will be provided by Pearl as summarized in Table 6—1.

Table 6—1. 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/ 120 inhalations	Taken as 2 inhalations BID
BGF MDI 160/14.4/9.6 µg ex-actuator	80/7.2/4.8 µg/actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
GFF MDI 14.4/9.6 µg ex-actuator	7.2/4.8 µg/actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
Placebo			
Placebo MDI[a]	Formulation does not contain active ingredient	MDI 120 inhalations	Subjects will use the placebo MDI for training purpose only to demonstrate proper use of the MDI on Day -1, Day 1 and Day 8 (and on other treatment days as needed per site discretion)

Abbreviations: BID=twice daily; BGF MDI = budesonide, glycopyrrolate, and formoterol fumarate inhalation aerosol; MDI=metered dose inhaler. GFF=Glycopyrronium and Formoterol Fumarate; HFA=hydrofluoroalkane; MDI=metered dose inhaler

[a] Placebo MDI for training purposes. All placebos are created by Pearl with the image of the active test product, with no active moieties.

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.

Following Screening and determination of eligibility, dosing will span a single Treatment Period in one of three treatment groups. The treatment and study visit schedule is illustrated in Table 8—1.

6.4 Study Drug Packaging and Box Labeling Information

Blinded investigational drug will be packaged in individual boxes as outlined in Table 6—2. Box configuration is subject to change as a result of packaging constraints.

Table 6—2. Description of Boxes

Drug Supplies	Individual Box Contents
Blinded	1 MDI

MDI=metered dose inhaler

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

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

ID = identification; # = number

6.5 Emergency Unblinding of Treatment Assignment

The Sponsor will provide emergency unblinding envelopes with the clinical supplies for the purpose of subject treatment unblinding. Emergency unblinding envelopes (bright red in color), which contain the unblinded treatment information associated with each randomization number, are also provided and to be stored in a separate, secure location accessible only by the Site Investigator.

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 Storage Requirements

Blinded Supplies should be kept in a secured location. BGF MDI and GFF MDI should be stored below 25° C (77° F). Excursions permitted up to 30° C (86° F).

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

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

Individual BGF MDI and GFF MDI will be packaged in a foil pouch and contained in an individual visit treatment box. Both the visit treatment box and the foil overwrap will have a label with a component ID number. The visit treatment box is labeled with a 2-part label. Write the subject number and treatment visit number on each of the 2-part labels.

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

The MDI must be primed in a separate room, away from the subject treatment area. Each dose will consist of 2 puffs from the MDI. Subjects will be dispensed the MDI and instructed to continue taking study medication twice daily, 2 puffs in the morning and 2 puffs in the evening approximately 12 hours apart. Refer to Appendix 1 for instructions on administration and cleaning of BGF MDI and GFF MDI.

6.8 Study Drug Accountability/Return of Clinical Supplies

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

Sites should check with the Pearl representative for appropriate documentation that needs to be completed for drug accountability.

The Investigator or designee should not open the individual clinical supply containers until all pre-dose assessments have been completed and the subject is eligible to be randomized/continue with the study. Any deviation from this must be discussed with the Clinical Monitor.

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

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

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

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) that is reviewing the study documents. The ICF 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 Investigator.

7.2 Eligibility of Subjects

Eligibility screening of healthy subjects will be completed within 28 days prior to administration of the first dose of study drug and will be documented on the eCRF. Confirmation of eligibility will be performed at clinic admission Visit 2 (Day -1) and Visit 3 (Day 1) of the Treatment Period. Subjects will remain in the clinic from clinic admission Visit 2 (Day -1, Clinic Admission) until Day 9. Screen failure and the reason for screen-failure will be documented in the study site source documents and captured in the CRF.

7.3 Pharmacokinetic Assessments

Note: Pharmacokinetic sampling will occur in conjunction with the Treatment Period. Sample collections will be scheduled for the nominal time point and actual collection times will be recorded in the source documents (Refer to Table 8—2 and Table 8—3).

7.3.1 Blood Sample Collection Schedule

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

Approximately 6 mL of whole blood will be collected within 60 minutes *prior* to administration of study drug.

POST-Dose Administration Sample Collection –On Day 1 ONLY:

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

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

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

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

Time point	Time windows
2 min	±1 min
6 min	±1 min
20 min	±2 min
40 min	±2 min
1 hr	±2 min
2 hr	±5 min
4 hr	±5 min
8 hr	±10 min
10 hr	±10 min
12 hr	±10 min
24 hr	±10 min

7.3.2 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 [redacted] plasma collection tube) containing ethylenediaminetetraacetic 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.

7.3.3 Procedure for Shipping Samples

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

7.4 Safety Assessments

The study procedures manual includes allowed time windows for safety assessments. Kindly refer to this manual for nominal time window details.

7.4.1 Medical History

Relevant medical history, based on the opinion of the Investigator, will be obtained from the subject at Screening, and recorded on the source document. Medical history will capture the subject's family health history, history of hospitalization, and history of surgeries.

7.4.2 Physical Examination

A complete physical examination including height and weight will be performed at the time of Screening and on the day of clinic admission Visit 2 (Day -1) and Visit 4 (Day 8). The findings 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
- Abdominal
- Neurologic
- Extremities
- Dermatologic
- Lymph nodes

7.4.3 Vital Signs

Vital sign determinations, including BP, PR, 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 clinic admission Visit 2 (Day -1), Day 2 through Day 7, and on Visit 3 (Day 1) and Visit 4 (Day 8) within 2 hours prior to administration of study drug and 30 minutes, 2 hours, 4hours, 12 hours, and 24 hours post administration of study drug (Refer to study procedures manual, Table 8—1, Table 8—2 and Table 8—3).

7.4.4 12-Lead Electrocardiogram

Twelve-lead ECGs will be recorded at Screening and on the day of the clinic admission Visit 2 (Day -1) (baseline represents pre-dose on Day 1). Twelve-lead ECGs will be obtained :

- pre-dose within 2 hours prior to dosing on Visit 3 (Day 1),
- within 1 hour prior to dosing on Visit 4 (Day 8)
- at 30 minutes and 2, 12, and 24 hours post-dosing Day 1 and Day 8

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 after the first dosing through the treatment period until follow-up telephone will be reported as TEAEs and followed closely by the Investigator in order to assure the safety of the study subject.

7.4.5 Clinical Laboratory Tests

Note: Subjects must be **fasting for at least 8 hours prior** to any scheduled complete clinical laboratory assessment blood draw (chemistry and hematology –including glucose and potassium). Fasting is not required for clinical laboratory assessments of glucose and potassium only at Visit 3 (Day 1) and Visit 4 (Day 8).

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—3 will be collected at Screening, on the day of clinic admission Visit 2 (Day -1) and Visit 4 (Day 9 sample). Fasting is required as shown in Table 8—1, Table 8—2, and Table 8—3.

At 30 minutes and 2 hours *post*-administration of study drug on Visit 3 (Day 1) blood samples will be drawn for assessments for glucose and potassium. Fasting is not required. (Refer to study procedures manual, Table 8—2).

At pre-dose (within 60 minutes) and 30 minutes, 2 hours and 12 hours *post*-administration of study drug on Visit 4 (Day 8) blood samples will be drawn for assessments for glucose and potassium. Fasting is not required. (Refer to Table 8—3).

Standardized meals will be administered at specified times after observing fasting times for blood draws.

There are no restrictions regarding clear fluid intake.

Table 7—3 Laboratory Tests

Hematology	Chemistry	
Hematocrit [a] Hemoglobin Serum Iron Ferritin Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential Mean corpuscular volume (MCV) Mean cell hemoglobin (MCH) MCH concentration (MCHC)	Creatinine [b] Potassium (K+) [c] Sodium (Na+) Chloride (Cl-) Magnesium (Mg++) Calcium Inorganic phosphate Glucose [c] Urea Bilirubin (Total) Blood Urea Nitrogen (BUN)	Bilirubin (direct) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Gamma-glutamyltransferase (GGT) Alkaline phosphatase Total Protein Albumin
Urinalysis: Macroscopic examination routinely including specific gravity, pH, protein, glucose, ketones, blood, and urobilinogen. A microscopic examination will be performed 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, syphilis, 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 females of non-childbearing potential: A serum hCG test at Screening and urine hCG test at admission. In addition, a serum FSH test (status confirmation in post-menopausal women) for confirmation of non-childbearing status will be performed at Screening only.		

Abbreviations: 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] eGFR will be calculated by the Modification of Diet in Renal Disease (MDRD) equation following : http://www.columbiamedicine.org/divisions/gharavi/calc_egfr.php

C-MDRD (modified for Chinese) equation:

$eGFR = 175 \times (\text{Serum Creatinine})^{-1.234} \times (\text{Age})^{-0.179} \times (0.79 \text{ if Female})$

[c] Additionally, within 60 minutes prior to dosing and at 30 minutes, 2 hours, and 12 hours (Visit 4 only) post-dose of Treatment..

7.4.5.1 Laboratory Sample Collection, Storage and Shipping

Detailed instructions for laboratory sample collection, processing, and shipping instructions will be provided in the laboratory manual for PK testing and other standard testing set-up will be used for local testing.

Approximately 194 mL of blood will be collected per subject during the study as follows. The exact blood volume is based on local laboratory requirements and may change slightly as local laboratory procedure changes:

- HCG+FSH: 1sample each as appropriate at 2mls =2mls
- Serology: 1 sample at 5ml and 1 sample at 4ml=9ml
- Chemistry: 3 samples at 6mls each=18mls
- Hematology:3 samples at 1mls each =3mls
- Serial glucose and potassium: 6 samples at 3mls each=18mls
- Serial PK: 24 samples at 6ml each=144mls

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 laboratory manual.

7.5 Adverse Events

7.5.1 Performing Adverse Events Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's eCRF. If the AE is unexpected the Investigator must report the AE immediately to Pearl Therapeutics. In addition, certain AEs (as described in Section 7.5.8) 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.

7.5.2 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 (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Adverse events include, but are not limited to:

- Any symptom or condition not previously reported by the subject (medical history).
- An exacerbation of a pre-existing symptom or condition.
- A significant increase in frequency or intensity of a pre-existing episodic event or condition.
- A drug interaction.
- A condition first detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, blood transfusion) are not considered AEs and the condition that results in the procedure is considered an AE (e.g., 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).

7.5.3 Pre-Randomization Adverse Events

Adverse events that occur between the time subject signs the ICF for the study and the time when that subject receives first dose of study drug will be summarized as medical history and not as an AE unless the event meets the definition of an SAE as defined in Section 7.5.8.

7.5.4 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.

7.5.5 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.

7.5.6 Relationship

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

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

7.5.7 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 (e.g., 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 (e.g., 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 (e.g., an abnormality that results in study drug dose reduction, suspension, or discontinuation)

- A laboratory abnormality that results in any therapeutic intervention (e.g., concomitant medication or therapy)
- Other laboratory abnormality judged by the Investigator to be of any particular clinical concern (e.g., significant fall in hemoglobin not requiring transfusion)

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

7.5.8 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).

7.5.8.1 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 Pharmacovigilance or designee. All SAEs must be reported to Pearl Pharmacovigilance no later than 24 hours after the Investigator recognizes/classifies the event as a SAE. All SAEs should be documented and reported using the eCRF. At a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report using the appropriate form (eg, SAE Report Form in the eCRF). After the initial report, as necessary, the Investigator must provide any additional information regarding the SAE to the Pearl Pharmacovigilance or designee within two working days after receiving the information. Follow-up information will be a detailed written report that may include copies of hospital records, case reports, and autopsy reports, and other pertinent documents. Additionally the Investigator will notify the ethics committee, the CFDA, and Shanghai FDA as per reporting requirements.

Post-study SAEs following the last dose of study drug must be reported to Pearl Therapeutics as described in Section 7.5.8.4.

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

7.5.8.2 Supplemental Investigations of SAEs

The Investigator and supporting personnel responsible for subject care should discuss with the Pearl Pharmacovigilance or designee 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.

7.5.8.3 Post-Study Follow-Up of Adverse Events

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

7.5.8.4 Notification of Post-Study Serious Adverse Events

Investigators are not obligated to actively follow subjects after the completion of the study. However, if the Investigation becomes aware of a post-study SAEs occurring up to 14 days following the last dose of study drug administration must be reported to Pearl Therapeutics, whether or not the event is attributable to the 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.

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

The Investigator is responsible for promptly notifying her/his IRB/IEC of all SAEs, including any follow-up information, occurring at her/his site and any SAE regulatory report, including any follow-up reports 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.

7.5.8.6 Health Authority Safety Reports

Pearl Therapeutics or its representatives will submit a safety report to the China Food and Drug Administration (CFDA) 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 CFDA 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.

7.5.9 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.

7.5.10 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.

7.6 Termination of the Study

An Investigator may choose to discontinue study participation at any time with sufficient notice by the Investigator for any reason as per the terms of the contract 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 schedule of events is provided in Table 8—1. Detailed schedules of inpatient assessments on Visit 3 (Day 1) and Visit 4 (Day 8) are provided in Table 8—2 and Table 8—3, respectively.

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

Procedure	Screening		Inpatient Treatment			Follow up
	Visit 1	Visit 2 Clinic Admission	Visit 3	Assessments	Visit 4	Telephone Follow up
Study Day	**-28 to -2**	**-1**	**1**	**2 to 7**	**8**	**5 to7 days post last dose**
Informed Consent	X					
Medical History	X	X				
Demographics	X					
Physical Examination	X	X			X	
Vital Signs (BP, Temperature, PR, Respiratory Rate)	X	X	X	X	X	
Eligibility Review	X[a]	X[a]	X	X[b]	X[b]	
Placebo MDI Usage Demonstration/Practice [c]	X[d]	X	X	X[d]	X	
12-lead ECG	X	X	X		X	
Clinical Laboratory Testing[e]	X	X	X		X	
Adverse Events	X[f]	X[f]	X	X	X	X
Concomitant Medications	X	X	X	X	X	X
Urine Drug Screen	X	X				
Alcohol Breathalyzer	X	X				
Pregnancy Test (women only)[g]	X[h]	X				
Serology: (HIV, HBsAg, HepC, Syphilis Ab)	X					
PK Assessment			X		X	
Obtain randomization number			X			
Dispense randomized study MDI			X			
Study Drug Administration[i]			X[j]	X[j]	X[j]	
Inpatient Admission		X				
Inpatient Discharge					X[k]	

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

[a] Chest x-ray and abdominal ultrasound to be completed during screening or on Day -1 to determine eligibility

[b] Review if subject can continue

[c] Inhalation monitoring tools may be utilized to ensure appropriate training of subjects for the correct use of their inhaler

[d] Subjects will use the placebo MDI for training purpose only to demonstrate proper use of the MDI on other treatment days as needed per site discretion.

[e] For GFR exclusion criteria refer to calculation in Section7.4.5 Complete clinical laboratory testing - chemistry and hematology (includes glucose and potassium) for Visit 1, Visit 2 (Day -1), and Visit 4 (i.e., on Day 9 which is 24 hours post-dose on Day 8). Glucose and potassium only at Visit 3 and Visit 4 (Day 8).

[f] Only SAEs will be recorded prior to first dose.as defined in Section 7.5.8. All AEs prior to first dose will be recorded as Medical History

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

[h] Follicle-stimulating hormone (FSH for post-menopausal) test for women of non-childbearing potential at Screening only.

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

[j] See the Schedule of Inpatient Period Assessments; Table 8-2, and 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 the Treatment Period. 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.

[k] Discharge will occur on the morning of Day 9 due to 24-hour PK sample collection and other assessments (Table 8-3)

Table 8—2 Schedule of Assessments on Day 1 of Inpatient Treatment (Visit 3)

Procedure	Time Relative to Drug Administration													
	Pre-dose	0 hr	2 min	6 min	20 min	30 min	40 min	1 hr	2 hrs	4 hrs	8 hrs	10 hrs	12 hrs	24 hrs
PK Blood Draw	X[a]		X	X	X		X	X	X	X	X	X	X	X
Placebo MDI Usage Demonstration/Practice	X	X												
Administration of Study Medication [b]		X												
12-lead Safety ECG	X[c]					X			X				X	X
Clinical Laboratory Tests						X[d]			X[d]					
Vital Signs	X[e]					X			X	X			X	X
Adverse Events		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

Abbreviations: ECG=electrocardiogram; PK=pharmacokinetic

[a] PK Blood draw will be taken within 60 minutes prior to dosing

[b] All study drugs will be administered by oral inhalation. A single dose of study drug will be administered on Day 1.

[c] Twelve-lead safety ECGs will be recorded within 120 minutes prior to dosing, and as scheduled above.

[d] Glucose and potassium only- fasting not required

[e] Vital signs will be recorded within 120 minutes prior to dosing and as scheduled above

Table 8—3. Schedule of Assessments on Day 8 of Inpatient Treatment (Visit 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	24 hrs
PK Blood Draw	X[a]		X	X	X		X	X	X	X	X	X	X	X
Placebo MDI Usage Demonstration/Practice	X	X												
Administration of Study Medication [b]		X												
12-lead Safety ECG [c]	X[a]					X			X				X	X
Clinical Laboratory Tests	X[a,e]					X[e]			X[e]				X[e]	X[d]
Vital Signs	X[a]					X			X	X			X	X
Physical Examination														X
Adverse Events		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

Abbreviations: ECG=electrocardiogram; PK=pharmacokinetic

[a] Within 60 minutes prior to dosing

[b] All study drugs will be administered by oral inhalation. A final single-dose administration of study drug will occur on the morning of Day 8.

[c] Twelve-lead safety ECGs will be recorded within 60 minutes prior to dosing, and as scheduled above.

[d] Complete clinical laboratory testing - chemistry and hematology (includes glucose and potassium) fasting required.

[e] Glucose and potassium only– fasting not required.

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

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
- Placebo MDI usage demonstration and practice as needed
- 12-lead ECG
- Clinical laboratory evaluations (including urinalysis)
- Document concomitant medications
- Urine drug testing
- Alcohol breathalyzer test
- Serum pregnancy test (women only; for all women of childbearing potential and non-childbearing potential)
- Chest x-ray and abdominal ultrasound (or conduct at Day -1) if needed (per exclusion criteria 13 and 14 respectively).
- Follicle-stimulating hormone test for women of non-childbearing potential
- Serology (HIV, HBsAg, and hepatitis C, Syphilis Ab)
- Review of eligibility criteria
- 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 7.5.8)

8.2 Visit 2 (Admission to Clinic, Day -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
- Chest x-ray and abdominal ultrasound if not conducted at screening and can’t remitted and if needed (per exclusion criteria 13 and 14 respectively).
- Review of eligibility criteria including chest x-ray and abdominal ultrasound results

- 12-lead ECG
- Collect blood samples for clinical laboratory testing chemistry and hematology (including glucose and potassium) (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)
- Admission to clinic
- Placebo MDI usage demonstration and practice

8.3 Visit 3 (Day 1 of Treatment)

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

- Pre- (within 120 minutes) and post-dose (30 minutes, and 2, 4, 12, and 24 hours) vital signs per Table 8—2.
- Review of eligibility criteria
- Placebo MDI usage demonstration and practice
- Perform 12-lead ECG (within 120 minutes pre-dose and 30 minutes, and 2, 12, and 24 hours post-dose) per Table 8—2
- Collect blood samples for glucose and potassium clinical laboratory testing at 30 minutes and 2 hours post-dose 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 7.5.8)
- Documentation of concomitant medications
- Collect pre- (within 60 minutes) and post-dose (at 2, 6, 20, and 40 minutes, and at Hour(s) 1, 2, 4, 8, 10, 12, and 24) PK samples per Table 8—2
- Obtain randomization number if eligibility is met
- Randomization and treatment assignment
- 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.

Subjects will remain in the clinic until completion of study treatment.

8.4 Days 2–7 of Treatment

- Vital signs
- Documentation of AEs
- Documentation of Concomitant medications
- Placebo MDI usage demonstration and practice (if needed)
- Review if subject can continue administration of study drug; every morning and evening by oral inhalation approximately 12 hours apart (Refer to Appendix 1 for details regarding study drug administration).
  - **Note:** Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination

8.5 Visit 4 (Day 8 of Treatment)

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

- Pre- (within 60 minutes) and post-dose (30 minutes, and 2, 4, 12 and 24 hours) vital signs per Table 8—3
- Physical examination
- Review if subject can continue
- Placebo MDI usage demonstration and practice
- Perform 12-lead ECG (within 60 minutes pre-dose and 30 minutes, 2, 12, and 24 hours post-dose) per Table 8—3
- Collect blood samples for Glucose and Potassium samples only (within 60minutes pre-dose, 30 minutes and 2 hours post-dose and 12 hours post dose) Table 8—3
- Collect blood samples for clinical laboratory testing chemistry and hematology (including glucose and potassium) including urinalysis 24 hours post dose (Day 9).
- Documentation of AEs
- Documentation of concomitant medications
- Collect pre- (within 60 minutes) and post-dose (at 2, 6, 20, and 40 minutes, and at Hour(s) 1, 2, 4, 8, 10, 12, and 24) PK samples per Table 8—2
- 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.

After all scheduled protocol specified assessments are complete, and safety data has been reviewed by the Investigator, the subject will be discharged from the clinic.

8.6 Follow-Up Telephone Call

Upon completion of the treatment, a follow-up phone call will be completed at least 5 days but no longer than 7 days from the date of last administration on Visit 4 (Day 8). Subjects will be asked about any new or outstanding AEs, and any new concomitant medication. This will be documented appropriately in the subject source documents and eCRFs.

- Documentation of AEs
- Documentation of concomitant medications

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:

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

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 month/year 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 will include C_{max}, t_{max}, $t_{½}$, AUC_{0-12}, AUC_{0-t}, $AUC_{0\infty}$, CL/F, Vd/F, λ_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. Descriptive statistics and graphs will be used to describe the plasma concentrations and PK parameters for budesonide, glycopyrronium, and formoterol as applicable for each treatment group. All PK parameters will be presented by visit [Visit 3 (Day 1) or Visit 4 (Day 8)] for each treatment with number of measurements, number of subjects with non-missing data (n), mean, standard deviation, coefficient of variation (CV%), median, minimum, maximum, geometric mean, and geometric CV % . For t_{max} the geometric mean and the CV % will be omitted, and only the number of observations (n), median, minimum and

maximum will be provided. The plasma concentration data at each time point and visit will be summarized for each treatment group, and listed by subject.

9.5 Safety Analyses

Safety data will be summarized by treatment and listed. The safety of BGF MDI will be assessed from AE reporting including SAE reporting, vital signs (BP, PR, 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 Randomization

Following determination of study eligibility, subjects will be randomized in a 1:1:1 ratio to one of the 3 treatment groups: BGF 320/14.4/9.6 µg, BGF 160/14.4/9.6 µg, or GFF MDI 14.4/9.6 µg.

9.7 Determination of Sample Size

Previous studies with BGF MDI suggest that the inter-subject variability of glycopyrronium after single-dose administration may be as high as [redacted]

9.8 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), Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects), and regulatory requirement if applicable.'

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 (e.g., advertisements or information that supports or supplements the ICF) are reviewed and approved by the appropriate IRB/IEC.
The Investigator agrees to allow the IRB/IEC direct access to all relevant documents.
The IRB/IEC must be constituted in accordance with all applicable regulatory requirements.

Pearl 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. The subject will be provided with two original ICFs. One original will be retained by the study Investigator and the subject will retain the second original.

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, rules and regulations.

10.6 Quality Control and Assurance

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

10.11 Investigator's Final Report

Shortly after completion of the Investigator's participation in the study, the Investigator will submit an end of study summary report to Pearl Therapeutics.

10.12 Publication Policy

The study site will have the opportunity to publish the results of the study, provided that “THE SPONSOR” has had the opportunity to review and comment on the study site’s proposed publication prior to its being submitted for publication with the prior advice of “LEGAL” (intellectual property council) and with proper regard to the protection of subjects’ identities.

11 REFERENCE LIST

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12 APPENDICES

Appendix 1 Administration of Study Drug

All subjects will receive one treatment by random assignment to one of three predetermined parallel treatment groups as listed in Section 6.2 of this protocol. This is a double-blind study. The Pearl products (BGF MDI and GFF MDI) are identical in form and function and indistinguishable from each other.

Subjects will use the placebo MDI for training purpose only to demonstrate proper use of the MDI by two oral inhalations on Day -1, Day 1 and Day 8 (and on other treatment days as needed) using a bulk-supplied Placebo MDI (with an inhalation monitor if needed).

BGF MDI and GFF MDI Administration: For specific guidance for the Handling and Instructions for Use of BGF MDI and GFF MDI, please refer to the Investigator Brochure (IB). For each BGF MDI and GFF MDI administration the MDIs must be primed before the first use. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that the inhaler is ready to use. Priming involves releasing 4 sprays into the air before the first use of the inhaler.. 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. Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination. 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
- GFF MDI 14.4/9.6 µg

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
GFF MDI 14.4/9.6 µg ex-actuator	7.2/4.8 µg /actuation	MDI	Taken as 2 inhalations

Abbreviations: BGF MDI=budesonide, glycopyrronium, and formoterol fumarate inhalation aerosol; MDI=metered dose inhaler. GFF=Glycopyrronium and Formoterol Fumarate; HFA=hydrofluoroalkane; 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.

SUBJECT INSTRUCTIONS FOR USE OF BGF MDI, AND GFF MDI

How do I store the Inhaler?

The inhaler should be stored below 25°C (77°F). Excursions permitted up to 30°C (86°F).

The contents of the canister are under pressure. Do not puncture or throw the canister into a fire or incinerator. Do not use or store it near heat or open flame. Storage above 48.8 °C (120ºF) may cause the canister to burst.

Keep the product and all medicines out of the reach of children.

For Oral Inhalation Only

Parts of the Inhaler:

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

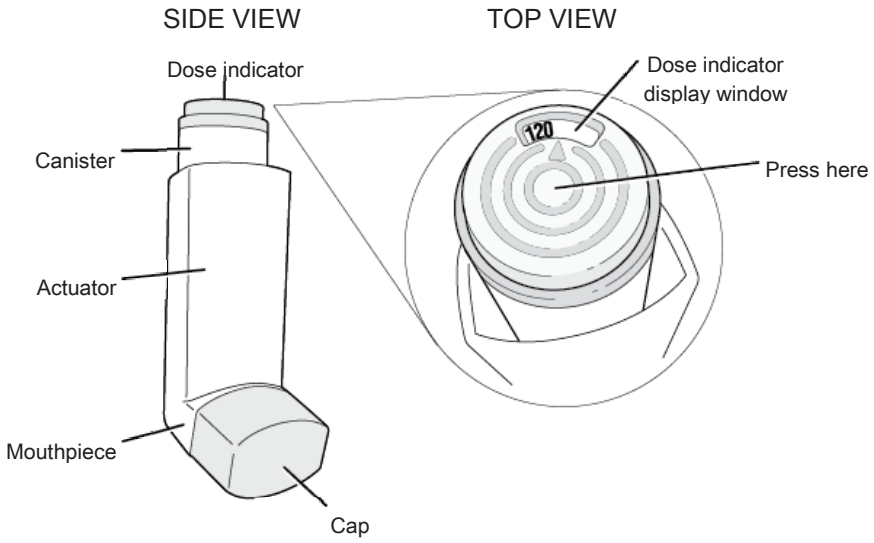


Figure 1

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

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

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

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

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

Figure 2a
120 puffs

Figure 2b
110 puffs

Figure 2c
100 puffs

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

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

Figure 2d

Preparing the Inhaler for Use:

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

Take the inhaler out of the foil pouch.

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

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

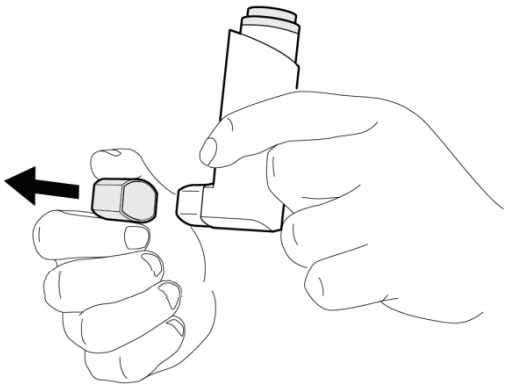


Figure 3

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

Priming the Inhaler:

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

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

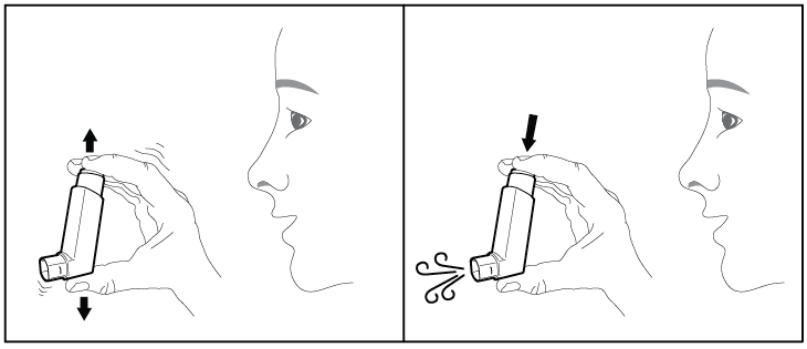
Shake the inhaler well before each puff.

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

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

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

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



Using the Inhaler:

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

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

- **Step 1** Remove the **Cap** from the **Mouthpiece**.

- **Step 2** Shake the inhaler well before each puff.
- **Step 3**: While holding the inhaler with the **Mouthpiece** pointing towards you breathe out through your mouth to empty as much air from your lungs as possible.
- **Step 4**: Close your lips around the **Mouthpiece** and tilt your head back slightly to make sure your tongue is away from the **Mouthpiece**.
- **Step 5**: Take a deep breath in (inhale) slowly through your mouth while pressing down firmly on the center (not 'off center') of the **Dose indicator** until the **Canister** stops moving in the **Actuator** and a puff has been released. Then, stop pressing the **Dose indicator**.
- **Step 6**: When you have finished breathing in, remove the **Mouthpiece** from your mouth and hold your breath for 10 seconds or as long as comfortable.
- **Step 7**: Then, breathe out normally. Take your second puff of medicine by repeating Step 2 through Step 7.
- **Step 8:** Replace the **Cap** back on the **Mouthpiece.**

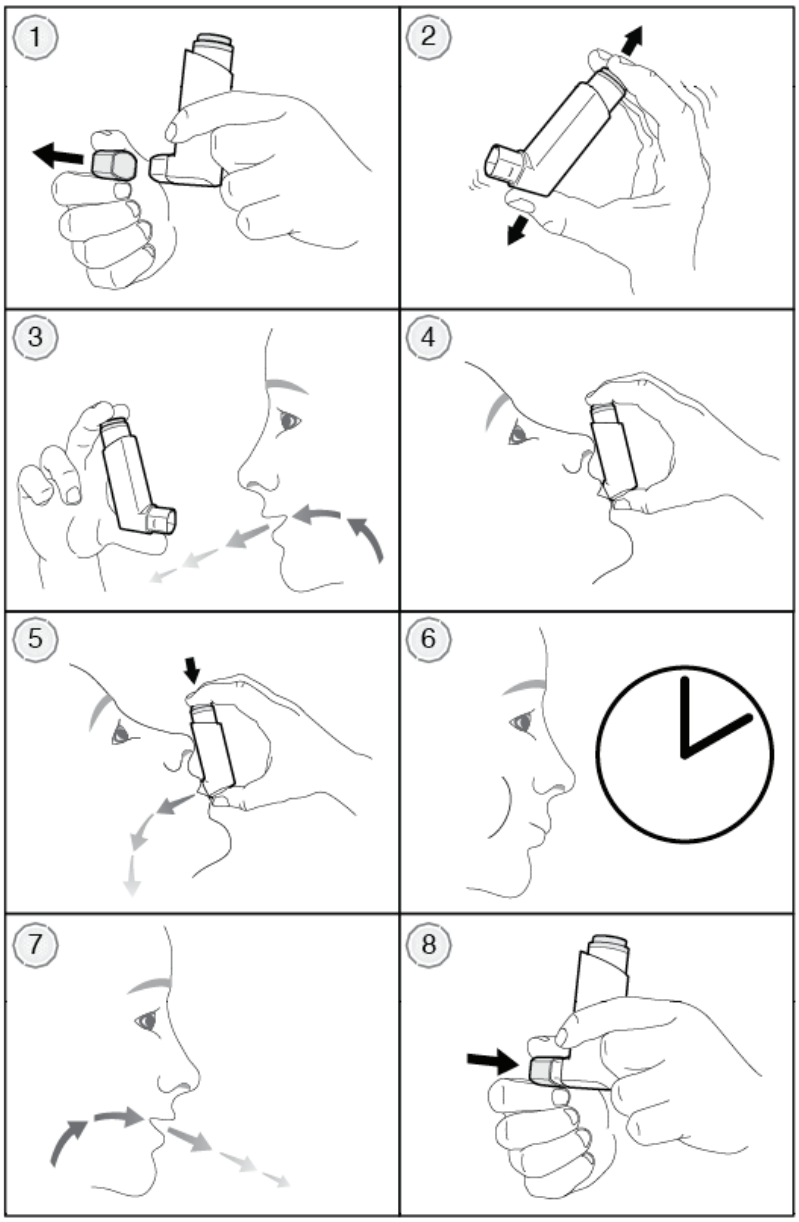


Figure 5

1. **How to clean the Inhaler**:

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

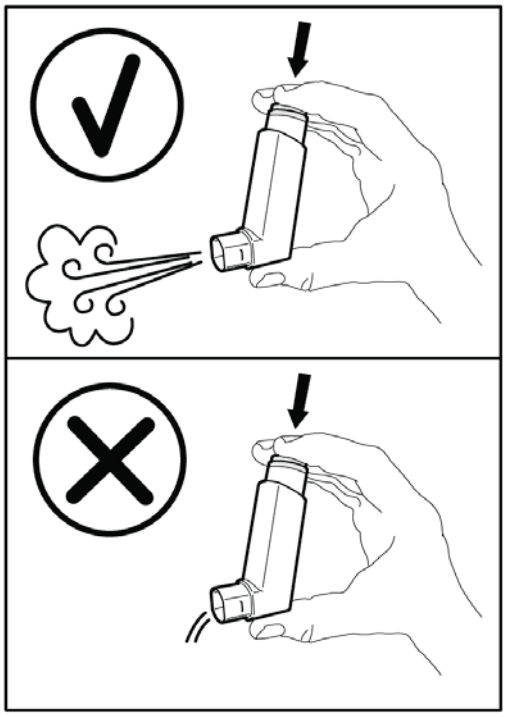
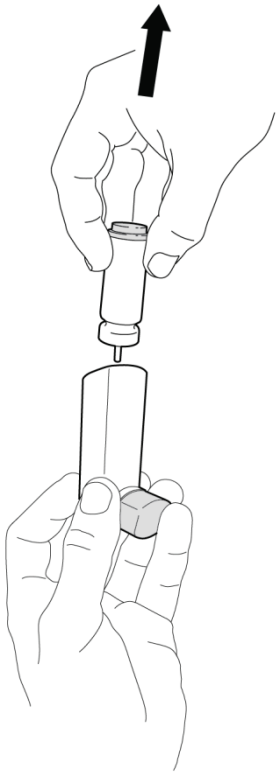


Figure 6

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

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

Figure 7



Step 2: Set the **Canister** aside where it will not get wet.

Step 3: Take the **Cap** off the **Mouthpiece.**

Step 4: Rinse the **Actuator** through the top with warm running water for 30 seconds. Then rinse the actuator again through the Mouthpiece (**see Figure 8**).

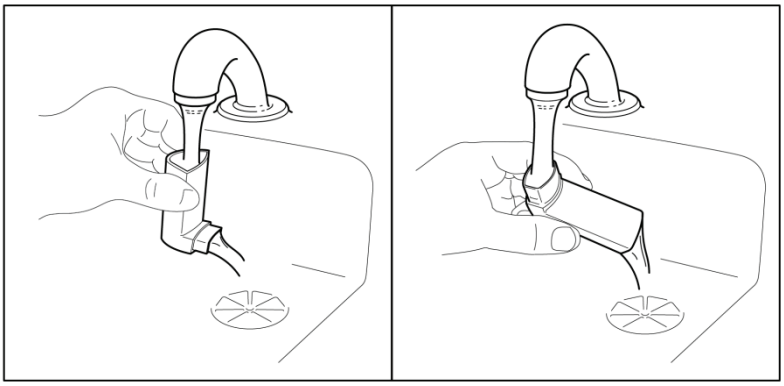


Figure 8

Step 5: Shake all of the water droplets out of the **Actuator**.

Step 6: Look in the **Actuator** and the **Mouthpiece** to make sure it is clean and clear**.**

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

Step 7: Let the **Actuator** dry completely, such as overnight as shown in **Figure 9**.

Do Not put the **Canister** back into the **Actuator** if it is still wet.

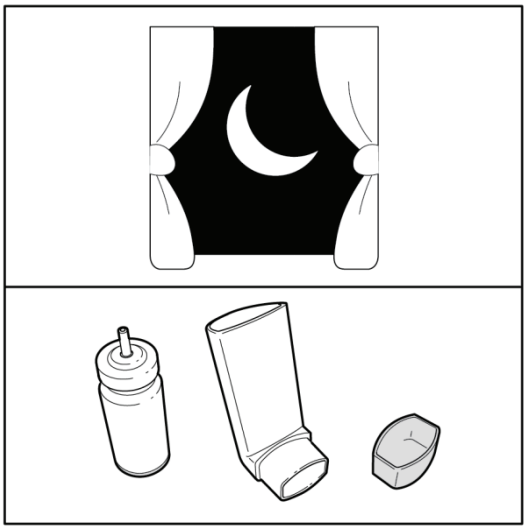


Figure 9

Reassembly of the Inhaler and Instructions for Use after Cleaning:

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

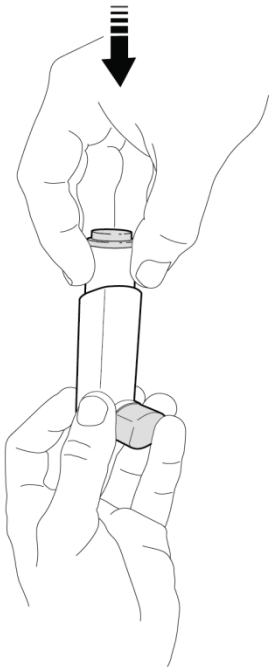


Figure 10

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

Appendix 2 Sponsor Signatory

Study Title: A Phase I, Randomized, Double-Blind Study Parallel-Group, to Assess the Pharmacokinetics and Safety of Two Doses of PT010 and a Single Dose of PT003 in Healthy Chinese Adult Subjects Following A Single Administration and After Chronic Administration for 7 Days

Study Number: PT010010-03

Final Date: 12 May 2017

Signature: [redacted] Date: [redacted]

Name: [redacted]

Title: [redacted] Pearl Therapeutics, Inc.

Appendix 3 Investigator's Signature

Study Title: A Phase I, Randomized, Double-Blind Study Parallel-Group, to Assess the Pharmacokinetics and Safety of Two Doses of PT010 and a Single Dose of PT003 in Healthy Chinese Adult Subjects Following A Single Administration and After Chronic Administration for 7 Days

Study Number: PT010010-03

Final Date: 12 May 2017

I agree:

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

Signature:_____ Date:_____

Name: _____ Affiliation: _____