12.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

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

- Original Protocol – [redacted]
- Amendment #1 – [redacted]

CLINICAL TRIAL PROTOCOL: PT010001-00

Study Title: A Phase I, Randomized, Double-Blind Within Device, Single-Dose, Four-Period, Six-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Three Doses of Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (BGF MDI), One Dose of Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI), and Two Doses of Symbicort® Inhalation Aerosol in Healthy Volunteers

Study Number: PT010001-00

Study Phase: Phase I

Product Name: Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (BGF MDI; PT010)

IND Number: 118313

Investigators: Single Center

Sponsor: [redacted]

Sponsor Contact: [redacted]

	Version Number	Date
Original Protocol:	Version 1.0	[redacted]

Confidentiality Statement

Property of Pearl Therapeutics Inc.

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

SYNOPSIS

Sponsor:

Pearl Therapeutics, Inc.

[redacted]

Name of Finished Product:

- Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (Budesonide, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler; BGF MDI; PT010)
- Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler; GFF MDI; PT003)
- Budesonide and Formoterol Fumarate Dihydrate Inhalation Aerosol (Symbicort® MDI)

Name of Active Ingredients:

- Budesonide
- Glycopyrronium
- Formoterol fumarate dihydrate

Study Title:

A Phase I, Randomized, Double-Blind Within Device, Single-Dose, Four-Period, Six-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Three Doses of Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (BGF MDI), One Dose of Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (GFF MDI), and Two Doses of Symbicort® Inhalation Aerosol in Healthy Volunteers

Study Number:

PT010001-00

Study Phase: Phase I

Primary Objective(s):

The primary objective of the study is to determine a dose of budesonide that when formulated with glycopyrronium and formoterol fumarate in BGF MDI provides comparable systemic exposure [pharmacokinetics (PK)] to budesonide following administration of Symbicort MDI 320/9 µg (2 inhalations of 160/4.5 µg).

Secondary Objective(s):

The secondary objectives of the study are:

- To assess if a drug-drug interaction (DDI) occurs when budesonide is formulated with glycopyrronium and formoterol fumarate in BGF MDI compared to GFF MDI alone.
- To evaluate the safety and tolerability of the treatments administered; i.e., BGF MDI, Symbicort MDI and GFF MDI.

Study Design:

This is a healthy volunteer Phase I study with a randomized, double-blind within device, four-period, six- treatment, cross-over design. All study drugs will be administered by oral inhalation. The six treatments are:

- BGF MDI 320/14.4/9.6 µg
- BGF MDI 160/14.4/9.6 µg
- BGF MDI 80/14.4/9.6 µg
- GFF MDI 14.4/9.6 µg
- Symbicort MDI 320/9 µg
- Symbicort MDI 160/9 µg

Following determination of study eligibility, subjects will be randomized to one of 12 treatment sequences. Each treatment sequence will contain BGF MDI 320/14.4/9.6 µg, GFF MDI 14.4/9.6 µg, and Symbicort MDI 320/9 µg, and one of the remaining three treatments. At the target of 84 subjects randomized, each sequence will be used 7 times. If all subjects complete the study, the design is balanced for both period and first-order carryover effects. Treatments will be blinded within the two devices.

Study Population:

Eighty-four healthy male and female subjects are planned for enrollment in the study. Full inclusion and exclusion criteria are listed in Section 5.1 and Section 5.2, respectively.

Test Product; Dose; and Mode of Administration:

All dosing of the study drug will be by oral inhalation. The three doses of BGF MDI (320/14.4/9.6 µg, 160/14.4/9.6 µg and 80/14.4/9.6 µg), two doses of Symbicort MDI (320/9 µg and 160/9 µg), and a single dose of GFF MDI (14.4/9.6 µg) will be administered on separate test days. There are two different MDI devices used within the study. The Pearl products (BGF MDI and GFF MDI) are identical in form and function and are indistinguishable from each other. The two Symbicort MDIs are identical in form and function and are indistinguishable from each other. However, they are different from the Pearl Therapeutics products. As such, the test products will be double-blind within device. The characteristics of the three BGF MDI doses, the two Symbicort MDI doses and the GFF MDI dose that will be administered during the study are provided below:

Product Name & Potency	Product Strength	Dosage Form	Comments
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
BGF MDI 80/14.4/9.6 µg ex-actuator	40/7.2/4.8 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
Symbicort MDI 320/9 µg ex-actuator	160/4.5 µg/actuation	MDI	Taken as 2 inhalations
Symbicort MDI 160/9 µg ex-actuator	80/4.5µg/actuation	MDI	Taken as 2 inhalations

BGF MDI = Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol; GFF MDI = Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; MDI = Metered Dose Inhaler.
Note: All study drugs will be administered by oral inhalation.

Reference Therapy, Dose, and Mode of Administration:
The reference therapies are two dose levels of Symbicort MDI (320/9 µg and 160/9 µg) and a single dose level of GFF MDI (14.4/9.6 µg). All reference therapies will be administered by oral inhalation.

Duration of Treatment:
This study will include a screening period of up to 21 days and four single-dose treatment periods separated by a minimum washout period of 3 days to a maximum of 14 days for added scheduling flexibility. The planned participation in the study is between 34 and 67 days.

Pharmacokinetic Assessments: The pharmacokinetics (PK) of BGF MDI, Symbicort MDI and GFF MDI will be assessed and compared from plasma concentrations of each drug. Time points for PK blood sample collection during each of the four single-dose periods will be at 30 minutes prior to dosing and then at 2, 6, 20, and 40 minutes post dose and 1, 2, 4, 8, 10 and 12 hours post dose (see Table 5 for the Schedule of Inpatient Period Assessments). PK parameters at all doses will include C_{max}, t_{max}, $t_{½}$, AUC_{0-12}, $AUC_{0-t,}$ CL/F, Vd/F, and λ_z. Other PK parameters may be calculated, as appropriate.

Safety Assessments: The safety of BGF MDI, Symbicort MDI and GFF MDI will be assessed from physical examination findings, adverse event (AE) reporting including SAE reporting, vital signs (blood pressure, heart rate, respiratory rate and body temperature), clinical laboratory values (hematology, biochemistry, and urinalysis), and findings from 12-lead safety electrocardiograms (ECGs).

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

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

The primary endpoints are the AUC_{0-12} and C_{max} of budesonide for doses of BGF MDI compared to Symbicort MDI with most interest being in the comparison of the highest strengths. These PK parameters will be compared between relevant treatments after dose normalization and log transformation using mixed models repeated measures with adjustment for period and sequence, subject as a random effect, and modeling of within subject correlation. Estimated geometric mean ratios (GMRs) with 90% confidence intervals (CIs) will be produced and compared to bounds of 80% and 125%. The AUC_{0-12} and C_{max} of formoterol fumarate and glycopyrrolate exposure will also be compared between treatments to evaluate the potential for drug-drug interactions (DDIs).

The sample size of 84 randomized subjects provides over 90% power to demonstrate bioequivalence of budesonide AUC_{0-12} and C_{max} for the comparison of BGF MDI 320/14.4/9.6 µg to Symbicort MDI 320/9 µg under assumptions of a 5% true difference and intra-subject coefficient of variation (CV) values of 25% and 30% for AUC_{0-12} and C_{max}, respectively.

Date of Original Protocol: Version 1.0, [redacted]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
AV	Atrioventricular
BGF MDI	Budesonide, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler
BMI	Body mass index
$CaCl_2$	Calcium chloride
CBC	Complete blood cell (count)
CFR	Code of Federal Regulations
CI	Confidence interval
CKD EPI	Chronic Kidney Disease Epidemiology Collaboration Equation
COPD	Chronic obstructive pulmonary disease
CRO	Contract Research Organization
CV	Coefficient of variation
DDI	Drug-drug interaction
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision
DSPC	Distearoylphosphatidylcholine
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GFF MDI	Glycopyrronium and formoterol fumarate metered dose inhaler
GGT	Gamma-glutamyltransferase
GMR	Geometric mean ratio

GOLD	Global Initiative for Chronic Obstructive Lung Disease
HbsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HFA	Hydrofluoroalkane
HPLC/MS/MS	High Performance Liquid Chromatography Mass Spectrometry
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intra-uterine device
LABA	Long-acting β2-agonist
LAMA	Long-acting muscarinic antagonist
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
MDI	Metered dose inhaler
PCV	Packed cell volume
PK	Pharmacokinetics
RBC	Red blood cell (count)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard operating procedure
THC	Tetrahydrocannabinol
TURP	Trans-urethral resection of prostate
US	United States
WBC	White blood cell (count)

TRADEMARK INFORMATION

Trademarks not owned by Pearl Therapeutics, Inc.:

Aerolizer

Aqua

Breezhaler

Cuvposa

Foradil

Oxis

Pulmicort

Rhinocort

Robinul

Seebri

Symbicort

Turbuhaler

Respules

1 INTRODUCTION

Pearl Therapeutics is developing budesonide, glycopyrronium, and formoterol fumarate (BGF) metered dose inhaler (MDI) as a long-term twice daily (BID) morning and evening maintenance treatment for the reduction in the frequency of exacerbations and improvement in airflow obstruction in patients with moderate to very severe chronic obstructive pulmonary disease (COPD) who are at risk of COPD exacerbations. The Pearl Therapeutics internal product code for BGF MDI is PT010.

Pearl Therapeutics has not conducted any nonclinical or clinical studies with the triple combination product. However, budesonide, glycopyrronium, and formoterol fumarate are components (alone or in combination) of approved inhalation products for treatment of patients with COPD and their safety and efficacy are well characterized. Clinical and nonclinical studies conducted with the Pearl Therapeutics dual combination product, glycopyrronium and formoterol fumarate (GFF) MDI and its individual components, glycopyrronium (GP) MDI and formoterol fumarate (FF) MDI and clinical and nonclinical studies conducted with Symbicort® MDI support the evaluation of BGF MDI in this initial Phase I study in healthy volunteers (Study PT010001). GFF MDI, GP MDI and FF MDI are currently being evaluated in Phase III clinical studies in patients with COPD. Clinical studies conducted with Symbicort MDI are also being referenced, as this is the only product in the US containing budesonide that is approved for use in patients with COPD.

1.1 Chronic Obstructive Pulmonary Disease

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. COPD 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), 2013].

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are β2-agonists, anticholinergics, and methylxanthines used as monotherapy or in combination. Treatment with long-acting bronchodilators is more convenient and more effective at producing maintained symptom relief than treatment with short-acting bronchodilators. Combining bronchodilators from different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator (GOLD, 2013). Long-acting β2-agonists (LABAs) and long-acting muscarinic antagonist (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 and quality of life and reduces the frequency of exacerbations in COPD patients with a forced expiratory volume in 1 second (FEV_1) value of <60% of predicted. Withdrawal from treatment of ICS may lead to exacerbations in some patients. When combined with a LABA, an ICS is

more effective than the individual components in improving lung function, quality of life and reducing exacerbations in patients with moderate to very severe COPD. Furthermore, the addition of a LABA/ICS combination to tiotropium improves lung function and quality of life and may further reduce exacerbations, but more studies of triple therapy are needed (GOLD, 2013).

1.2 Glycopyrronium

Glycopyrronium (the active moiety of glycopyrronium bromide, also referred to as glycopyrrolate) is a LAMA that exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. Glycopyrronium is approved in many countries in multiple formulations for different indications, including COPD.

An inhaled formulation of glycopyrronium (Seebri® Breezhaler® Inhalation Powder, glycopyrronium bromide) was recently approved throughout the European Union (EU) and in Canada, Australia and Japan. In the EU, Seebri Breezhaler is approved as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. The recommended dose is 44 µg of glycopyrronium (equivalent to 55 µg of glycopyrronium bromide) administered once daily (QD) using the Seebri Breezhaler inhaler.

The clinical development program for Seebri Breezhaler included 12 clinical studies, five Phase I studies, four Phase II clinical studies and three Phase III clinical studies. Overall, the clinical development program included a total of 1,361 patients with COPD exposed to Seebri Breezhaler 44 µg QD, with a total of 842 patients exposed for ≥26 weeks and 428 patients exposed for ≥38 weeks [Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Seebri Breezhaler, 2012]. In addition to the published data with Seebri Breezhaler (also referred to as NVA237), there is also a large body of published data evaluating the safety and efficacy of inhaled glycopyrronium in healthy volunteers, patients with COPD and patients with asthma.

Glycopyrronium is also approved as Robinul® in the United States (US) and many countries worldwide as an intravenous/intramuscular (IV/IM) injection or as an oral tablet and is indicated for systemic administration in adults for use as a preoperative antimuscarinic to reduce salivary, tracheobronchial, and pharyngeal secretions; to reduce the volume and free acidity of gastric secretions; and to block cardiac vagal inhibitory reflexes during induction of anesthesia and intubation. Robinul is also indicated as adjunctive therapy for the treatment of peptic ulcer disease when rapid anticholinergic effect is desired. While the recommend dose varies across these indications, for peptic ulcer disease the usual recommended dose of Robinul Injection (also referred to as Glycopyrrolate Injection) is 0.2 mg at 4 hour intervals, administered 3 or 4 times daily by the IV or IM route. Where more profound effect is required, 0.4 mg may be given [Robinul US Product Information, 2007]. Glycopyrronium is also approved as an oral tablet (Robinul and Robinul Forte). Robinul (glycopyrrolate 1 mg tablets) and Robinul Forte (glycopyrrolate 2 mg tablets) are indicated for use in adults as an adjunctive therapy in peptic ulcer disease and are dosed BID to three times daily (TID) up to 6 mg per day (Robinul and Robinul Forte US Product Information, 2011).

Glycopyrronium is also approved in the US as an oral solution (Cuvposa®) which is indicated to reduce chronic severe drooling in patients aged 3 to 16 with neurologic conditions associated

with problem drooling (e.g., cerebral palsy). The maximum recommended dose of Cuvposa is 0.1 mg/kg TID, not to exceed 1.5 to 3 mg per dose.

1.3 Formoterol Fumarate

Formoterol fumarate is a potent and selective LABA approved in the US (e.g., Foradil® Aerolizer®) and worldwide (e.g., Oxis® Turbuhaler®, Foradil) for use in asthma and COPD. Formoterol fumarate is also approved in the US and worldwide in combination with budesonide (e.g., Symbicort MDI, Symbicort Turbuhaler) for use in patients with asthma and COPD. When inhaled, formoterol fumarate acts locally in the lung as a bronchodilator. Formoterol fumarate stimulates β2-adrenoreceptors in the airways, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction.

In patients with COPD, formoterol fumarate is typically administered at an orally inhaled dose of 12 µg BID with doses up to 24 µg BID approved in some countries. Although formoterol fumarate is classified as a LABA, it has a rapid onset of action similar to short-acting β2-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 patients with COPD have demonstrated that the onset of action with formoterol fumarate is faster than with anticholinergic 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 2,500 patients demonstrated that formoterol fumarate is effective and well-tolerated in patients with COPD (Dahl, 2001; Rossi, 2002; Aalbers, 2002; Campbell, 2005; Campbell, 2007).

1.4 Budesonide

Budesonide is a well-established corticosteroid approved worldwide in both intranasal and inhaled formulations. Inhaled budesonide formulations currently approved in the US include Rhinocort® Nasal Inhaler, Rhinocort Aqua® Nasal Spray, Pulmicort® Turbuhaler®, Symbicort Inhalation Aerosol (Symbicort MDI), and Pulmicort Respules®.

Inhaled budesonide is approved for use in patients with COPD when combined with formoterol fumarate dihydrate in Symbicort MDI. In the US, Symbicort is available as an MDI and only the 320/9 µg dose administered as two inhalations of 160/4.5 µg strength (BID) is approved for use in patients with COPD. Symbicort MDI 320/9 µg BID is indicated as a maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and emphysema.

Inflammation is a component in the pathogenesis of COPD. The predominant inflammatory cells in COPD include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of ICS on pulmonary and systemic inflammation in patients with COPD are controversial and their role in the management of stable COPD is limited to specific indications. Regular treatment with ICS has been shown to improve symptoms, lung function and quality of life and reduce the frequency of exacerbations in COPD patients with a FEV_1 value <60% of predicted (GOLD, 2013).

In clinical studies, Symbicort MDI 320/9 µg administered BID demonstrated significant improvements in lung function compared to budesonide MDI 320 µg BID, formoterol fumarate

(Oxis Turbuhaler) 9 µg BID, or placebo in patients with COPD. In the clinical studies, improvements in secondary endpoints of morning and evening peak expiratory flow and reduction in rescue medication use were supportive of the efficacy of Symbicort MDI 320/9 µg. (Symbicort Inhalation Aerosol Prescribing Information, 2012; Rennard, 2009; Tashkin, 2008). The GOLD guidelines acknowledge that combination therapy with an ICS and LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients to moderate to very severe COPD (GOLD, 2013).

1.5 Pearl Therapeutics' BGF MDI

Pearl Therapeutics is developing BGF MDI using its porous particle technology platform. The same porous particle technology platform is used for GFF MDI, GP MDI and FF MDI. This technology is based on spray dried porous particles comprised of distearoylphosphatidylcholine (DSPC) and calcium chloride ($CaCl_2$) that are co-suspended with micronized active pharmaceutical ingredients (APIs) in an hydrofluoroalkane (HFA) propellant to form stable suspension based MDIs. The fraction of the APIs mixed with the porous particles can be adjusted across a wide range of doses. The unique attributes of this technology enables reproducible administration of very low doses of potent therapeutics.

1.6 Study Rationale

BGF MDI is a novel fixed-dose triple combination MDI product formulated with budesonide, glycopyrronium, and formoterol for use in patients with COPD. As described in the GOLD guidelines, in some patients, the addition of a LABA/ICS to a LAMA improves lung function, quality of life and may further reduce exacerbations. As per GOLD guidelines, patients categorized in the D group (those with many symptoms and high risk of exacerbations) the first choice of treatment is an ICS/LABA or LAMA with some evidence for triple therapy. Pearl Therapeutics has planned this study to evaluate the pharmacokinetics following three single doses of three strengths of BGF MDI relative to a single dose of two strengths of Symbicort MDI and a single dose of one strength of GFF MDI.

Symbicort MDI 320/9 µg (given as 2 inhalations of 160/4.5 µg) BID is indicated for maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and emphysema. This study is being conducted to identify a BGF MDI dose that provides comparable systemic levels of budesonide to the dose of Symbicort MDI approved for COPD (320/9 µg). Three doses of BGF MDI and two doses of Symbicort are included in the study to allow a Finney assay or similar approach to be conducted to identify equivalent doses across both formulations. GFF MDI is also included in the study to allow the assessment of any drug-drug interactions (DDI) in BGF MDI when budesonide is added to GFF MDI.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of the study is to determine a dose of budesonide that when formulated with glycopyrronium and formoterol fumarate in BGF MDI provides comparable systemic exposure [pharmacokinetics (PK)] to budesonide following administration of Symbicort MDI 320/9 µg (2 inhalations of 160/4.5 µg).

2.2 Secondary Objective(s)

The secondary objectives of the study are:

- To assess if a drug-drug interaction (DDI) occurs when budesonide is formulated with glycopyrronium and formoterol fumarate in BGF MDI compared to glycopyrronium, and formoterol fumarate only in GFF MDI.
- To evaluate the safety and tolerability of the treatments administered; i.e., BGF MDI, Symbicort MDI and GFF MDI.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

This study is being conducted in healthy volunteers. Therefore, efficacy will not be evaluated.

3.2 Safety Endpoints

The safety of BGF MDI, Symbicort MDI and GFF MDI will be assessed from physical examination findings, adverse event (AE) reporting including SAE reporting, vital signs (blood pressure, heart rate, respiratory rate and body temperature), clinical laboratory values (hematology, biochemistry, and urinalysis), and findings from 12-lead safety electrocardiograms (ECGs).

3.3 Pharmacokinetic Endpoints

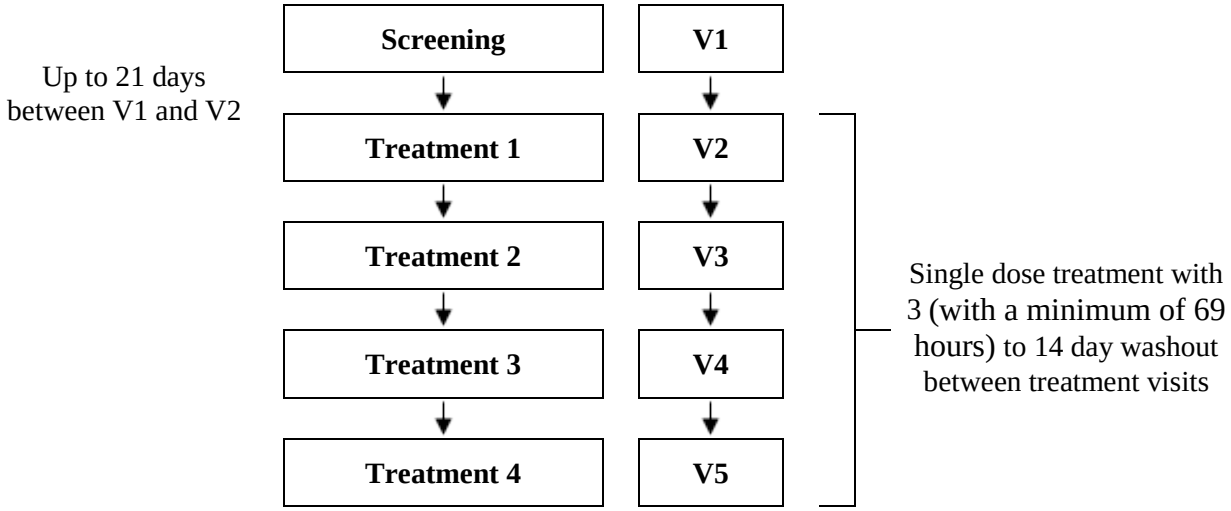
The PK of BGF MDI, Symbicort MDI and GFF MDI will be assessed and compared from plasma concentrations of each drug. Time points for PK blood sample collection during each of the four single-dose periods will be at 30 minutes prior to dosing and then at 2, 6, 20, and 40 minutes post dose and 1, 2, 4, 8, 10 and 12 hours post dose (see Table 5 for the Schedule of Inpatient Period Assessments). PK parameters at all doses will include C_{max}, t_{max}, $t_{½}$, AUC_{0-12}, $AUC_{0-t,}$ CL/F, Vd/F, and λ_z. Other PK parameters may be calculated, as appropriate.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a single-dose healthy volunteer Phase I study with a randomized, double-blind within device, four-period, six-treatment, crossover design. The overall study design is summarized and illustrated in Figure 1.

Figure 1. Study Design



Subjects who provide informed consent, undergo screening procedures and qualify for the study will be randomized to one of 12 treatment sequences. Each treatment sequence will contain BGF MDI 320/14.4/9.6 µg, GFF MDI 14.4/9.6 µg, and Symbicort MDI 320/9 µg and one of the remaining three treatments. At the target of 84 subjects randomized, each sequence will be used 7 times. If all subjects complete the study, the design is balanced for both period and first-order carryover effects. Treatments will be blinded within the two devices.

There are two different MDI devices used within the study. The Pearl products (BGF MDI and GFF MDI) are identical in form and function and are indistinguishable from each other. The two Symbicort MDIs are identical in form and function and are indistinguishable from each other. However, they are different from the Pearl Therapeutics products. As such, the test products will be double-blind within device.

Each inpatient treatment session will be separated by an outpatient washout period of at least 3 calendar days (with a minimum of 69 hours) and not exceeding 14 days between doses. For each treatment period, subjects will report to the clinic on the day prior to each dosing day (Day -1: admission day), at which time continuing eligibility will be assessed. If the subject continues to meet eligibility criteria, the subject will be admitted into the inpatient unit.

Safety data will be closely monitored and baseline and post dosing serial blood draws for PK analysis (see Table 5 in Appendix 1) will be obtained during each inpatient treatment period. After all scheduled assessments are completed and all available safety data have been reviewed

by the Principal Investigator, subjects will be discharged from the clinic. Following each treatment period, subjects will return to the clinic after their washout period of at least 3 calendar days (with a minimum of 69 hours) between doses for their next treatment period until all four treatment periods have been completed. Other safety assessments will be obtained as listed in Table 4 and Table 5 located in Appendix 1.

4.2 Rationale for Study Design and Control Group

This study is a Phase I, single-dose, four-period, six-treatment, crossover study that will assess the safety and PK of three doses of BGF MDI and two doses of Symbicort MDI and one dose of GFF MDI in healthy subjects. The two Symbicort MDI dose levels and the one GFF MDI dose level will serve as active comparators, which will allow for differentiation of any PK and tolerability issues associated exclusively with each of the three BGF MDI doses.

This protocol includes the following PK sampling times:-30 minutes pre-dose and 2, 6, 20 and 40 minutes and 1, 2, 4, 8, 10 and 12 hours post-dose. The rationale for the PK sample collection times are given below.

PK considerations

1. Budesonide: Orally inhaled budesonide is rapidly absorbed in the lungs and peak concentration is typically reached within 20 minutes. Thus, from a PK perspective, the 2, 6, 20 and 40 minute time points will provide adequate data to describe C_{max} and t_{max} for budesonide both in BGF MDI and Symbicort MDI at the doses that will be studied.
2. Glycopyrronium: Based on previous studies of GP that included PK assessments, peak plasma concentrations occurred rapidly after GP MDI inhalation (data on file) with median time to maximum concentration (C_{max}) generally occurring within 6 minutes (0.100 hour) after dosing. Thus, from a PK perspective, the 2, 6, 20 and 40 minute time points will provide adequate data to describe C_{max} and t_{max} for GP both in BGF MDI and GFF MDI at the doses that will be studied.
3. Formoterol fumarate: Based on previous studies of FF that included PK assessments, peak plasma concentrations occurred within 1 hour after FF MDI inhalation (data on file) with median time to C_{max} occurring about 0.933 hours after FF MDI 9.6 µg dosing. From a PK perspective, the 20 min, 40 min, 1 hour and 2 hour time points will provide adequate data to describe C_{max} and t_{max} for FF in BGF MDI, Symbicort MDI and GFF MDI at the doses that will be studied.

Conclusion

The planned PK sampling times provide an adequate selection of PK data points required to describe the PK of budesonide, GP and FF in terms of t_{max} and C_{max} values for each MDI component as well as to estimate AUC_{0-12}.

4.3 Study Duration and Dates

This study will include a screening period of up to 21 days and four single-dose treatment periods separated by a minimum washout period of 3 days to a maximum of 14 days for added scheduling flexibility. The maximum participation in the study is between 34 and 67 days.

5 STUDY POPULATION SELECTION

Eighty-four healthy male or female subjects will be enrolled in this study. Subjects who withdraw from the study after receiving at least one single dose treatment will not be replaced.

5.1 Inclusion Criteria

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

1. Signed and dated IRB-approved informed consent form (ICF) before any protocol-specific screening procedures are performed.
2. Male and female subjects between the ages of 18 and 45 years (inclusive).
3. Be in good general health as determined by a thorough medical history and physical examination, ECG, vital signs and clinical laboratory evaluation.
4. Willing and able to complete all study assessments and procedures.
5. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception from the Screening Period through 14 days after the Final Study Visit: hormonal contraception, condom with spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD). 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 for 14 days after the final visit as a safety precaution.
6. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months, do not require contraception during the study. Post- menopausal must be confirmed by a serum FSH test at screening and the reason must be documented in the eCRF.
7. Males with female partners of childbearing potential must agree to use a highly effective, medically acceptable form of contraception from the Screening Period through 14 days after the Final Study Visit. 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 for 14 days from the final visit as a safety precaution.
8. Have a BMI between 18.5 and 32 kg/m^2 (inclusive) and a minimum weight of 50 kg at the screening visit.
9. Results of complete blood cell (CBC) count (including white blood cell (WBC) 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 range or determined to be not clinically significant by the Investigator. Specifically, serum potassium must be ≥3.5 mmol/L and serum magnesium ≥0.8 mmol/L. Urinalysis testing should be within the normal range or determined to be not clinically significant by the Investigator.

5.2 Exclusion Criteria

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

1. Pregnant or nursing female subjects or subjects who are trying to conceive.
2. For female subjects, a positive serum human chorionic gonadotropin (hCG) test at screening or a positive urine hCG at admission for any of the five treatment periods.
3. Subjects with clinically significant neurologic, cardiovascular, hepatic, renal, endocrinologic, pulmonary, hematological, psychiatric, or other medical illness that would interfere with participation in this study.
4. Subjects with a history of ECG abnormalities including PR>220 msec; QRS complex >110 msec; QTcF>450 msec; or any significant morphological changes other than nonspecific T-wave changes. In addition, subjects who demonstrate any of these or any other significant 12-lead ECG abnormalities prior to the first treatment period (i.e., safety ECGs performed at screening, baseline, or pre-dose of the first treatment period) 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 with the inability to coordinate the use of the placebo MDI under supervision from site staff.
7. Cancer: Subjects who have cancer that has not been in complete remission for at least 5 years. Note: Subjects with squamous cell carcinoma or basal cell carcinoma of the skin are eligible, if in the opinion of the Investigator, the condition has been adequately worked up, is clinically controlled and the subject's participation in the study would not represent a safety concern.
8. Supine blood pressure >140/90 mm/Hg or resting heart rate ≥100 bpm at screening, baseline (Day -1) or pre-dose of the first treatment period.
9. Subjects with symptomatic prostatic hypertrophy that is clinically significant in the opinion of the Investigator.
10. Subjects with a trans-urethral resection of the prostate (TURP) or full resection of the prostate within six months prior to Visit 1 are excluded from the study.
11. Subjects with bladder neck obstruction or urinary retention that is clinically significant in the opinion of the Investigator.
12. Subjects with a diagnosis of glaucoma that in the opinion of the Investigator has not been adequately treated. All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective β-blockers such as betaxolol, carteolol, levobunolol, metipranolol, and timolol.
13. History of substance-related disorders (with the exception of caffeine-related and nicotine-related disorders) as defined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) within 1 year of screening.

14. History of smoking or the use of nicotine containing products within 3 months of screening by self-reporting.
15. A positive alcohol breathalyzer or urine drug screen for drugs of abuse at the screening visit or at the beginning of each inpatient period.
16. Treatment with an investigational drug within 30 days or five half-lives (whichever is longer) prior to the beginning of the screening period.
17. Treatment with any prescription or non-prescription drugs (including vitamins, herbal, and dietary supplements) within seven days or five half-lives of the screening visit, whichever is longer. Acetaminophen will be permitted at doses of ≤2 grams/day.
18. Subjects with a history of an allergic reaction or hypersensitivity to any drug or to any component of the formulation(s) used in this study.
19. Blood collection of greater than 500 mL within 56 days prior to screening.
20. Seropositivity for human immunodeficiency virus (HIV) at screening.
21. Positive for hepatitis B surface antigen (HbsAg) or positive hepatitis C antibody at screening.
22. Subjects with a chronic medical condition that requires ongoing treatment with medication.
23. Subjects with a history of major surgery within four weeks or minor surgery within 2 weeks of drug administration.
24. 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 four weeks of drug administration.
25. Any other condition and/or situation that causes the Investigator to deem a subject unsuitable for the study (e.g., due to expected study medication non-compliance, inability to medically tolerate the study procedures, or a subject's unwillingness to comply with study-related procedures).
26. Subjects with abnormal-GFR (eGFR<90 mL/min) using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD EPI).

5.3 Subject Identification

All subjects who undergo screening will be assigned a unique screening identification number at the Screening visit (Visit 1). Only subjects continuing to meet entry inclusion/exclusion criteria at Visit 2 will be assigned a unique subject randomization number.

5.4 Prior, Concomitant, and Prohibited Medications

Investigational therapies are not permitted within 30 days or five half-lives (whichever is longer) prior to beginning the screening period. All medications approved for control of intraocular pressure are allowed including topical ophthalmic non-selective β-blockers such as betaxolol, carteolol, levobunolol, metipranolol, and timolol. Otherwise, the use of prescription or over-the-

counter medications within 7 days or five half-lives (whichever is longer) prior to beginning the screening period is not permitted. Acetaminophen will be permitted at doses of ≤2 grams/day as determined to be necessary by the Investigator. With the exception of treatments for control of intraocular pressure, ongoing treatment for chronic conditions will not be allowed.

Major surgical interventions are not permitted within four weeks of study drug administration and minor surgical interventions are not allowed within two weeks of study drug administration. Any medications that were being taken prior to signing the informed consent form (ICF) will be documented as prior study medications and must be stopped prior to entry.

5.5 Other Restrictions, Illicit Drugs or Drugs of Abuse

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

Illicit drugs or drugs of abuse will not be allowed from the within 1 year of Screening (Visit 1) to whenever the subject discontinues the study.

Subjects are not allowed to consume grapefruits or grapefruit juice throughout the study.

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

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. Treatments will be blinded in terms of dose administered within the two devices. The Pearl Therapeutics products (BGF MDI and GFF MDI) are identical in form and function and indistinguishable from each other. The two Symbicort MDIs are identical in form and function and indistinguishable from each other; however they are different from the Pearl Therapeutics products. As such, the test products will be double-blind within device. The characteristics of the three BGF MDI doses, the two Symbicort MDI doses and the GFF MDI dose that will be administered during the study are provided in Table 1.

Study personnel will be provided with a written randomization scheme for allocation of subjects to 1 of 12 treatment sequences and to manage the distribution of clinical supplies. The study will be conducted at a single center, and subjects will be randomized to 1 of 12 treatment sequences, as listed below where A, B, and C represent BGF MDI 320/14.4/9.6 µg, Symbicort MDI 320/9 µg, and to GFF MDI 14.4/9.6 µg by random assignment, and D, E, and F represent BGF MDI 160/14.4/9.6 µg, BGF MDI 80/14.4/9.6 µg, and Symbicort MDI 160/9 µg by random assignment. Seven of the planned 84 subjects will be included in each treatment sequence. The design is balanced for period and first order carryover effects.

Sequence 1: ABCD	Sequence 7: CAEB
Sequence 2: BDAC	Sequence 8: ECBA
Sequence 3: CADB	Sequence 9: ABCF
Sequence 4: DCBA	Sequence 10: BFAC
Sequence 5: ABCE	Sequence 11: CAFB
Sequence 6: BEAC	Sequence 12: FCBA

For each subject, single dose administration of study drug during each of the four treatment periods should occur at approximately the same time of day.

6.2 Dispensing Study Drug

All subjects will receive BGF MDI 320/14.4/9.6 µg, GFF MDI 14.4/9.6 µg, and Symbicort MDI 320/9 µg and one of the remaining three treatments by random assignment to 1 of 12 predetermined treatment sequences (see Section 6.1). At screening, subjects will be instructed in the proper use of an MDI using a bulk-supplied placebo MDI and at that time, must demonstrate the ability to coordinate use of the MDI.

For each MDI administration, the MDI device will be primed in the study site pharmacy by the pharmacist and then delivered to the inpatient clinic. Just prior to dosing, subjects will again be given detailed instruction regarding the proper use of the MDI device to ensure comprehension of its use. At the time of dosing, a health care provider will be present to ensure that the required number of activations of the MDI device is properly administered by the subject.

6.3 Product Descriptions

The BGF MDI active drug substances are budesonide, glycopyrronium, and formoterol fumarate dihydrate. Symbicort MDI 320/9 µg and 160/9 µg and GFF MDI 14.4/9.6 µg are active controls.

Investigational materials will be provided by Pearl Therapeutics as summarized in Table 1.

Table 1: Product Descriptions

Product Name & Potency	Product Strength	Dosage Form	Comments
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
BGF MDI 80/14.4/9.6 µg ex-actuator	40/7.2/4.8 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
Symbicort MDI 320/9 µg ex-actuator	160/4.5 µg/actuation	MDI	Taken as 2 inhalations
Symbicort MDI 160/9 µg ex-actuator	80/4.5µg/actuation	MDI	Taken as 2 inhalations

BGF MDI = Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol; GFF MDI = Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; MDI = Metered Dose Inhaler.
Note: All study drugs will be administered by oral inhalation.

Following screening and determination of eligibility, dosing will be spread over four single-dose treatment periods using 12 treatment sequences. The treatment and study visit schedule is illustrated in Figure 1 located in Section 4.1.

6.4 Primary Packaging and Labeling Information

Study drug will be provided as packaged supplies. Each subject will receive one dose of each of four treatments.

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

Symbicort MDI: Each of the strengths of Symbicort MDI are supplied as a pressurized aluminum canister with an attached counting device, a red plastic actuator body with a white mouthpiece, and attached grey dust cap. Each 120 actuation canister has a fill weight of 10.2 grams. Each canister is packaged in a foil overwrap pouch with desiccant sachet and placed in a carton. Each carton contains one canister and a Medication Guide.

6.5 Unblinding Procedures

Pearl Therapeutics will provide disclosure envelopes with the clinical supplies for the purpose of unblinding. The Investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. Whenever possible, the Investigator must first discuss options with the Medical Monitor or appropriate study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the Investigator must notify Pearl Therapeutics 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

BGF MDI and GFF MDI: Prior to dispensing, BGF MDI and GFF MDI should be stored protected with foil overwrap and desiccant at room temperature [20 to 25°C (68 to 77°F)]; excursions to the range of 15 to 30°C (59 to 86°F) are permitted. After the product is removed from the foil overwrap, it should be stored at room temperature [20 to 25°C (68 to 77°F)]; excursions to the range of 15 to 30°C (59 to 86°F) are permitted.

Symbicort MDI: Store at controlled room temperature [20 to 25°C (68 to 77°F)] and the inhaler should be stored in the upright position with the mouthpiece down. The canister should be at room temperature before use and shake well for 5 seconds. Do not expose to heat or open flame, including the sun. Exposure to temperatures over 120ºF may cause bursting. Do not puncture or incinerate even when empty.

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

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

Instructions regarding the administration of study drug are provided in Appendix 2.

6.8 Drug Accountability/Return of Clinical Supplies

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

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the appropriate designated assistants have access. Storage conditions for the clinical supplies should be observed, monitored and documented. Clinical supplies are to be dispensed only in

accordance with the protocol. The Investigator is responsible for keeping accurate records of the clinical supplies received from [redacted], the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the study. Study medication should be handled in accordance with Good Pharmacy Practices. The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned to [redacted].

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

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

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

7 STUDY PROCEDURES

7.1 Informed Consent

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

7.2 Inclusion/Exclusion Criteria

Eligibility screening of healthy subjects will be completed within 21 days prior to administration of the first study drug and will be documented on the eCRF. Confirmation of eligibility will be performed at each clinic admission (Day -1) for each of the four treatment periods.

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

7.3 Medical History

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

7.4 Physical Examination

A complete physical examination including height and weight will be performed at the time of screening (height and weight at screening only) and at the final visit at the completion of the fourth treatment period. The findings of each examination will be recorded on the source documents and clinically significant abnormalities will be recorded on the eCRF. The physical examination will include:

- Documentation of height
- Documentation of weight
- General appearance
- Head, eyes, ears, nose, and throat
- Respiratory
- Cardiovascular
- Musculoskeletal
- Abdomen
- Neurologic
- Extremities
- Dermatologic
- Lymphatic

7.5 Vital Signs

Vital sign determinations, including blood pressure, heart rate, respiratory rate and body temperature will be performed after a 5 minute supine period at the screening visit, on the day of each clinic admission (Day -1) and on each treatment day (Day 1) at 30 minutes prior to administration of study drug and 30 minutes, 2 hours and 12 hours post administration of study drug (see Table 4 and Table 5 located in Appendix 1).

7.6 Electrocardiography

Twelve-lead safety ECGs will be recorded at screening, on each clinic admission day (Day -1) of each treatment period. On each treatment day (Day 1), 12-lead ECGs will be obtained within one hour prior to dosing (baseline) and at 30 minutes and 2 and 12 hours post dosing (see Table 4 and Table 5 in Appendix 1). Subjects should be supinely resting for at least 5 minutes before and during the ECG recording procedure. Subjects with any ECG abnormalities should be evaluated by the Investigator to determine if each abnormality is clinically significant. All clinically significant abnormalities will be reported as AEs and followed closely by the Investigator in order to assure the safety of the study subject.

7.7 Clinical Laboratory Tests

7.7.1 Laboratory Parameters

Laboratory testing (hematology with differential, serum chemistry and urinalysis) will be performed using standard methods. Blood and urine samples for the clinical laboratory tests listed in Table 2will be collected at the screening visit, on the day of clinic admission (Day -1) and at 12 hours post administration of study drug on Day 1 during each of the four treatment periods. In addition, blood will be drawn for glucose and potassium level determinations within 30 minutes prior to dosing and at 30 minutes, 2 hours and 4 hours post administration of study drug on Day 1 (see Table 4 and Table 5 located in Appendix 1). Subjects must be fasting for at least 4 hours prior to any clinical laboratory assessment blood draw. Meals during the dosing day of each treatment period (Day 1) will be standardized after the 4 hour post dose clinical laboratory draw. There are no restrictions regarding clear fluid intake.

Table 2: List of Laboratory Tests

Hematology	Blood Chemistry	
Hematocrit*	Creatinine**	Bilirubin (direct)
Hemoglobin	Potassium (K+)***	AST
Platelet count	Sodium (Na+)	ALT
Red blood cell (RBC) count	Chloride (Cl-)	Gamma-glutamyltransferase (GGT)
WBC count	Magnesium (Mg++)	Alkaline phosphatase
WBC differential	Calcium	Total Protein
Mean cell volume (MCV)	Inorganic phosphate	Albumin
Mean cell haemoglobin (MCH)	Glucose***	
MCH concentration (MCHC)	Urea	
	Bilirubin (Total)	

*Packed cell volume (PCV)
**Serum creatinine value will be used to calculate eGFR using CKD EPI.
***Additionally, within 30 minutes prior to dosing and at 30 minutes, 2 hours and 4 hours post dose of each treatment period

Urinalysis: Macroscopic examination routinely including specific gravity, pH, protein, glucose, ketones, blood and urobilinogen. A microscopic examination will be performed if warranted based on macroscopic results.

Urine drug screen: A urine sample will be collected and analyzed (positive or negative) for drugs of abuse including amphetamine, opiate, cocaine, barbiturates benzodiazepines, and marijuana [tetrahydrocannabinol (THC)].

Breathalyzer Test: A breathalyzer test will be performed for the presence of alcohol (positive or negative).

Serology: Testing for HbsAg, Hepatitis C antibody and HIV will be performed at the screening visit 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 the screening visit and urine hCG test at admission for each of the four treatment periods.

For females of non-childbearing potential: A serum hCG test at the screening visit and urine hCG test at admission for each of the four treatment periods and the follow-up visit. In addition, a serum, FSH test for confirmation of non-childbearing status will be performed at screening only.

7.7.2 Sample Collection, Storage, and Shipping

Detailed instructions for laboratory sample collection, processing, and shipping instructions will be provided in the laboratory manual.

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.

7.8 Pharmacokinetic Assessments

Pharmacokinetic sampling will occur in conjunction with treatment periods 1, 2, 3 and 4.

Approximately 10 mL of whole blood will be collected at 30 minutes prior to dose administration and at 2, 6, 20 and 40 minutes and 1, 2, 4, 8, 10 and 12 hours post dose administration. Samples will be collected via an indwelling intravenous cannula [per the study site's Standard Operating Procedure (SOP)] or, if necessary, by direct venipuncture into vacuum collection tubes (for example Vacutainer 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 less than or equal to -60°C. Refer to Appendix 3 for plasma collection, storage and handling.

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

Sample collections will be scheduled for the nominal time point and actual collection times recorded in the source documents. Refer to Appendix 1, Table 5.

7.9 Adverse Events Assessments

7.9.1 Performing Adverse Event Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's eCRF and on the AE Reporting Form. If an AE is classified as "serious" as described in Section 7.9.6.1, it must be reported to Pearl Therapeutics or its designee no later than 24 hours after the Investigator recognizes/classifies the event as a SAE.

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

AEs will be collected from the time of administration of the first dose of study drug to the time of study termination, or study exit. For ongoing AEs at the time of the Final Visit, study termination, or study exit, additional data, such as AE resolution date, will be collected and reported to Pearl Therapeutics. If this data is collected after the study database is locked, it will be reported to Pearl Therapeutics, but will not be included in the study database.

7.9.2 Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonisation (ICH) and the U.S. CFR [21 CFR 312.32] 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.

AEs include, but are not limited to:

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

An AE does not include:

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

AEs that occur between the time the subject signs the ICF for the study and the time when that subject is randomized will be summarized as medical history and not as study AEs unless the event meets the definition of a SAE as defined in Section 7.9.6.1.

AE's that occur during a washout period will be attributed to the most recent study drug that was administered.

7.9.3 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.

7.9.4 Relationship

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

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

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

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

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

7.9.5 Clinical Laboratory Adverse Events

Many laboratory abnormalities observed during the course of a study will be included under a reported AE describing a clinical syndrome (e.g., elevated blood urea nitrogen [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 (i.e., concomitant medication or therapy).
- Any 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.

7.9.6 Serious Adverse Events (SAEs)

7.9.6.1 Definition

A SAE is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes:

- Death

- Life-threatening AE
- Hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

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

7.9.6.2 Reporting SAEs

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

This verbal and faxed report must be followed no later than three working days by a written report **signed by the Investigator**. The information in both the initial report and follow-up report(s) will also be captured in the electronic database. The Sponsor is responsible for submitting the report to all applicable regulatory authorities.

Contact the Medical Safety Physician for safety reporting at:

PEARL THERAPEUTICS, INC.
Business Hour Phone: [redacted]
After Hours Phone: [redacted]
Fax Reports Phone: [redacted]

7.9.6.3 Supplemental Investigation of SAEs

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

7.9.6.4 Post Study Follow-Up of Adverse Events

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

AEs ongoing at the Follow-up/Final Visit will be followed for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes or resolves. If resolved, a resolution date should be reported to Pearl Therapeutics. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals as is practical.

7.9.6.5 Notification of Post Study SAEs

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

7.9.6.6 IRB Notification of SAEs

The Investigator is responsible for promptly notifying her/his IRB/IEC of all SAEs, including any follow-up information, occurring at her/his site and any SAE regulatory report, including any follow-up reports that she/he 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 ICF or other measures based on its review of an SAE report.

7.9.6.7 Health Authority Safety Reports

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

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

IRB/IEC as soon as possible. Documentation of the submission to the IRB/IEC must be retained for each safety report.

7.9.7 Overdose

An overdose is defined as a dose greater than the highest dose level of each study drug evaluated in this study as described in Section 6.3of the protocol (Product Descriptions), which 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 documentation may include, but not be limited to the Investigators Brochure.

7.9.8 Pregnancy

Any pregnancy that occurs from screening until study completion must be reported to Pearl Therapeutics.

To ensure subject safety, each pregnancy must be reported to Pearl Therapeutics within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child.

7.9.9 Treatment-Emergent Adverse Events

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

7.10 Concomitant Medication Assessments

The Investigator or designated qualified personnel will assess and record concomitant medication usage on the eCRF. Specific information regarding concomitant medication and prior therapy usage is provided in Section 5.4.

7.11 Removal of Subjects from the Trial or Study Drug

The Investigator may withdraw a subject from the study for any of the following reasons:

- The occurrence of a protocol violation
- The occurrence of a serious or intolerable AE
- The occurrence of a clinically significant change in a laboratory parameter(s)
- The sponsor or Investigator terminates the study
- The subject requests to be discontinued from the study.

Subjects removed from the study will not be replaced.

7.12 Termination of the Study

The study may be terminated prematurely with sufficient notice in advance by the Investigator for any reason as per the terms of the contract with Pearl Therapeutics. The reason should be communicated in writing to 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

8.1 Screening Visit (Up to 21 Days Prior to Randomization)

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

- Informed consent.
- Demographics and relevant medical history.
- Physical examination.
- Vital signs.
- Review of eligibility criteria.
- Placebo MDI usage demonstration and practice.
- Screening 12-lead Safety ECG.
- Clinical laboratory evaluations.
- Urine drug testing.
- Alcohol breathalyzer test.
- Serum hCG test for all women of childbearing potential and all women of non-childbearing potential.
- FSH test for confirmation of non-childbearing status for women of non-childbearing potential only.
- Serology (HIV, HBsAg and hepatitis C).
- Document concomitant medications.

8.2 Clinic Admission (Day -1)

The subjects will be admitted to the clinic on Day -1, the day prior to administration of Treatment Period 1 study drug. The results of the following baseline procedures and assessments, which will be performed prior to the first treatment period only, will be documented in the eCRF and/or source documents:

- Clinic admission on Day -1.
- Vital signs at clinic admission on Day -1.
- MDI usage demonstration on Day -1.
- Review eligibility criteria on Day -1.
- Collect blood samples for clinical laboratory testing on Day -1.
- Urine drug testing on Day -1.

- Alcohol breathalyzer test on Day -1.
- 12-lead Safety ECG on Day -1.
- Urine pregnancy test for all women (childbearing and non-childbearing potential) on Day -1.
- Document concomitant medications on Day -1.

8.3 Treatment Period 1 (Day 1)

The following study activities and assessments will be performed in conjunction with the first treatment period:

- Placebo MDI usage demonstration and practice on Day 1.
- Pre- and post-dose documentation of vital signs per Table 5 in Appendix 1.
- Administration of study drug on Day 1 (see Appendix 2 for details regarding study drug dispensing and administration).
- Collection of pre- and post-dose PK samples per Table 5 in Appendix 1.
- On Day 1, collect blood samples for clinical laboratory testing (glucose and potassium only) within 30 minutes prior to dosing and at 30 minutes and 2 and 4 hours post-dose and complete clinical laboratory testing at 12 hours post dose.
- Perform 12-lead Safety ECG within 1 hour prior to dosing and at 30 minutes, 2 hours and 12 hours post-dose on Day 1.
- Documentation of AEs on Day 1 (Note: AEs that occur prior to dosing will be recorded as Medical History).
- Documentation of concomitant medications on Day 1.
- After all scheduled assessments are complete and all available safety data has been reviewed by the Investigator, discharge from clinic upon completion of all protocol-specified procedures and complete a washout period of at least 3 calendar days (with a minimum of 69 hours) and not exceeding 14 days between doses.

8.3.1 Treatment Periods 2, 3 and 4

During these additional three treatment periods, subjects will be admitted to the study clinic as inpatients on Day -1 and remain inpatients until completion of all protocol-specified procedures listed below:

- Clinic admission on Day -1.
- Vital signs at clinic admission on Day -1.
- Review eligibility criteria on Day -1.
- Placebo MDI usage demonstration and practice on Day -1.

- Collect blood samples for clinical laboratory testing on Day -1.
- Perform 12-lead Safety ECG at clinic admission on Day -1.
- Urine drug testing on Day -1.
- Alcohol breathalyzer test on Day -1.
- Urine pregnancy test for all women (childbearing and non-childbearing potential) on Day -1.
- Placebo MDI usage demonstration and practice on Day 1.
- Pre- and post-dose documentation of vital signs per Table 5 in Appendix 1.
- Administration of study drug on Day 1 (see Appendix 2 for details regarding study drug dispensing and administration).
- Collection of pre- and post-dose PK samples per Table 5in Appendix 1.
- On Day 1, collect blood samples for clinical laboratory testing (glucose and potassium only) within 30 minutes prior to dosing and at 30 minutes and 2 and 4 hours post-dose and complete clinical laboratory testing at 12 hours post dose.
- Perform 12-lead Safety ECG within 1 hour prior to dosing and at 30 minutes, 2 hours and 12 hours post-dose on Day 1.
- Documentation of AEs on Day 1.
- Documentation of concomitant medications on Day -1 and Day 1.
- After all scheduled assessments are complete and all available safety data has been reviewed by the Principal Investigator, discharge from clinic and initiate a washout period of at least 3 calendar days (with a minimum of 69 hours) and not exceeding 14 days between doses (Treatments 2 and 3).

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

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

Safety analyses will be performed on data from all subjects in the Safety Population. AEs, clinical laboratory evaluations, and other safety measures (e.g., vital signs, ECGs) will be listed and summarized. No formal statistical analysis of safety data is planned. All available data will be reviewed throughout the study, as the data become available.

9.2 Determination of Sample Size

The sample size was chosen primarily in order to provide adequate power to assess the bioequivalence of BGF MDI to Symbicort MDI 320/9 µg with respect to budesonide exposure and secondarily to provide information about the comparison of BGF MDI to GFF MDI. The focus is on the high strength of BGF MDI. Eighty-four randomized subjects are expected to provide approximately 75 completers. At this sample size, assuming a true difference of 5%, if the intra-subject coefficients of variations (CVs) for budesonide are 25% and 30% for AUC_{0-12} and C_{max}, respectively, then the power to demonstrate bioequivalence using 90% CIs for the geometric mean ratio (GMR) and bounds of 80% to 125% is approximately 99% and 97%, respectively, for BGF MDI 320/14.4/9.6 µg. For the comparison of BGF MDI 320/14.4/9.6 µg to GFF MDI 14.4/9.6 µg, assuming intra-subject CVs of 30% and 35% for the AUC_{0-12} and C_{max} of formoterol fumarate, respectively, the power to demonstrate bioequivalence is approximately 97% and 92%, respectively. For glycopyrrolate, since the intra-subject CVs are assumed to be 60% for both AUC_{0-12} and C_{max}, wider criteria will be used for evaluating bioequivalence. For glycopyrrolate, the power is approximately 97% for each parameter for the comparison of BGF MDI 320/14.4/9.6 µg to GFF MDI 14.4/9.6 µg to demonstrate comparability using bounds of 67% to 150% in addition to requiring that the point estimate for the GMR is between 80% and 125%.

9.3 Analysis Populations

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

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

9.4 Demographics and Baseline Characteristics

Demographic information will include date of birth, gender, ethnicity and race. Demographics and baseline characteristics will be summarized descriptively. Height and weight, which are

considered baseline characteristics and documented as part of the physical examination performed at the screening visit, will be reported with the demographic information listed above.

9.5 Analysis of Pharmacokinetic Variables

PK analysis will be performed using the PK population. PK parameters at all doses will include C_{max}, t_{max}, $t_{½}$, AUC_{0-12}, $AUC_{0-t,}$ CL/F, Vd/F, and λ_z. Other PK parameters may be calculated, as appropriate. The initial calculation of PK parameters will be performed using non-compartmental analysis. Model-based parameter estimation may be performed following examination of the data.

The comparison of natural ln-transformed values of C_{max}, AUC_{0-12}, and AUC_{0-t} for each analyte will be performed using a linear mixed model in which treatment and period will be fixed effects and subject as a random effect. Variance components estimates will be obtained using the restricted maximum likelihood (REML) method. An unstructured covariance matrix will be used; if this model fails to converge, other covariance matrices will be evaluated (e.g., compound symmetry, first order auto regressive) with the model yielding the lowest value of Akaike Information Criterion (AIC) being selected.

The ratios of geometric least squares means and the corresponding 90% CI for each treatment comparison will be determined by exponentiation of the mean differences between treatments and 90% CI on the logarithm scale. Bioequivalence will be determined by comparing the 90% CI for the GMR to bounds of 80% to 125% for budesonide and formoterol. Due to the high variability of glycopyrrolate, bounds of 67% to 150% will be used in combination with requiring that the point estimate for the GMR is between 80% and 125%.

In addition, the geometric mean budesonide parameter values for each treatment group will be plotted against dose and a Finney assay will be used to estimate the relative potency of BGF MDI to Symbicort MDI. If the linear or parallel line assumptions required for the Finney assay appear to be violated, then an Emax model will be used to estimate relative potency. The bias-corrected and accelerated bootstrap will be used to construct 90% CIs.

9.6 Safety Analysis

The safety of BGF MDI, Symbicort MDI and GFF MDI will be assessed from physical examination findings, AE reporting, vital signs (blood pressure, heart rate, respiratory rate and body temperature), clinical laboratory values (hematology, blood chemistry, and urinalysis), and 12-lead safety ECG findings.

9.7 Interim Analysis

No interim analysis is planned for this study.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

The study administration structure is provided in Table 3.

Table 3: Study Administrative Structure

Phase 1 Unit Principal Investigator:	[redacted]
Sponsor Contact:	[redacted]
Sponsor Medical Monitor:	[redacted]
Study Monitoring:	Pearl Therapeutics [redacted]
Centralized ECG	[redacted]
PK Sample Analysis and Reporting	[redacted]
Data Management& Statistical Analyses:	[redacted]
Pharmacovigilance	[redacted]
Medical Writing:	[redacted]
Clinical Laboratory Testing	[redacted]
Clinical Trial Supply:	[redacted]

10.2 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.

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

The study will be conducted in accordance with GCP. These standards respect the following guidelines:

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

The Investigator (or Pearl Therapeutics, where applicable) is responsible for ensuring that this protocol, the site's 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.

10.4 Subject Information and Consent

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

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

10.5 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/patient data used and disclosed in connection with this study in accordance with all applicable privacy laws (i.e., Health Insurance Portability and Accountability Act), rules and regulations.

10.6 Quality Control and Assurance

Pearl Therapeutics is responsible for implementing and maintaining quality control and quality assurance systems with written 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.

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

- Return of all study data to Pearl 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.

10.9 Retention of Data

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

10.10 Financial Disclosure

The Principal Investigator or sub-Investigators named on the Form FDA 1572 will need to complete a financial disclosure form prior to study initiation, at any time during the study execution if new information needs to be disclosed, and for one year after study completion.

Investigators should make the IRB/IEC aware of any financial interests that the Investigator has in the investigational product.

10.11 Investigator's Final Report

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

11 REFERENCE LIST

a. GOLD (Global Initiative for Chronic Obstructive Lung Disease). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. National Institutes of Health updated 2011. Available at: www.goldcopd.com. Accessed January 28, 2013.

b. Committee for Medicinal Products for Human Use (CHMP) European Public Assessment Report for Seebri Breezhaler, 17 October 2012.

c. Robinul Injection US Product Information, Baxter Healthcare Corporation, 2007

d. Robinul and Robinul Forte US Product Information, Shionogi Inc., 2011.

e. Anderson, GP. Formoterol: Pharmacology, molecular basis of agonism, and mechanism of long duration of a highly potent and selective $\beta_2$adrenoceptor agonist bronchodilator. Life Sciences 1993;52;Issue26:2145-2160.

f. Berger WE, Nadel JA. Efficacy and safety of formoterol for the treatment of chronic obstructive pulmonary disease. Respir Med 2008;102:173-188.

g. Dahl R, Greefhorst LA, Nowak D, et al. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. Am J RespirCrit Care Med 2001;164:778-784.

h. Rossi A, Kristufek P, Levine BE, et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow release theophylline in the treatment of COPD. Chest 2002;121:1058-1069.Aalbers, 2002

i. Campbell M, Eliraz A, Johansson G, et al. Formoterol for maintenance and as-needed treatment of chronic obstructive pulmonary disease. Respir Med 2005;99:1511-1520.

j. Campbell SC, Criner GJ, Levine BE, et al. Cardiac safety of formoterol 12 µg twice daily in patients with chronic obstructive pulmonary disease. PulmPharmacolTher2007;20:571-579.

k. Symbicort Inhalation Aerosol US Prescribing Information, Astra Zenenca, 2012

l. Rennard SI, Tashkin DP, McElhattan J, Goldman M, Ramachandran S, Martin UJ, Silkoff PE. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. Drugs 2009; 69(5):549-65

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

Appendix 1 Schedule of Events

Table 4: Study Visit Schedule

Procedure	Screening From Day -21	Inpatient Treatment Periods 1 Through 4	
		Day -1	Day 1
Informed Consent	✓		
Medical History	✓	✓	
Demographics	✓		
Physical Examination	✓		
Vital Signs	✓[a]	✓[a]	✓[a]
Eligibility Review	✓	✓	
Placebo MDI Usage Demonstration/Practice	✓	✓	✓
12-lead ECG	✓[a]	✓[a]	✓[a]
Clinical Laboratory Testing	✓	✓	✓[f]
Adverse Events			✓
Concomitant Medications	✓	✓	✓
Urine Drug Screen	✓	✓	
Alcohol Breathalyzer	✓	✓	
Pregnancy Test (women only)	✓[b, e]	✓[b]	
Serology: (HIV, HBsAg, Hep C)	✓		
PK Assessment			✓[a]
Study Drug Administration			✓[a]
Inpatient Discharge			✓[c]

a See the Schedule for Inpatient Period Assessments (Table 5) for detail regarding times and events for the screening and baseline 12-lead safety ECG, drug administration, and PK assessments during Treatment Periods 1 to 6.
b. For all women (childbearing potential and non-childbearing potential) (serum at screening and urine thereafter).
c. After all scheduled assessments are complete and all available safety data have been reviewed by the Investigator.
d. Complete a washout period of at least 3 days and not exceeding 14 days between doses.
e. FSH for women of non-childbearing potential at screening only.
f. Glucose, and Potassium ONLY - done within 30 minutes prior to dosing and at 30 minutes and 2 and 4 hours post-dose

Table 5: Schedule of Inpatient Period Assessments[a]

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

a Twelve-lead safety ECGs will be recorded at screening, on Day -1 to confirm eligibility, within one hour prior to dosing and as scheduled above.
b Within 60 minutes of dosing
c Glucose and potassium only
[d] Complete clinical laboratory testing

Appendix 2 Administration of Study Drug

All subjects will receive four of the six treatments by random assignment to 1 of 12 predetermined treatment sequences as listed in Section 6.1 of this protocol. This is a double-blind within device study, with two different MDI devices used within the study. The Pearl Therapeutics products (BGF MDI and GFF MDI) are identical in form and function and indistinguishable from each other. The two Symbicort MDIs are identical in form and function and indistinguishable from each other; however they are different from the Pearl Therapeutics products. As such, subjects, Investigators and the sponsor will not be aware of which Pearl MDI dose is being administered and will not be aware of which Symbicort MDI dose is being administered during each of the four treatment periods. However, because the appearance of the Symbicort MDI differs from that of the Pearl Therapeutics MDIs and cannot be effectively over-laid for blinding purposes, the two Symbicort MDI treatment periods will be able to be differentiated from the four Pearl Therapeutics MDI treatment periods.

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

BGF MDI and GFF MDI Administration: A Pharmacy Manual containing BGF MDI and GFF MDI dosage preparation and administration information will be provided to the study site. For each BGF MDI and GFF MDI administration, the MDI device will be primed (four actuations to waste) in the study site pharmacy by the pharmacist and then delivered to the inpatient clinic. Just prior to dosing, subjects will again be given detailed instruction regarding the proper use of the MDI device to ensure comprehension of its use. At the time of dosing, a health care 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 BGF MDI treatment arms and one GFF MDI treatments are:

- BGF MDI 320/14.4/9.6 µg
- BGF MDI 160/14.4/9.6 µg
- BGF MDI 80/14.4/9.6 µg
- GFF MDI 14.4/9.6 µg

Symbicort MDI Administration: A Pharmacy Manual containing Symbicort MDI dosage preparation and administration information will be provided to the study site. Each Symbicort MDI should be administered by the orally inhaled route. The pharmacist will prime Symbicort MDI before using for the first time by releasing two test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, the inhaler should be primed again by shaking well before each spray and releasing two test sprays into the air away from the face.

The two Symbicort MDI treatments are:

- Symbicort MDI 320/9 µg
- Symbicort MDI 160/9 µg

The MDI dose delivery specifications for the six treatments are provided in Table 6.

Table 6: MDI Dose Delivery Specifications

Product Name & Potency	Product Strength	Dosage Form	Comments
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
BGF MDI 80/14.4/9.6 µg ex-actuator	40/7.2/4.8 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
Symbicort MDI 320/9 µg ex-actuator	160/4.5 µg/actuation	MDI	Taken as 2 inhalations
Symbicort MDI 160/4.5 µg ex-actuator	80/4.5 µg/actuation	MDI	Taken as 2 inhalations

Appendix 3 Plasma Collection, Processing and Handling (PK Samples)

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

Shipping Address:

[redacted]

ATTENTION: Sample Management

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

Appendix 4 Sponsor Signatory

Study Title: A Phase I, Randomized, Double-Blind Within Device, Single-Dose, Four-Period, Six-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Three Doses of Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (BGF MDI), One Dose of Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI), and Two Doses of Symbicort® Inhalation Aerosol in Healthy Volunteers

Study Number: PT010001-00

Final Date: Version 1.0, [redacted]

Amendment 1 Date: N/A

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

Name: [redacted]

Title: [redacted] Pearl Therapeutics Inc.

Appendix 5 Investigator's Agreement and Signature Page

Study Title: A Phase I, Randomized, Double-Blind Within Device, Single-Dose, Four-Period, Six-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Three Doses of Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (BGF MDI), One Dose of Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI), and Two Doses of Symbicort® Inhalation Aerosol in Healthy Volunteers

Study Number: PT010001-00 **Final Date:** Version 1.0, [redacted]

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

I agree:

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

Signed:_____ Date:_____

CLINICAL TRIAL PROTOCOL: PT010001-01

Study Title:	A Phase I, Randomized, Double-Blind Within Device, Single-Dose, Four-Period, Six-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Three Doses of Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (BGF MDI), One Dose of Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI), and Two Doses of Symbicort® Inhalation Aerosol in Healthy Volunteers
Study Number:	PT010001-01
Study Phase:	Phase I
Product Name:	Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (BGF MDI; PT010)
IND Number:	118313
Investigators:	Single Center
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]

Version Number		Date
Original Protocol:	Version 1.0	[redacted]
Amendment 1:	Version 1.1	

Confidentiality Statement

SUMMARY OF CHANGES AMENDMENT 1 VERSION 1.1 (PT010001-01)

The protocol is amended (Version 2.0 Dated [redacted] to include the following changes to Version 1.0 Dated [redacted]

- Cover Page (page 1): Change for Investigator's name to Single Center
- Clarification for CKD-EPI formula use on page 10. Added wording referencing the National Kidney Disease Education Program (NKDEP).
- Updated Pre Dose PK and Glucose/Potassium collection time along with Pre Dose ECG and Vital Signs to within 60 minutes from 30 minutes prior to dosing throughout the protocol.

  Original Text: Within 30 minutes of dosing
  Updated Text: Within 60 minutes of dosing
- Addition of Follow-Up Phone Call on 7 days (+7 days) from last dosing date on Period 4 on pages 20 and 42. The phone call will include assessment of any new or outstanding Adverse Events along with inquiry of any concomitant medication taken since dosing and changes to birth control.
- Updated text throughout PK sections to match the Statistical Analysis Plan (SAP).
- To account for any potential unscheduled lab draws, clarification added throughout the protocol:

  Original Text: For clinical laboratory assessment blood draws, subjects will be fasting at least 4 hours.
  Updated Text: For scheduled clinical laboratory assessment blood draws, subjects will be fasting at least 4 hours.
- Added bullet point on page 38 to include placebo device training at Day -1.
- Added wording surrounding use of surgical mask 30 minutes before and after dosing on pages 41 and 42.
- Added bullet point on page 42 to include physical exam on Period 4 only prior to discharge.
- Table of Assessments on Pages 51 and 52 updated to be consistent throughout the protocol.

SYNOPSIS

Sponsor:

Pearl Therapeutics, Inc.

[redacted]

Name of Finished Product:

- Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (Budesonide, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler; BGF MDI; PT010)
- Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler; GFF MDI; PT003)
- Budesonide and Formoterol Fumarate Dihydrate Inhalation Aerosol (Symbicort® MDI)

Name of Active Ingredients:

- Budesonide
- Glycopyrronium
- Formoterol fumarate dihydrate

Study Title:

A Phase I, Randomized, Double-Blind Within Device, Single-Dose, Four-Period, Six-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Three Doses of Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (BGF MDI), One Dose of Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (GFF MDI), and Two Doses of Symbicort® Inhalation Aerosol in Healthy Volunteers

Study Number:

PT010001-01

Study Phase: Phase I

Primary Objective(s):

The primary objective of the study is to determine a dose of budesonide that when formulated with glycopyrronium and formoterol fumarate in BGF MDI provides comparable systemic exposure [pharmacokinetics (PK)] to budesonide following administration of Symbicort MDI 320/9 µg (2 inhalations of 160/4.5 µg).

Secondary Objective(s):

The secondary objectives of the study are:

- To assess if a drug-drug interaction (DDI) occurs when budesonide is formulated with glycopyrronium and formoterol fumarate in BGF MDI compared to GFF MDI alone.
- To evaluate the safety and tolerability of the treatments administered; i.e., BGF MDI, Symbicort MDI and GFF MDI.

Study Design:

This is a healthy volunteer Phase I study with a randomized, double-blind within device, four-period, six- treatment, cross-over design. All study drugs will be administered by oral inhalation. The six treatments are:

- BGF MDI 320/14.4/9.6 µg
- BGF MDI 160/14.4/9.6 µg
- BGF MDI 80/14.4/9.6 µg
- GFF MDI 14.4/9.6 µg
- Symbicort MDI 320/9 µg
- Symbicort MDI 160/9 µg

Following determination of study eligibility, subjects will be randomized to one of 12 treatment sequences. Each treatment sequence will contain BGF MDI 320/14.4/9.6 µg, GFF MDI 14.4/9.6 µg, and Symbicort MDI 320/9 µg, and one of the remaining three treatments. At the target of 84 subjects randomized, each sequence will be used 7 times. If all subjects complete the study, the design is balanced for both period and first-order carryover effects. Treatments will be blinded within the two devices.

Study Population:

Eighty-four healthy male and female subjects are planned for enrollment in the study. Full inclusion and exclusion criteria are listed in Section 5.1 and Section 5.2, respectively.

Test Product; Dose; and Mode of Administration:

All dosing of the study drug will be by oral inhalation. The three doses of BGF MDI (320/14.4/9.6 µg, 160/14.4/9.6 µg and 80/14.4/9.6 µg), two doses of Symbicort MDI (320/9 µg and 160/9 µg), and a single dose of GFF MDI (14.4/9.6 µg) will be administered on separate test days. There are two different MDI devices used within the study. The Pearl products (BGF MDI and GFF MDI) are identical in form and function and are indistinguishable from each other. The two Symbicort MDIs are identical in form and function and are indistinguishable from each other. However, they are different from the Pearl Therapeutics products. As such, the test products will be double-blind within device. The characteristics of the three BGF MDI doses, the two Symbicort MDI doses and the GFF MDI dose that will be administered during the study are provided below:

Product Name & Potency	Product Strength	Dosage Form	Comments
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
BGF MDI 80/14.4/9.6 µg ex-actuator	40/7.2/4.8 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
Symbicort MDI 320/9 µg ex-actuator	160/4.5 µg/actuation	MDI	Taken as 2 inhalations
Symbicort MDI 160/9 µg ex-actuator	80/4.5µg/actuation	MDI	Taken as 2 inhalations

BGF MDI = Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol; GFF MDI = Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; MDI = Metered Dose Inhaler.
Note: All study drugs will be administered by oral inhalation.

Reference Therapy, Dose, and Mode of Administration:

The reference therapies are two dose levels of Symbicort MDI (320/9 µg and 160/9 µg) and a single dose level of GFF MDI (14.4/9.6 µg). All reference therapies will be administered by oral inhalation.

Duration of Treatment:

This study will include a screening period of up to 21 days and four single-dose treatment periods separated by a minimum washout period of 3 days to a maximum of 14 days for added scheduling flexibility. The planned participation in the study is between 34 and 84 days.

Pharmacokinetic Assessments: The pharmacokinetics (PK) of BGF MDI, Symbicort MDI and GFF MDI will be assessed and compared from plasma concentrations of each drug. Time points for PK blood sample collection during each of the four single-dose periods will be within 60 minutes prior to dosing and then at 2, 6, 20, and 40 minutes post dose and 1, 2, 4, 8, 10 and 12 hours post dose (see Table 4 for the Schedule of Inpatient Period Assessments). PK parameters at all doses will include C_{max}, t_{max}, $t_{½}$, AUC_{0-12}, $AUC_{0-t,}$ CL/F, Vd/F, and λ_z. Other PK parameters may be calculated, as appropriate.

Safety Assessments: The safety of BGF MDI, Symbicort MDI and GFF MDI will be assessed from physical examination findings, adverse event (AE) reporting including SAE reporting, vital signs (blood pressure, heart rate, respiratory rate and body temperature), clinical laboratory values (hematology, biochemistry, and urinalysis), and findings from 12-lead safety electrocardiograms (ECGs).

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

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

The primary endpoints are the AUC_{0-12} and C_{max} of budesonide for doses of BGF MDI compared to Symbicort MDI with most interest being in the comparison of the highest strengths. These PK parameters will be compared between relevant treatments and log transformation using mixed models repeated measures with adjustment for period and modeling of within subject correlation. Sequence will also be included in models if it explains significant variability ($p<0.10$). Estimated geometric mean ratios (GMRs) with 90% confidence intervals (CIs) will be produced and compared to bounds of 80% and 125%. The AUC_{0-12} and C_{max} of formoterol fumarate and glycopyrrolate exposure will also be compared between treatments to evaluate the potential for drug-drug interactions (DDIs).

The sample size of 84 randomized subjects provides over 90% power to demonstrate bioequivalence of budesonide AUC_{0-12} and C_{max} for the comparison of BGF MDI 320/14.4/9.6 µg to Symbicort MDI 320/9 µg under assumptions of a 5% true difference and intra-subject coefficient of variation (CV) values of 25% and 30% for AUC_{0-12} and C_{max}, respectively.

Date of Original Protocol: Version 1.0, [redacted]
Date of Protocol Amendment 1: Version 2.0, [redacted]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
AV	Atrioventricular
BGF MDI	Budesonide, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler
BMI	Body mass index
$CaCl_2$	Calcium chloride
CBC	Complete blood cell (count)
CFR	Code of Federal Regulations
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation (according to National Kidney Disease Education Program)
COPD	Chronic obstructive pulmonary disease
CRO	Contract Research Organization
CV	Coefficient of variation
DDI	Drug-drug interaction
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision
DSPC	Distearoylphosphatidylcholine
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GFF MDI	Glycopyrronium and formoterol fumarate metered dose inhaler
GGT	Gamma-glutamyltransferase

GMR	Geometric mean ratio
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HbsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HFA	Hydrofluoroalkane
HPLC/MS/MS	High Performance Liquid Chromatography Mass Spectrometry
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intra-uterine device
LABA	Long-acting β2-agonist
LAMA	Long-acting muscarinic antagonist
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
MDI	Metered dose inhaler
PCV	Packed cell volume
PK	Pharmacokinetics
RBC	Red blood cell (count)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard operating procedure
THC	Tetrahydrocannabinol
TURP	Trans-urethral resection of prostate
US	United States
WBC	White blood cell (count)

TRADEMARK INFORMATION

Trademarks not owned by Pearl Therapeutics, Inc.:

Aerolizer

Aqua

Breezhaler

Cuvposa

Foradil

Oxis

Pulmicort

Rhinocort

Robinul

Seebri

Symbicort

Turbuhaler

Respules

1 INTRODUCTION

Pearl Therapeutics is developing budesonide, glycopyrronium, and formoterol fumarate (BGF) metered dose inhaler (MDI) as a long-term twice daily (BID) morning and evening maintenance treatment for the reduction in the frequency of exacerbations and improvement in airflow obstruction in patients with moderate to very severe chronic obstructive pulmonary disease (COPD) who are at risk of COPD exacerbations. The Pearl Therapeutics internal product code for BGF MDI is PT010.

Pearl Therapeutics has not conducted any nonclinical or clinical studies with the triple combination product. However, budesonide, glycopyrronium, and formoterol fumarate are components (alone or in combination) of approved inhalation products for treatment of patients with COPD and their safety and efficacy are well characterized. Clinical and nonclinical studies conducted with the Pearl Therapeutics dual combination product, glycopyrronium and formoterol fumarate (GFF) MDI and its individual components, glycopyrronium (GP) MDI and formoterol fumarate (FF) MDI and clinical and nonclinical studies conducted with Symbicort® MDI support the evaluation of BGF MDI in this initial Phase I study in healthy volunteers (Study PT010001). GFF MDI, GP MDI and FF MDI are currently being evaluated in Phase III clinical studies in patients with COPD. Clinical studies conducted with Symbicort MDI are also being referenced, as this is the only product in the US containing budesonide that is approved for use in patients with COPD.

1.1 Chronic Obstructive Pulmonary Disease

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. COPD 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), 2013].

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are β2-agonists, anticholinergics, and methylxanthines used as monotherapy or in combination. Treatment with long-acting bronchodilators is more convenient and more effective at producing maintained symptom relief than treatment with short-acting bronchodilators. Combining bronchodilators from different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator (GOLD, 2013). Long-acting β2-agonists (LABAs) and long-acting muscarinic antagonist (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 and quality of life and reduces the frequency of exacerbations in COPD patients with a forced expiratory volume in 1 second (FEV_1) value of <60% of predicted. Withdrawal from treatment of ICS may lead to exacerbations in some patients. When combined with a LABA, an ICS is

more effective than the individual components in improving lung function, quality of life and reducing exacerbations in patients with moderate to very severe COPD. Furthermore, the addition of a LABA/ICS combination to tiotropium improves lung function and quality of life and may further reduce exacerbations, but more studies of triple therapy are needed (GOLD, 2013).

1.2 Glycopyrronium

Glycopyrronium (the active moiety of glycopyrronium bromide, also referred to as glycopyrrolate) is a LAMA that exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. Glycopyrronium is approved in many countries in multiple formulations for different indications, including COPD.

An inhaled formulation of glycopyrronium (Seebri® Breezhaler® Inhalation Powder, glycopyrronium bromide) was recently approved throughout the European Union (EU) and in Canada, Australia and Japan. In the EU, Seebri Breezhaler is approved as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. The recommended dose is 44 µg of glycopyrronium (equivalent to 55 µg of glycopyrronium bromide) administered once daily (QD) using the Seebri Breezhaler inhaler.

The clinical development program for Seebri Breezhaler included 12 clinical studies, five Phase I studies, four Phase II clinical studies and three Phase III clinical studies. Overall, the clinical development program included a total of 1,361 patients with COPD exposed to Seebri Breezhaler 44 µg QD, with a total of 842 patients exposed for ≥26 weeks and 428 patients exposed for ≥38 weeks [Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Seebri Breezhaler, 2012]. In addition to the published data with Seebri Breezhaler (also referred to as NVA237), there is also a large body of published data evaluating the safety and efficacy of inhaled glycopyrronium in healthy volunteers, patients with COPD and patients with asthma.

Glycopyrronium is also approved as Robinul® in the United States (US) and many countries worldwide as an intravenous/intramuscular (IV/IM) injection or as an oral tablet and is indicated for systemic administration in adults for use as a preoperative antimuscarinic to reduce salivary, tracheobronchial, and pharyngeal secretions; to reduce the volume and free acidity of gastric secretions; and to block cardiac vagal inhibitory reflexes during induction of anesthesia and intubation. Robinul is also indicated as adjunctive therapy for the treatment of peptic ulcer disease when rapid anticholinergic effect is desired. While the recommend dose varies across these indications, for peptic ulcer disease the usual recommended dose of Robinul Injection (also referred to as Glycopyrrolate Injection) is 0.2 mg at 4 hour intervals, administered 3 or 4 times daily by the IV or IM route. Where more profound effect is required, 0.4 mg may be given [Robinul US Product Information, 2007]. Glycopyrronium is also approved as an oral tablet (Robinul and Robinul Forte). Robinul (glycopyrrolate 1 mg tablets) and Robinul Forte (glycopyrrolate 2 mg tablets) are indicated for use in adults as an adjunctive therapy in peptic ulcer disease and are dosed BID to three times daily (TID) up to 6 mg per day (Robinul and Robinul Forte US Product Information, 2011).

Glycopyrronium is also approved in the US as an oral solution (Cuvposa®) which is indicated to reduce chronic severe drooling in patients aged 3 to 16 with neurologic conditions associated

with problem drooling (e.g., cerebral palsy). The maximum recommended dose of Cuvposa is 0.1 mg/kg TID, not to exceed 1.5 to 3 mg per dose.

1.3 Formoterol Fumarate

Formoterol fumarate is a potent and selective LABA approved in the US (e.g., Foradil® Aerolizer®) and worldwide (e.g., Oxis® Turbuhaler®, Foradil) for use in asthma and COPD. Formoterol fumarate is also approved in the US and worldwide in combination with budesonide (e.g., Symbicort MDI, Symbicort Turbuhaler) for use in patients with asthma and COPD. When inhaled, formoterol fumarate acts locally in the lung as a bronchodilator. Formoterol fumarate stimulates β2-adrenoreceptors in the airways, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction.

In patients with COPD, formoterol fumarate is typically administered at an orally inhaled dose of 12 µg BID with doses up to 24 µg BID approved in some countries. Although formoterol fumarate is classified as a LABA, it has a rapid onset of action similar to short-acting β2-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 patients with COPD have demonstrated that the onset of action with formoterol fumarate is faster than with anticholinergic 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 2,500 patients demonstrated that formoterol fumarate is effective and well-tolerated in patients with COPD (Dahl, 2001; Rossi, 2002; Aalbers, 2002; Campbell, 2005; Campbell, 2007).

1.4 Budesonide

Budesonide is a well-established corticosteroid approved worldwide in both intranasal and inhaled formulations. Inhaled budesonide formulations currently approved in the US include Rhinocort® Nasal Inhaler, Rhinocort Aqua® Nasal Spray, Pulmicort® Turbuhaler®, Symbicort Inhalation Aerosol (Symbicort MDI), and Pulmicort Respules®.

Inhaled budesonide is approved for use in patients with COPD when combined with formoterol fumarate dihydrate in Symbicort MDI. In the US, Symbicort is available as an MDI and only the 320/9 µg dose administered as two inhalations of 160/4.5 µg strength (BID) is approved for use in patients with COPD. Symbicort MDI 320/9 µg BID is indicated as a maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and emphysema.

Inflammation is a component in the pathogenesis of COPD. The predominant inflammatory cells in COPD include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of ICS on pulmonary and systemic inflammation in patients with COPD are controversial and their role in the management of stable COPD is limited to specific indications. Regular treatment with ICS has been shown to improve symptoms, lung function and quality of life and reduce the frequency of exacerbations in COPD patients with a FEV_1 value <60% of predicted (GOLD, 2013).

In clinical studies, Symbicort MDI 320/9 µg administered BID demonstrated significant improvements in lung function compared to budesonide MDI 320 µg BID, formoterol fumarate

(Oxis Turbuhaler) 9 µg BID, or placebo in patients with COPD. In the clinical studies, improvements in secondary endpoints of morning and evening peak expiratory flow and reduction in rescue medication use were supportive of the efficacy of Symbicort MDI 320/9 µg. (Symbicort Inhalation Aerosol Prescribing Information, 2012; Rennard, 2009; Tashkin, 2008). The GOLD guidelines acknowledge that combination therapy with an ICS and LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients to moderate to very severe COPD (GOLD, 2013).

1.5 Pearl Therapeutics' BGF MDI

Pearl Therapeutics is developing BGF MDI using its porous particle technology platform. The same porous particle technology platform is used for GFF MDI, GP MDI and FF MDI. This technology is based on spray dried porous particles comprised of distearoylphosphatidylcholine (DSPC) and calcium chloride ($CaCl_2$) that are co-suspended with micronized active pharmaceutical ingredients (APIs) in an hydrofluoroalkane (HFA) propellant to form stable suspension based MDIs. The fraction of the APIs mixed with the porous particles can be adjusted across a wide range of doses. The unique attributes of this technology enables reproducible administration of very low doses of potent therapeutics.

1.6 Study Rationale

BGF MDI is a novel fixed-dose triple combination MDI product formulated with budesonide, glycopyrronium, and formoterol for use in patients with COPD. As described in the GOLD guidelines, in some patients, the addition of a LABA/ICS to a LAMA improves lung function, quality of life and may further reduce exacerbations. As per GOLD guidelines, patients categorized in the D group (those with many symptoms and high risk of exacerbations) the first choice of treatment is an ICS/LABA or LAMA with some evidence for triple therapy. Pearl Therapeutics has planned this study to evaluate the pharmacokinetics following three single doses of three strengths of BGF MDI relative to a single dose of two strengths of Symbicort MDI and a single dose of one strength of GFF MDI.

Symbicort MDI 320/9 µg (given as 2 inhalations of 160/4.5 µg) BID is indicated for maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and emphysema. This study is being conducted to identify a BGF MDI dose that provides comparable systemic levels of budesonide to the dose of Symbicort MDI approved for COPD (320/9 µg). Three doses of BGF MDI and two doses of Symbicort are included in the study to allow a Finney (Finney, 1978) method or similar approach to be conducted to identify equivalent doses across both formulations. GFF MDI is also included in the study to allow the assessment of any drug-drug interactions (DDI) in BGF MDI when budesonide is added to GFF MDI.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of the study is to determine a dose of budesonide that when formulated with glycopyrronium and formoterol fumarate in BGF MDI provides comparable systemic exposure [pharmacokinetics (PK)] to budesonide following administration of Symbicort MDI 320/9 µg (2 inhalations of 160/4.5 µg).

2.2 Secondary Objective(s)

The secondary objectives of the study are:

- To assess if a drug-drug interaction (DDI) occurs when budesonide is formulated with glycopyrronium and formoterol fumarate in BGF MDI compared to glycopyrronium, and formoterol fumarate only in GFF MDI.
- To evaluate the safety and tolerability of the treatments administered; i.e., BGF MDI, Symbicort MDI and GFF MDI.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

This study is being conducted in healthy volunteers. Therefore, efficacy will not be evaluated.

3.2 Safety Endpoints

The safety of BGF MDI, Symbicort MDI and GFF MDI will be assessed from physical examination findings, adverse event (AE) reporting including SAE reporting, vital signs (blood pressure, heart rate, respiratory rate and body temperature), clinical laboratory values (hematology, biochemistry, and urinalysis), and findings from 12-lead safety electrocardiograms (ECGs).

3.3 Pharmacokinetic Endpoints

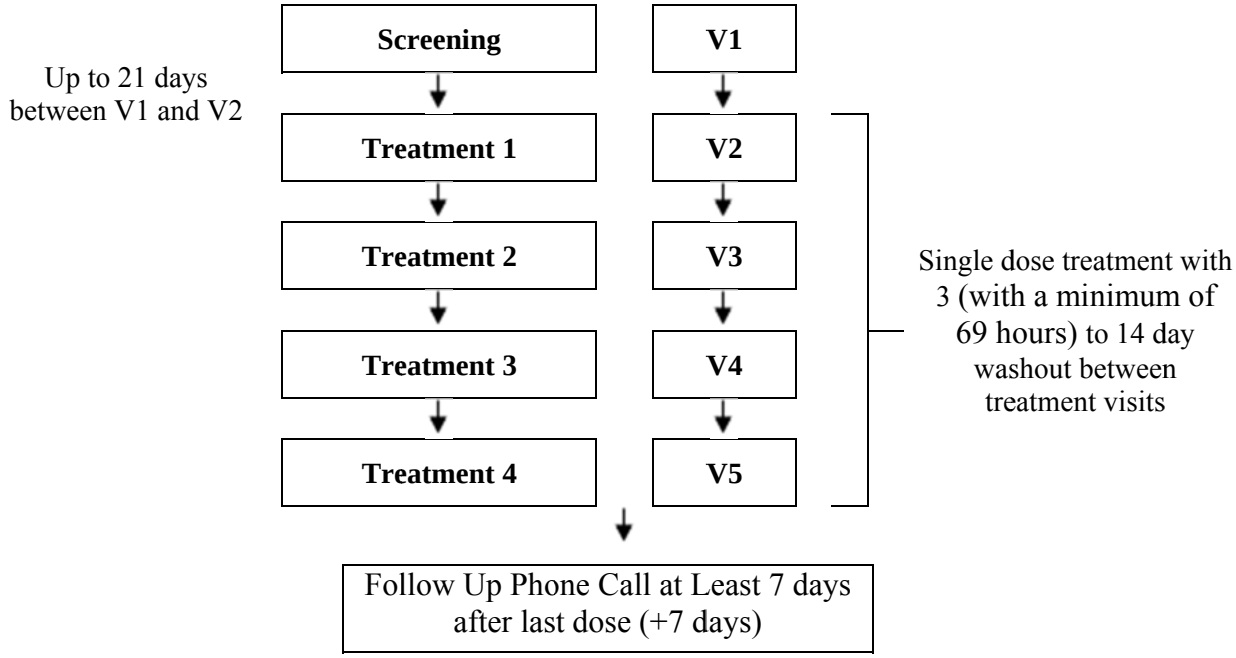
The PK of BGF MDI, Symbicort MDI and GFF MDI will be assessed and compared from plasma concentrations of each drug. Time points for PK blood sample collection during each of the four single-dose periods will be within 60 minutes prior to dosing and then at 2, 6, 20, and 40 minutes post dose and 1, 2, 4, 8, 10 and 12 hours post dose (see Table 4 for the Schedule of Inpatient Period Assessments). PK parameters at all doses will include C_{max}, t_{max}, $t_{½}$, AUC_{0-12}, $AUC_{0-t,}$ CL/F, Vd/F, and λ_z. Other PK parameters may be calculated, as appropriate.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a single-dose healthy volunteer Phase I study with a randomized, double-blind within device, four-period, six-treatment, crossover design. The overall study design is summarized and illustrated in Figure 1.

Figure 1. Study Design



Subjects who provide informed consent, undergo screening procedures and qualify for the study will be randomized to one of 12 treatment sequences. Each treatment sequence will contain BGF MDI 320/14.4/9.6 µg, GFF MDI 14.4/9.6 µg, and Symbicort (section 6.17) MDI 320/9 µg and one of the remaining three treatments. At the target of 84 subjects randomized, each of the 12 sequences will be used 7 times. If all subjects complete the study, the design is balanced for both period and first-order carryover effects. Treatments will be blinded within the two devices.

There are two different MDI devices used within the study. The Pearl products (BGF MDI and GFF MDI) are identical in form and function and are indistinguishable from each other. The two Symbicort MDIs are identical in form and function and are indistinguishable from each other. However, they are different from the Pearl Therapeutics products. As such, the test products will be double-blind within device.

Each inpatient treatment session will be separated by an outpatient washout period of at least 3 calendar days (with a minimum of 69 hours) and not exceeding 14 days between doses. For each treatment period, subjects will report to the clinic on the day prior to each dosing day (Day -1: admission day), at which time continuing eligibility will be assessed. If the subject continues to meet eligibility criteria, the subject will be admitted into the inpatient unit.

Safety data will be closely monitored and baseline and post dosing serial blood draws for PK analysis (see Table 4 in Appendix 1) will be obtained during each inpatient treatment period. After all scheduled assessments are completed and all available safety data have been reviewed by the Principal Investigator, subjects will be discharged from the clinic. Following each treatment period, subjects will return to the clinic after their washout period of at least 3 calendar days (with a minimum of 69 hours) between doses for their next treatment period until all four treatment periods have been completed. Other safety assessments will be obtained as listed in Table 4 located in Appendix 1. A follow up phone call will be conducted 7 days (+7 days) after completion of the last dose date on Period 4.

4.2 Rationale for Study Design and Control Group

This study is a Phase I, single-dose, four-period, six-treatment, crossover study that will assess the safety and PK of three doses of BGF MDI and two doses of Symbicort MDI and one dose of GFF MDI in healthy subjects. The two Symbicort MDI dose levels and the one GFF MDI dose level will serve as active comparators, which will allow for differentiation of any PK and tolerability issues associated exclusively with each of the three BGF MDI doses.

This protocol includes the following PK sampling times: within 60 minutes pre-dose and 2, 6, 20 and 40 minutes and 1, 2, 4, 8, 10 and 12 hours post-dose. The rationale for the PK sample collection times are given below.

PK considerations

1. Budesonide: Orally inhaled budesonide is rapidly absorbed in the lungs and peak concentration is typically reached within 20 minutes. Thus, from a PK perspective, the 2, 6, 20 and 40 minute time points will provide adequate data to describe C_{max} and t_{max} for budesonide both in BGF MDI and Symbicort MDI at the doses that will be studied.
2. Glycopyrronium: Based on previous studies of GP that included PK assessments, peak plasma concentrations occurred rapidly after GP MDI inhalation (data on file) with median time to maximum concentration (C_{max}) generally occurring within 6 minutes (0.100 hour) after dosing. Thus, from a PK perspective, the 2, 6, 20 and 40 minute time points will provide adequate data to describe C_{max} and t_{max} for GP both in BGF MDI and GFF MDI at the doses that will be studied.
3. Formoterol fumarate: Based on previous studies of FF that included PK assessments, peak plasma concentrations occurred within 1 hour after FF MDI inhalation (data on file) with median time to C_{max} occurring about 0.933 hours after FF MDI 9.6 µg dosing. From a PK perspective, the 20 min, 40 min, 1 hour and 2 hour time points will provide adequate data to describe C_{max} and t_{max} for FF in BGF MDI, Symbicort MDI and GFF MDI at the doses that will be studied.

Conclusion

The planned PK sampling times provide an adequate selection of PK data points required to describe the PK of budesonide, GP and FF in terms of t_{max} and C_{max} values for each MDI component as well as to estimate AUC_{0-12}.

4.3 Study Duration and Dates

This study will include a screening period of up to 21 days and four single-dose treatment periods separated by a minimum washout period of 3 days to a maximum of 14 days for added scheduling flexibility. A follow up phone call will be conducted at least 7 days (+7 days) after completion of the last dose date on Period 4. The maximum participation in the study is between 34 and 84 days.

5 STUDY POPULATION SELECTION

Eighty-four healthy male or female subjects will be enrolled in this study. Subjects who withdraw from the study after receiving at least one single dose treatment will not be replaced. Subjects who are re-evaluated will maintain 1 screening number throughout the study.

5.1 Inclusion Criteria

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

1. Signed and dated IRB-approved informed consent form (ICF) before any protocol-specific screening procedures are performed.
2. Male and female subjects between the ages of 18 and 45 years (inclusive).
3. Be in good general health as determined by a thorough medical history and physical examination, ECG, vital signs and clinical laboratory evaluation.
4. Willing and able to complete all study assessments and procedures.
5. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception from the Screening Period through 14 days after the Final Study Visit: hormonal contraception, condom with spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, injectable contraceptive, or intra-uterine device (IUD). 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 for 14 days after the final visit as a safety precaution.
6. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months, do not require contraception during the study. Post- menopausal must be confirmed by a serum FSH test at screening and the reason must be documented in the medical history eCRF.
7. Males with female partners of childbearing potential must agree to use a highly effective, medically acceptable form of contraception from the Screening Period through at least 7 days after the Final Study Visit. 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 for 7 days from the final visit as a safety precaution.
8. Have a BMI between 18.5 and 32 kg/m^2 (inclusive) and a minimum weight of 50 kg at the screening visit.
9. Results of complete blood cell (CBC) count (including white blood cell (WBC) 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 range or determined to be not clinically significant by the Investigator. Specifically, serum potassium must be ≥3.5 mmol/L and serum

magnesium ≥0.8 mmol/L. Urinalysis testing should be within the normal range or determined to be not clinically significant by the Investigator.

5.2 Exclusion Criteria

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

1. Pregnant or nursing female subjects or subjects who are trying to conceive.
2. For female subjects, a positive serum human chorionic gonadotropin (hCG) test at screening or a positive urine hCG at admission for any of the five treatment periods.
3. Subjects with clinically significant neurologic, cardiovascular, hepatic, renal, endocrinologic, pulmonary, hematological, psychiatric, or other medical illness that would interfere with participation in this study.
4. Subjects with a history of ECG abnormalities including PR>220 msec; QRS complex >110 msec; QTcF>450 msec; or any significant morphological changes other than nonspecific T-wave changes. In addition, subjects who demonstrate any of these or any other significant 12-lead ECG abnormalities prior to the first treatment period (i.e., 12-lead ECGs performed at screening, baseline, or pre-dose of the first treatment period) 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 with the inability to coordinate the use of the placebo MDI under supervision from site staff.
7. Cancer: Subjects who have cancer that has not been in complete remission for at least 5 years. Note: Subjects with squamous cell carcinoma or basal cell carcinoma of the skin are eligible, if in the opinion of the Investigator, the condition has been adequately worked up, is clinically controlled and the subject's participation in the study would not represent a safety concern.
8. Supine blood pressure >140/90 mm/Hg or resting heart rate ≥100 bpm at screening, baseline (Day -1) or pre-dose of the first treatment period.
9. Subjects with symptomatic prostatic hypertrophy that is clinically significant in the opinion of the Investigator.
10. Subjects with a trans-urethral resection of the prostate (TURP) or full resection of the prostate within six months prior to Visit 1 are excluded from the study.
11. Subjects with bladder neck obstruction or urinary retention that is clinically significant in the opinion of the Investigator.
12. Subjects with a diagnosis of glaucoma that in the opinion of the Investigator has not been adequately treated. All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective β-blockers such as betaxolol, carteolol, levobunolol, metipranolol, and timolol.

13. History of substance-related disorders (with the exception of caffeine-related and nicotine-related disorders) as defined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) within 1 year of screening.
14. History of smoking or the use of nicotine containing products within 3 months of screening by self-reporting.
15. A positive alcohol breathalyzer or urine drug screen for drugs of abuse at the screening visit or at the beginning of each inpatient period.
16. Treatment with an investigational drug within 30 days or five half-lives (whichever is longer) prior to the beginning of the screening period.
17. Treatment with any prescription or non-prescription drugs (including vitamins, herbal, and dietary supplements) within seven days or five half-lives of the screening visit, whichever is longer. Acetaminophen will be permitted at doses of ≤2 grams/day.
18. Subjects with a history of an allergic reaction or hypersensitivity to any drug or to any component of the formulation(s) used in this study.
19. Blood collection of greater than 500 mL within 56 days prior to screening.
20. Seropositivity for human immunodeficiency virus (HIV) at screening.
21. Positive for hepatitis B surface antigen (HbsAg) or positive hepatitis C antibody at screening.
22. Subjects with a chronic medical condition that requires ongoing treatment with medication.
23. Subjects with a history of major surgery within four weeks or minor surgery within 2 weeks of drug administration.
24. 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 four weeks of drug administration.
25. Any other condition and/or situation that causes the Investigator to deem a subject unsuitable for the study (e.g., due to expected study medication non-compliance, inability to medically tolerate the study procedures, or a subject's unwillingness to comply with study-related procedures).
26. Subjects with abnormal-GFR (eGFR<90 mL/min) using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI).

5.3 Subject Identification

All subjects who undergo screening will be assigned a unique screening identification number at the Screening visit (Visit 1). Only subjects continuing to meet entry inclusion/exclusion criteria at Period 1 will be assigned a unique subject randomization number.

5.4 Prior, Concomitant, and Prohibited Medications

Investigational therapies are not permitted within 30 days or five half-lives (whichever is longer) prior to beginning the screening period. All medications approved for control of intraocular pressure are allowed including topical ophthalmic non-selective β-blockers such as betaxolol, carteolol, levobunolol, metipranolol, and timolol. Otherwise, the use of prescription or over-the-counter medications within 7 days or five half-lives (whichever is longer) prior to beginning the screening period is not permitted. Acetaminophen will be permitted at doses of ≤2 grams/day as determined to be necessary by the Investigator. With the exception of treatments for control of intraocular pressure, ongoing treatment for chronic conditions will not be allowed.

Major surgical interventions are not permitted within four weeks of study drug administration and minor surgical interventions are not allowed within two weeks of study drug administration. Any medications that were being taken prior to signing the informed consent form (ICF) will be documented as prior study medications and must be stopped prior to entry.

5.5 Other Restrictions, Illicit Drugs or Drugs of Abuse

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

Illicit drugs or drugs of abuse will not be allowed from the within 1 year of Screening (Visit 1) to whenever the subject discontinues the study.

Subjects are not allowed to consume grapefruits or grapefruit juice throughout the study.

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

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. Treatments will be blinded in terms of dose administered within the two devices. The Pearl Therapeutics products (BGF MDI and GFF MDI) are identical in form and function and indistinguishable from each other. The two Symbicort MDIs are identical in form and function and indistinguishable from each other; however they are different from the Pearl Therapeutics products. The exception to this is if a subject is assigned to one of the eight treatment sequences which consists of only one Symbicort MDI treatment. In this case, the dose will be known to be equal to 320/9 µg but only after all periods are complete. The characteristics of the three BGF MDI doses, the two Symbicort MDI doses and the GFF MDI dose that will be administered during the study are provided in Table 1.

An unblinded pharmacist will be provided with a written randomization scheme for allocation of subjects to 1 of 12 treatment sequences and to manage the distribution of clinical supplies. The study will be conducted at a single center, and subjects will be randomized to 1 of 12 treatment sequences, as listed below where A, B, and C represent BGF MDI 320/14.4/9.6 µg, Symbicort MDI 320/9 µg, and to GFF MDI 14.4/9.6 µg by random assignment, and D, E, and F represent BGF MDI 160/14.4/9.6 µg, BGF MDI 80/14.4/9.6 µg, and Symbicort MDI 160/9 µg by random assignment. Seven of the planned 84 subjects will be included in each treatment sequence. The design is balanced for period and first order carryover effects.

Sequence 1: ABCD	Sequence 7: CAEB
Sequence 2: BDAC	Sequence 8: ECBA
Sequence 3: CADB	Sequence 9: ABCF
Sequence 4: DCBA	Sequence 10: BFAC
Sequence 5: ABCE	Sequence 11: CAFB
Sequence 6: BEAC	Sequence 12: FCBA

For each subject, single dose administration of study drug during each of the four treatment periods should occur at approximately the same time of day.

6.2 Dispensing Study Drug

All subjects will receive BGF MDI 320/14.4/9.6 µg, GFF MDI 14.4/9.6 µg, and Symbicort MDI 320/9 µg and one of the remaining three treatments by random assignment to 1 of 12 predetermined treatment sequences (see Section 6.1). At screening, subjects will be instructed in the proper use of an MDI using a bulk-supplied placebo MDI and at that time, must demonstrate the ability to coordinate use of the MDI.

For each MDI administration, the MDI device will be primed in the study site pharmacy by the pharmacist and then delivered to the inpatient clinic. Just prior to dosing, subjects will again be given detailed instruction regarding the proper use of the MDI device to ensure comprehension

of its use. At the time of dosing, a health care provider will be present to ensure that the required number of activations of the MDI device is properly administered by the subject.

6.3 Product Descriptions

The BGF MDI active drug substances are budesonide, glycopyrronium, and formoterol fumarate dihydrate. Symbicort MDI 320/9 µg and 160/9 µg and GFF MDI 14.4/9.6 µg are active controls.

Investigational materials will be provided by Pearl Therapeutics as summarized in Table 1.

Table 1: Product Descriptions

Product Name & Potency	Product Strength	Dosage Form	Comments
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
BGF MDI 80/14.4/9.6 µg ex-actuator	40/7.2/4.8 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
Symbicort MDI 320/9 µg ex-actuator	160/4.5 µg/actuation	MDI	Taken as 2 inhalations
Symbicort MDI 160/9 µg ex-actuator	80/4.5µg/actuation	MDI	Taken as 2 inhalations

BGF MDI = Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol; GFF MDI = Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; MDI = Metered Dose Inhaler.
Note: All study drugs will be administered by oral inhalation.

Following screening and determination of eligibility, dosing will be spread over four single-dose treatment periods using 12 treatment sequences. The treatment and study visit schedule is illustrated in Figure 1 located in Section 4.1.

6.4 Primary Packaging and Labeling Information

Study drug will be provided as packaged supplies. Each subject will receive one dose of each of four treatments.

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

Symbicort MDI: Each of the strengths of Symbicort MDI are supplied as a pressurized aluminum canister with an attached counting device, a red plastic actuator body with a white

mouthpiece, and attached grey dust cap. Each 120 actuation canister has a fill weight of 10.2 grams. Each canister is packaged in a foil overwrap pouch with desiccant sachet and placed in a carton. Each carton contains one canister and a Medication Guide.

6.5 Unblinding Procedures

Pearl Therapeutics will provide disclosure envelopes with the clinical supplies for the purpose of unblinding. The Investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. Whenever possible, the Investigator must first discuss options with the Medical Monitor or appropriate study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the Investigator must notify Pearl Therapeutics 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

BGF MDI and GFF MDI: Prior to dispensing, BGF MDI and GFF MDI should be stored protected with foil overwrap and desiccant at room temperature [20 to 25°C (68 to 77°F)]; excursions to the range of 15 to 30°C (59 to 86°F) are permitted. After the product is removed from the foil overwrap, it should be stored at room temperature [20 to 25°C (68 to 77°F)]; excursions to the range of 15 to 30°C (59 to 86°F) are permitted.

Symbicort MDI: Store at controlled room temperature [20 to 25°C (68 to 77°F)] and the inhaler should be stored in the upright position with the mouthpiece down. The canister should be at room temperature before use and shake well for 5 seconds. Do not expose to heat or open flame, including the sun. Exposure to temperatures over 120ºF may cause bursting. Do not puncture or incinerate even when empty.

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

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

Instructions regarding the administration of study drug are provided in Appendix 2.

6.8 Drug Accountability/Return of Clinical Supplies

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

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

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

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

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

7 STUDY PROCEDURES

7.1 Informed Consent

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

7.2 Inclusion/Exclusion Criteria

Eligibility screening of healthy subjects will be completed within 21 days prior to administration of the first study drug and will be documented on the eCRF. Confirmation of eligibility will be performed at each clinic admission (Day -1) for each of the four treatment periods.

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

7.3 Medical History

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

7.4 Physical Examination

A complete physical examination including height and weight will be performed at the time of screening (height and weight at screening only) and at the final visit at the completion of the fourth treatment period. The findings of each examination will be recorded on the source documents and clinically significant abnormalities will be recorded on the eCRF. The physical examination will include:

- Documentation of height
- Documentation of weight
- General appearance
- Head, eyes, ears, nose, and throat
- Respiratory
- Cardiovascular
- Musculoskeletal
- Abdomen
- Neurologic
- Extremities
- Dermatologic
- Lymphatic

7.5 Vital Signs

Vital sign determinations, including blood pressure, heart rate, respiratory rate and body temperature will be performed after a 5 minute supine period at the screening visit, on the day of each clinic admission (Day -1) and on each treatment day (Day 1) within 60 minutes prior to administration of study drug and 30 minutes, 2 hours and 12 hours post administration of study drug (Table 4 located in Appendix 1).

7.6 Electrocardiography

Twelve-lead ECGs will be recorded at screening, on each clinic admission day (Day -1) of each treatment period. On each treatment day (Day 1), 12-lead ECGs will be obtained within one hour prior to dosing (baseline) and at 30 minutes and 2 and 12 hours post dosing (see Table 4 in Appendix 1). Subjects should be supinely resting for at least 5 minutes before and during the ECG recording procedure. Subjects with any ECG abnormalities should be evaluated by the Investigator to determine if each abnormality is clinically significant. All clinically significant abnormalities will be reported as AEs and followed closely by the Investigator in order to assure the safety of the study subject.

7.7 Clinical Laboratory Tests

7.7.1 Laboratory Parameters

Laboratory testing (hematology with differential, serum chemistry and urinalysis) will be performed using standard methods. Blood and urine samples for the clinical laboratory tests listed in Table 2 will be collected at the screening visit and on the day of clinic admission (Day -1). At 12 hours post administration of study drug on Day 1 during each of the four treatment periods, serum chemistry and hematology will be collected. In addition, blood will be drawn for glucose and potassium level determinations within 60 minutes prior to dosing and at 30 minutes, 2 hours and 4 hours post administration of study drug on Day 1 (see Table 4 located in Appendix 1). Subjects must be fasting for at least 4 hours prior to any scheduled clinical laboratory assessment blood draw. Meals during the dosing day of each treatment period (Day 1) will be standardized after the 4 hour post dose clinical laboratory draw. There are no restrictions regarding clear fluid intake.

Table 2: List of Laboratory Tests

Hematology	Blood Chemistry	
Hematocrit*	Creatinine**	Bilirubin (direct)
Hemoglobin	Potassium (K+)***	AST
Platelet count	Sodium (Na+)	ALT
Red blood cell (RBC) count	Chloride (Cl-)	Gamma-glutamyltransferase (GGT)
WBC count	Magnesium (Mg++)	Alkaline phosphatase
WBC differential	Calcium	Total Protein
Mean cell volume (MCV)	Inorganic phosphate	Albumin
Mean cell haemoglobin (MCH)	Glucose***	
MCH concentration (MCHC)	Urea	
	Bilirubin (Total)	

*Packed cell volume (PCV)
**Serum creatinine value will be used to calculate eGFR using CKD-EPI.
***Additionally, within 60 minutes prior to dosing and at 30 minutes, 2 hours and 4 hours post dose of each treatment period

Urinalysis: Macroscopic examination routinely including specific gravity, pH, protein, glucose, ketones, blood and urobilinogen. A microscopic examination will be performed if warranted based on macroscopic results.

Urine drug screen: A urine sample will be collected and analyzed (positive or negative) for drugs of abuse including amphetamine, opiate, cocaine, barbiturates, benzodiazepines, and marijuana [tetrahydrocannabinol (THC)].

Breathalyzer Test: A breathalyzer test will be performed for the presence of alcohol (positive or negative).

Serology: Testing for HbsAg, Hepatitis C antibody and HIV will be performed at the screening visit 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 the screening visit and urine hCG test at admission for each of the four treatment periods.

For females of non-childbearing potential: A serum hCG test at the screening visit and urine hCG test at admission for each of the four treatment periods. In addition, a serum, FSH test for confirmation of non-childbearing status will be performed at screening only.

7.7.2 Sample Collection, Storage, and Shipping

Detailed instructions for laboratory sample collection, processing, and shipping instructions will be provided in the [redacted] laboratory manual.

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

7.8 Pharmacokinetic Assessments

Pharmacokinetic sampling will occur in conjunction with treatment periods 1, 2, 3 and 4.

Approximately 10 mL of whole blood will be collected within 60 minutes prior to dose administration and at 2, 6, 20 and 40 minutes and 1, 2, 4, 8, 10 and 12 hours post dose administration. Samples will be collected via an indwelling intravenous cannula [per the study site's Standard Operating Procedure (SOP)] or, if necessary, by direct venipuncture into vacuum collection tubes (for example Vacutainer 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 less than or equal to -60°C. Refer to Appendix 3 for plasma collection, storage and handling.

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

Sample collections will be scheduled for the nominal time point and actual collection times recorded in the source documents. Refer to Appendix 1, Table 4.

7.9 Adverse Events Assessments

7.9.1 Performing Adverse Event Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's eCRF and on the AE Reporting Form. If an AE is classified as "serious" as described in Section 7.9.6.1, it must be reported to Pearl Therapeutics or its designee no later than 24 hours after the Investigator recognizes/classifies the event as a SAE.

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

AEs will be collected from the time of administration of the first dose of study drug to the time of study termination, or study exit. For ongoing AEs at the time of the Final Visit, study termination, or study exit, additional data, such as AE resolution date, will be collected and reported to Pearl Therapeutics. If this data is collected after the study database is locked, it will be reported to Pearl Therapeutics, but will not be included in the study database.

7.9.2 Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonisation (ICH) and the U.S. CFR [21 CFR 312.32] 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.

AEs include, but are not limited to:

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

An AE does not include:

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

AEs that occur between the time the subject signs the ICF for the study and the time when that subject is randomized will be summarized as medical history and not as study AEs unless the event meets the definition of a SAE as defined in Section 7.9.6.1.

AE's that occur during a washout period will be attributed to the most recent study drug that was administered.

7.9.3 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.

7.9.4 Relationship

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

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

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

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

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

7.9.5 Clinical Laboratory Adverse Events

Many laboratory abnormalities observed during the course of a study will be included under a reported AE describing a clinical syndrome (e.g., elevated blood urea nitrogen [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 (i.e., concomitant medication or therapy).
- Any 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.

7.9.6 Serious Adverse Events (SAEs)

7.9.6.1 Definition

A SAE is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes:

- Death

- Life-threatening AE
- Hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

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

7.9.6.2 Reporting SAEs

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

This verbal and faxed report must be followed no later than three working days by a written report **signed by the Investigator**. The information in both the initial report and follow-up report(s) will also be captured in the electronic database. The Sponsor is responsible for submitting the report to all applicable regulatory authorities.

Contact the Medical Safety Physician for safety reporting at:

PEARL THERAPEUTICS, INC.
Business Hour Phone: [redacted]
After Hours Phone: [redacted]
Fax Reports Phone: [redacted]

7.9.6.3 Supplemental Investigation of SAEs

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

7.9.6.4 Post Study Follow-Up of Adverse Events

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

AEs ongoing at the Follow-up/Final Visit will be followed for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes or resolves. If resolved, a resolution date should be reported to Pearl Therapeutics. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals as is practical.

7.9.6.5 Notification of Post Study SAEs

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

7.9.6.6 IRB Notification of SAEs

The Investigator is responsible for promptly notifying her/his IRB/IEC of all SAEs, including any follow-up information, occurring at her/his site and any SAE regulatory report, including any follow-up reports that she/he 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 ICF or other measures based on its review of an SAE report.

7.9.6.7 Health Authority Safety Reports

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

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

IRB/IEC as soon as possible. Documentation of the submission to the IRB/IEC must be retained for each safety report.

7.9.7 Overdose

An overdose is defined as a dose greater than the highest dose level of each study drug evaluated in this study as described in Section 6.3 of the protocol (Product Descriptions), which 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 documentation may include, but not be limited to the Investigators Brochure.

7.9.8 Pregnancy

Any pregnancy that occurs from screening until study completion must be reported to Pearl Therapeutics.

To ensure subject safety, each pregnancy must be reported to Pearl Therapeutics within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child.

7.9.9 Treatment-Emergent Adverse Events

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

7.10 Concomitant Medication Assessments

The Investigator or designated qualified personnel will assess and record concomitant medication usage on the eCRF. Specific information regarding concomitant medication and prior therapy usage is provided in Section 5.4.

7.11 Removal of Subjects from the Trial or Study Drug

The Investigator may withdraw a subject from the study for any of the following reasons:

- The occurrence of a protocol violation
- The occurrence of a serious or intolerable AE
- The occurrence of a clinically significant change in a laboratory parameter(s)
- The sponsor or Investigator terminates the study
- The subject requests to be discontinued from the study.

Subjects removed from the study will not be replaced.

7.12 Termination of the Study

The study may be terminated prematurely with sufficient notice in advance by the Investigator for any reason as per the terms of the contract with Pearl Therapeutics. The reason should be communicated in writing to 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

8.1 Screening Visit (Up to 21 Days Prior to Randomization)

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

- Informed consent.
- Demographics and relevant medical history.
- Physical examination.
- Vital signs.
- Review of eligibility criteria.
- Placebo MDI usage demonstration and practice.
- Screening 12-lead ECG.
- Clinical laboratory evaluations.
- Urine drug testing.
- Alcohol breathalyzer test.
- Serum hCG test for all women of childbearing potential and all women of non-childbearing potential.
- FSH test for confirmation of non-childbearing status for women of non-childbearing potential only.
- Serology (HIV, HBsAg and hepatitis C).
- Document concomitant medications.

8.2 Clinic Admission (Day -1)

The subjects will be admitted to the clinic on Day -1, the day prior to administration of Treatment Period 1 study drug. The results of the following baseline procedures and assessments, which will be performed prior to the first treatment period only, will be documented in the eCRF and/or source documents:

- Clinic admission on Day -1.
- Vital signs at clinic admission on Day -1.
- MDI usage demonstration on Day -1.
- Placebo MDI usage demonstration and practice on Day -1.
- Review eligibility criteria on Day -1.
- Collect blood samples for clinical laboratory testing on Day -1.

- Urine drug testing on Day -1.
- Alcohol breathalyzer test on Day -1.
- 12-lead ECG on Day -1.
- Urine pregnancy test for all women (childbearing and non-childbearing potential) on Day -1.
- Document concomitant medications on Day -1.

8.3 Treatment Period 1 (Day 1)

The following study activities and assessments will be performed in conjunction with the first treatment period:

- Placebo MDI usage demonstration and practice on Day 1.
- Pre- and post-dose documentation of vital signs per Table 4 in Appendix 1.
- Administration of study drug on Day 1 (see Appendix 2 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.
- Collection of pre- and post-dose PK samples per Table 4 in Appendix 1.
- On Day 1, collect blood samples for clinical laboratory testing (glucose and potassium only) within 60 minutes prior to dosing and at 30 minutes and 2 and 4 hours post-dose and serum chemistry and hematology testing at 12 hours post dose.
- Perform 12-lead ECG within 1 hour prior to dosing and at 30 minutes, 2 hours and 12 hours post-dose on Day 1.
- Documentation of AEs on Day 1 (Note: AEs that occur prior to dosing will be recorded as Medical History).
- Documentation of concomitant medications on Day 1.
- After all scheduled assessments are complete and all available safety data has been reviewed by the Investigator, discharge from clinic upon completion of all protocol-specified procedures and complete a washout period of at least 3 calendar days (with a minimum of 69 hours) and not exceeding 14 days between doses.

8.3.1 Treatment Periods 2, 3 and 4

During these additional three treatment periods, subjects will be admitted to the study clinic as inpatients on Day -1 and remain inpatients until completion of all protocol-specified procedures listed below:

- Clinic admission on Day -1.
- Vital signs at clinic admission on Day -1.

- Review eligibility criteria on Day -1.
- Placebo MDI usage demonstration and practice on Day -1.
- Collect blood samples for clinical laboratory testing on Day -1.
- Perform 12-lead ECG at clinic admission on Day -1.
- Urine drug testing on Day -1.
- Alcohol breathalyzer test on Day -1.
- Urine pregnancy test for all women (childbearing and non-childbearing potential) on Day -1.
- Placebo MDI usage demonstration and practice on Day 1.
- Pre- and post-dose documentation of vital signs per Table 4 in Appendix 1.
- Administration of study drug on Day 1 (see Appendix 2 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.
- Collection of pre- and post-dose PK samples per Table 4 in Appendix 1.
- On Day 1, collect blood samples for clinical laboratory testing (glucose and potassium only) within 60 minutes prior to dosing and at 30 minutes and 2 and 4 hours post-dose and serum chemistry and hematology testing at 12 hours post dose.
- Perform 12-lead ECG within 1 hour prior to dosing and at 30 minutes, 2 hours and 12 hours post-dose on Day 1.
- Documentation of AEs on Day 1.
- Documentation of concomitant medications on Day -1 and Day 1.
- Physical Exam on treatment Period 4 only prior to discharge on Day 1.
- After all scheduled assessments are complete and all available safety data has been reviewed by the Principal Investigator, discharge from clinic and initiate a washout period of at least 3 calendar days (with a minimum of 69 hours) and not exceeding 14 days between doses (Treatments 2 and 3).

8.4 Follow Up Phone Call

Upon completion of the study, a follow up phone call with each subject will be completed at 7 days (+ 7 days) from the last dose date. Subjects will be asked about any new or outstanding Adverse Events, any new concomitant medication, and any changes to birth control method. This will be documented appropriately in the subject source binder and CRFs.

- Documentation of AEs and concomitant medications.
- Documentation of changes to birth control.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

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

Safety analyses will be performed on data from all subjects in the Safety Population. AEs, clinical laboratory evaluations, and other safety measures (e.g., vital signs, ECGs) will be listed and summarized. No formal statistical analysis of safety data is planned. All available data will be reviewed throughout the study, as the data become available.

9.2 Determination of Sample Size

The sample size was chosen primarily in order to provide adequate power to assess the bioequivalence of BGF MDI to Symbicort MDI 320/9 µg with respect to budesonide exposure and secondarily to provide information about the comparison of BGF MDI to GFF MDI. The focus is on the high strength of BGF MDI. Eighty-four randomized subjects are expected to provide approximately 75 completers. At this sample size, assuming a true difference of 5%, if the intra-subject coefficients of variations (CVs) for budesonide are 25% and 30% for AUC_{0-12} and C_{max}, respectively, then the power to demonstrate bioequivalence using 90% CIs for the geometric mean ratio (GMR) and bounds of 80% to 125% is approximately 99% and 97%, respectively, for BGF MDI 320/14.4/9.6 µg. For the comparison of BGF MDI 320/14.4/9.6 µg to GFF MDI 14.4/9.6 µg, assuming intra-subject CVs of 30% and 35% for the AUC_{0-12} and C_{max} of formoterol fumarate, respectively, the power to demonstrate bioequivalence is approximately 97% and 92%, respectively. For glycopyrrolate, since the intra-subject CVs are assumed to be 60% for both AUC_{0-12} and C_{max}, wider criteria will be used for evaluating bioequivalence. For glycopyrrolate, the power is approximately 97% for each parameter for the comparison of BGF MDI 320/14.4/9.6 µg to GFF MDI 14.4/9.6 µg to demonstrate comparability using bounds of 67% to 150% in addition to requiring that the point estimate for the GMR is between 80% and 125%.

9.3 Analysis Populations

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

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

9.4 Demographics and Baseline Characteristics

Demographic information will include date of birth, gender, ethnicity and race. Demographics and baseline characteristics will be summarized descriptively. Height and weight, which are

considered baseline characteristics and documented as part of the physical examination performed at the screening visit, will be reported with the demographic information listed above.

9.5 Analysis of Pharmacokinetic Variables

PK analysis will be performed using the PK population. PK parameters at all doses will include C_{max}, t_{max}, $t_{½}$, AUC_{0-12}, $AUC_{0-t,}$ CL/F, Vd/F, and λ_z. Other PK parameters may be calculated, as appropriate. The initial calculation of PK parameters will be performed using non-compartmental analysis. Model-based parameter estimation may be performed following examination of the data.

The comparison of natural ln-transformed values of Cmax, AUC_{0-12}, and AUC_0-t for each analyte will be performed using a mixed model repeated measures in which treatment and period will be fixed effects. Sequence will also be included in models if it explains significant variability ($p<0.10$). Variance components estimates will be obtained using the restricted maximum likelihood (REML) method. An unstructured covariance matrix will be used to model within subject correlation; if this model fails to converge, other covariance matrices will be evaluated (compound symmetry, first order auto regressive (AR(1)) with the model yielding the lowest value of Akaike Information Criterion (AIC) being selected. For AR(1), subject will be considered a random effect. For budesonide PK parameters, the analysis will be done with and without dose normalization. The ratios of geometric least squares means and the corresponding 90% CI for each treatment comparison will be determined by exponentiation of the mean differences between treatments and 90% CI on the logarithm scale. Bioequivalence will be determined by comparing the 90% CI for the GMR to bounds of 80% to 125% for budesonide and formoterol. Due to the high variability of glycopyrrolate, bounds of 67% to 150% will be used in combination with requiring that the point estimate for the GMR is between 80% and 125%.

In addition, the geometric mean budesonide parameter values for each treatment group will be plotted against dose and a Finney method will be used to estimate the relative potency of BGF MDI to Symbicort MDI. If the linear or parallel line assumptions required for the Finney method appear to be violated, then an Emax model will be used to estimate relative potency. The bias-corrected and accelerated bootstrap will be used to construct 90% CIs.

9.6 Safety Analysis

The safety of BGF MDI, Symbicort MDI and GFF MDI will be assessed from physical examination findings, AE reporting, vital signs (blood pressure, heart rate, respiratory rate and body temperature), clinical laboratory values (hematology, blood chemistry, and urinalysis), and 12-lead ECG findings.

9.7 Interim Analysis

No interim analysis is planned for this study.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

The study administration structure is provided in Table 3.

Table 3: Study Administrative Structure

Phase 1 Unit Principal Investigator:	[redacted]
Sponsor Contact:	[redacted]
Sponsor Medical Monitor:	[redacted]
Study Monitoring:	Pearl Therapeutics [redacted]
Centralized ECG	[redacted]
PK Sample Analysis and Reporting	[redacted]
Data Management& Statistical Analyses:	[redacted]
Pharmacovigilance	[redacted]
Medical Writing:	[redacted]
Clinical Laboratory Testing	[redacted]
Clinical Trial Supply:	[redacted]

10.2 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.

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

The study will be conducted in accordance with GCP. These standards respect the following guidelines:

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

The Investigator (or Pearl Therapeutics, where applicable) is responsible for ensuring that this protocol, the site's 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.

10.4 Subject Information and Consent

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

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

10.5 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/patient data used and disclosed in connection with this study in accordance with all applicable privacy laws (i.e., Health Insurance Portability and Accountability Act), rules and regulations.

10.6 Quality Control and Assurance

Pearl Therapeutics is responsible for implementing and maintaining quality control and quality assurance systems with written 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.

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

- Return of all study data to Pearl 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.

10.9 Retention of Data

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

10.10 Financial Disclosure

The Principal Investigator or sub-Investigators named on the Form FDA 1572 will need to complete a financial disclosure form prior to study initiation, at any time during the study execution if new information needs to be disclosed, and for one year after study completion.

Investigators should make the IRB/IEC aware of any financial interests that the Investigator has in the investigational product.

10.11 Investigator's Final Report

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

11 REFERENCE LIST

a. GOLD (Global Initiative for Chronic Obstructive Lung Disease). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. National Institutes of Health updated 2011. Available at: www.goldcopd.com. Accessed January 28, 2013.

b. Committee for Medicinal Products for Human Use (CHMP) European Public Assessment Report for Seebri Breezhaler, 17 October 2012.

c. Robinul Injection US Product Information, Baxter Healthcare Corporation, 2007

d. Robinul and Robinul Forte US Product Information, Shionogi Inc., 2011.

e. Anderson, GP. Formoterol: Pharmacology, molecular basis of agonism, and mechanism of long duration of a highly potent and selective $\beta_2$adrenoceptor agonist bronchodilator. Life Sciences 1993;52;Issue26:2145-2160.

f. Berger WE, Nadel JA. Efficacy and safety of formoterol for the treatment of chronic obstructive pulmonary disease. Respir Med 2008;102:173-188.

g. Dahl R, Greefhorst LA, Nowak D, et al. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. Am J RespirCrit Care Med 2001;164:778-784.

h. Rossi A, Kristufek P, Levine BE, et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow release theophylline in the treatment of COPD. Chest 2002;121:1058-1069.Aalbers, 2002

i. Campbell M, Eliraz A, Johansson G, et al. Formoterol for maintenance and as-needed treatment of chronic obstructive pulmonary disease. Respir Med 2005;99:1511-1520.

j. Campbell SC, Criner GJ, Levine BE, et al. Cardiac safety of formoterol 12 µg twice daily in patients with chronic obstructive pulmonary disease. PulmPharmacolTher2007;20:571-579.

k. Symbicort Inhalation Aerosol US Prescribing Information, Astra Zenenca, 2012

l. Rennard SI, Tashkin DP, McElhattan J, Goldman M, Ramachandran S, Martin UJ, Silkoff PE. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. Drugs 2009; 69(5):549-65

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

n. Finney, D.J. (1978). Statistical Method in Biological Assay, 3rd Ed. Griffin, London

Appendix 1 Schedule of Events

Table 4: Study Visit Schedule

Procedure	Screening From Day -21	Inpatient Treatment Periods 1 Through 4		Follow Up Phone Call
		Day -1	Day 1	7 Days after last dose period (+7 days)
Informed Consent	✓			
Medical History	✓	✓		✓
Demographics	✓			
Physical Examination	✓		✓[g]	
Vital Signs	✓[a]	✓[a]	✓[a]	
Eligibility Review	✓	✓		
Placebo MDI Usage Demonstration/Practice	✓	✓	✓	
12-lead ECG	✓[a]	✓[a]	✓[a]	
Clinical Laboratory Testing	✓	✓	✓[f,h]	
Adverse Events			✓	✓
Concomitant Medications	✓	✓	✓	✓
Urine Drug Screen	✓	✓		
Alcohol Breathalyzer	✓	✓		
Pregnancy Test (women only)	✓[b,e]	✓[b]		
Serology: (HIV, HBsAg, Hep C)	✓			
PK Assessment			✓[a]	
Study Drug Administration			✓[a]	
Inpatient Discharge			✓[c]	

a See the Schedule for Inpatient Period Assessments (Table 5) for detail regarding times and events for the screening and baseline 12-lead ECG, drug administration, and PK assessments during Treatment Periods 1 to 4.
b. For all women (childbearing potential and non-childbearing potential) (serum at screening and urine thereafter).
c. After all scheduled assessments are complete and all available safety data have been reviewed by the Investigator.
d. Complete a washout period of at least 3 days and not exceeding 14 days between doses.
e. FSH for women of non-childbearing potential at screening only.
f. Glucose, and Potassium ONLY - done within 60 minutes prior to dosing and at 30 minutes and 2 and 4 hours post-dose
g. Completed prior to discharge on Period 4 only, excluded height and weight.
h. Serum chemistry and hematology at 12 hours post dose.

Table 4: Schedule of Inpatient Period Assessments[a]

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

a Twelve-lead ECGs will be recorded at screening, on Day -1 to confirm eligibility, within one hour prior to dosing and as scheduled above. Completed within +/- 10 minutes of time point.
b Within 60 minutes of dosing
c Glucose and potassium only
[d] Complete clinical laboratory testing – serum chemistry and hematology

Appendix 2 Administration of Study Drug

All subjects will receive four of the six treatments by random assignment to 1 of 12 predetermined treatment sequences as listed in Section 6.1 of this protocol. This is a double-blind within device study, with two different MDI devices used within the study. The Pearl Therapeutics products (BGF MDI and GFF MDI) are identical in form and function and indistinguishable from each other. The two Symbicort MDIs are identical in form and function and indistinguishable from each other; however they are different from the Pearl Therapeutics products. As such, subjects, Investigators and the sponsor will not be aware of which Pearl MDI dose is being administered and will not be aware of which Symbicort MDI dose is being administered during each of the four treatment periods. However, because the appearance of the Symbicort MDI differs from that of the Pearl Therapeutics MDIs and cannot be effectively over-laid for blinding purposes, the two Symbicort MDI treatment periods will be able to be differentiated from the four Pearl Therapeutics MDI treatment periods.

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

BGF MDI and GFF MDI Administration: A Pharmacy Manual containing BGF MDI and GFF MDI dosage preparation and administration information will be provided to the study site. For each BGF MDI and GFF MDI administration, the MDI device will be primed (four actuations to waste) in the study site pharmacy by the pharmacist and then delivered to the inpatient clinic. Just prior to dosing, subjects will again be given detailed instruction regarding the proper use of the MDI device to ensure comprehension of its use. At the time of dosing, a health care 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 BGF MDI treatment arms and one GFF MDI treatments are:

- BGF MDI 320/14.4/9.6 µg
- BGF MDI 160/14.4/9.6 µg
- BGF MDI 80/14.4/9.6 µg
- GFF MDI 14.4/9.6 µg

Symbicort MDI Administration: A Pharmacy Manual containing Symbicort MDI dosage preparation and administration information will be provided to the study site. Each Symbicort MDI should be administered by the orally inhaled route. The pharmacist will prime Symbicort MDI before using for the first time by releasing two test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, the inhaler should be primed again by shaking well before each spray and releasing two test sprays into the air away from the face.

The two Symbicort MDI treatments are:

- Symbicort MDI 320/9 µg
- Symbicort MDI 160/9 µg

The MDI dose delivery specifications for the six treatments are provided in Table 5.

Table 5: MDI Dose Delivery Specifications

Product Name & Potency	Product Strength	Dosage Form	Comments
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
BGF MDI 80/14.4/9.6 µg ex-actuator	40/7.2/4.8 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
Symbicort MDI 320/9 µg ex-actuator	160/4.5 µg/actuation	MDI	Taken as 2 inhalations
Symbicort MDI 160/4.5 µg ex-actuator	80/4.5 µg/actuation	MDI	Taken as 2 inhalations

Appendix 3 Plasma Collection, Processing and Handling (PK Samples)

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

Shipping Address:

[redacted]

ATTENTION: Sample Management

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

Appendix 4 Sponsor Signatory

Study Title: A Phase I, Randomized, Double-Blind Within Device, Single-Dose, Four-Period, Six-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Three Doses of Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (BGF MDI), One Dose of Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI), and Two Doses of Symbicort® Inhalation Aerosol in Healthy Volunteers

Study Number: PT010001-01

Final Date: Version 1.0, [redacted]

Amendment 1 Date: Version 2.0, [redacted]

Signature: [redacted] Date: [redacted]

Name: [redacted]

Title: [redacted]
Pearl Therapeutics Inc.

Appendix 5 Investigator's Agreement and Signature Page

Study Title: A Phase I, Randomized, Double-Blind Within Device, Single-Dose, Four-Period, Six-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Three Doses of Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (BGF MDI), One Dose of Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI), and Two Doses of Symbicort® Inhalation Aerosol in Healthy Volunteers

Study Number: PT010001-01 **Final Date:** Version 1.0, [redacted]
Version 2.0, [redacted]

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

I agree:

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

Signed:_____ Date:_____