12.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

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

- Original Protocol – [redacted]
- Amendment # 1.0 – [redacted]

Clinical Trial Protocol: PT003010-00

Study Title:	A Phase I, Randomized, Double-Blind, Single-Dose, Four-Period, Four-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Two Doses of PT003 and Two Doses of PT001 in Japanese Healthy Subjects
Study Number:	PT003010-00
Study Phase:	Phase I
Product Name:	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; PT003, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler (GFF MDI) Glycopyrronium Inhalation Aerosol; PT001, Glycopyrrolate MDI (GP MDI)
IND Number:	107739
Investigators:	Single Center
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]

	Version Number	Date
Original Protocol	Version 1.0	[redacted]

Confidentiality Statement

SYNOPSIS

Sponsor:
Pearl Therapeutics, Inc.
[redacted]

Name of Finished Product:

- Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; PT003, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler (GFF MDI)
- Glycopyrronium Inhalation Aerosol; PT001, Glycopyrrolate MDI (GP MDI)

Name of Active Ingredients:

- Glycopyrronium
- Formoterol fumarate

Study Title:
A Phase I, Randomized, Double-Blind, Single-Dose, Four-Period, Four-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Two Doses of Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI) and Two Doses of Glycopyrronium Inhalation Aerosol (GP MDI) in Japanese Healthy Subjects

Study Number:
PT003010-00

Study Phase: Phase I

Primary Objective:
The primary objective of the study is to describe the pharmacokinetic (PK) profile of single administration of two doses of GFF MDI and two doses of GP MDI in adult Japanese healthy subjects.

Secondary Objective:
The secondary objective of the study is to assess the safety of two doses of GFF MDI and two doses of GP MDI in adult Japanese healthy subjects.

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

- GFF MDI 28.8/9.6 µg
- GFF MDI 14.4/9.6 µg
- GP MDI 28.8 µg
- GP MDI 14.4 µg

Following determination of study eligibility, subjects will be randomized to one of four treatment sequences balanced for carryover and period effects. At the target of 24 subjects randomized, each sequence will be used six times. If all subjects complete the study, the design is balanced for both period and first-order carryover effects.

Study Population:
Twenty-four adult Japanese healthy male and female subjects are planned for randomization in the study. The sample size of 24 randomized subjects is selected to provide approximately 20 completers. Full inclusion and exclusion criteria are listed in Section 5.

Test Product, Dose, and Mode of Administration:
All dosing of the study drug will be by oral inhalation. The two doses of GFF MDI (28.8/9.6 µg and 14.4/9.6 µg) and the two doses of GP MDI (28.8 µg and 14.4 µg) will be administered on separate test days. The characteristics of the two GFF MDI doses and the two GP MDI doses that will be administered during the study are provided below:

Product Name & Dose	Product Strength	Dosage Form	Administration
GFF MDI 28.8/9.6 µg ex-actuator	14.4/4.8 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
GP MDI 28.8 µg ex-actuator	14.4 µg/actuation	MDI	Taken as 2 inhalations
GP MDI 14.4 µg ex-actuator	7.2 µg/actuation	MDI	Taken as 2 inhalations

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

Duration of Treatment:
This study will include a Screening Period of up to 28 days and four single-dose Treatment Periods separated by a minimum Washout Period of 7 days to a maximum of 14 days for added scheduling flexibility. The planned participation in the study is between 33 and 98 days.

Pharmacokinetic Assessments: The PK of from GFF MDI and GP MDI will be assessed and compared using plasma concentrations of glycopyrronium and formoterol. Timepoints for PK blood sample collection during each of the four single-dose Treatment 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, 12, 16, and 24 hours post-dose. Pharmacokinetic parameters at all doses will include maximum plasma concentration (C_{max}), area under the curve from 0 to 12 hours (AUC_{0-12}), area under the curve from 0 to time of the last measurable plasma concentration (AUC_{0-t}), area under the curve from 0 extrapolated to infinity ($AUC_{0-\infty}$), time to maximum plasma concentration (t_{max}), apparent terminal elimination half-life ($t_{½}$), apparent total body clearance (CL/F), apparent volume of distribution (Vd/F), and terminal elimination rate constant (λ_z). Other PK parameters may be calculated, as appropriate.

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

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 drug. • 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 GFF MDI or GP MDI. For this population, data potentially affected by major protocol deviations will be removed (to be determined prior to unblinding). Summary statistics will be used to describe the PK parameters after treatment with GFF MDI or GP MDI. The sample size of 24 randomized subjects is selected to provide approximately 20 completers and reasonable estimates of the PK parameters in adult Japanese healthy subjects.
Date of Original Protocol: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ALT	Alanine Aminotransferase
API	Active Pharmaceutical Ingredients
AR(1)	First Order Auto Regressive
AST	Aspartate Aminotransferase
AUC_{0-12}	Area Under the Curve from 0 to 12 hours
AUC_{0-t}	Area Under the Curve from 0 to Time of the Last Measurable Plasma Concentration
$AUC_{0-\infty}$	Area Under the Curve from 0 Extrapolated to Infinity
BID	Bis In Die, Twice Daily
BP	Blood Pressure
CBC	Complete Blood Cell
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation (according to National Kidney Disease Education Program)
CL/F	Apparent Total Body Clearance
C_{max}	Maximum Plasma Concentration
COPD	Chronic Obstructive Pulmonary Disease
CV	Coefficient of variation
dL	Deciliter
DSPC	Distearoylphosphatidylcholine
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
eg.	Exempli Gratia, for example
EU	European Union
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration

FEV_1	Forced Expiratory Volume in One Second
FF MDI	Formoterol Fumarate Metered Dose Inhaler
FSH	Follicle-Stimulating Hormone
g	Gram
GCP	Good Clinical Practice
GFF MDI	Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler
GFR	Glomerular Filtration Rate
GMR	Geometric Mean Ratio
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP MDI	Glycopyrronium Metered Dose Inhaler
HbsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HFA	Hydrofluoroalkane
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroid
ICMJE	International Committee of Medical Journal Editors
ie.	Id Est, that is
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
ISMPP	International Society for Medical Publications Professionals
IV	Intravenous
LABA	Long-Acting β2 Agonist
LAMA	Long-Acting Muscarinic Antagonist
λ_z	Terminal Elimination Rate Constant

MDI	Metered Dose Inhaler
µg	Microgram
µL	Microliter
mg	Milligram
mL	Milliliter
mmHg	Millimeter of Mercury
msec (ms)	Millisecond
PK	Pharmacokinetics
QD	Once Daily
QTcF	QT corrected for heart rate with Fridericia's formula
RBC	Red Blood Cell
REML	Restricted Maximum Likelihood
SABA	Short-Acting β2-Agonists
SAE	Serious Adverse Event
[redacted]	[redacted]
SOP	Standard Operating Procedure
$t_{½}$	Apparent Terminal Elimination Half-life
[redacted]	[redacted]
TEAE	Treatment-emergent adverse event
TID	Three Times Daily
t_{max}	Time to Maximum Plasma Concentration
US	United States
Vd/F	Apparent Volume of Distribution
WBC	White Blood Cell

TRADEMARK INFORMATION

Trademarks not owned by Pearl Therapeutics, Inc.:

Aerolizer

Breezhaler

Cuvposa

Foradil

Oxis

Robinul

Seebri

Symbicort

Turbohaler

Ziploc

1 INTRODUCTION

Pearl Therapeutics, Inc. (hereafter referred to as Pearl) is developing a combination product, Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (PT003; hereafter referred to as glycopyrronium and formoterol fumarate metered dose inhaler [GFF MDI]), for the treatment of chronic obstructive pulmonary disease (COPD). In parallel, Pearl is also developing the individual product, Glycopyrronium Inhalation Aerosol (PT001; hereafter referred to as glycopyrronium metered dose inhaler [GP MDI]) for the treatment of COPD.

Glycopyrronium and formoterol fumarate are components (alone or in combination) of approved inhalation products for treatment of subjects with COPD and their safety and efficacy are well characterized. Clinical and non-clinical studies conducted with the Pearl dual combination product, GFF MDI and its individual components, glycopyrronium (GP) MDI and formoterol fumarate (FF) MDI support the evaluation of GFF MDI in this Phase I study in healthy subjects (Study PT003010). GFF MDI, GP MDI, and FF MDI are currently being evaluated in Phase III clinical studies in subjects with COPD.

1.1 Chronic Obstructive Pulmonary Disease

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

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 with increasing the dose of a single bronchodilator [GOLD, 2014]. Long-acting β2 agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) reduce bronchoconstriction through different mechanisms, and there is a long history of combination therapy for COPD with short-acting agents in these classes.

1.2 Glycopyrronium

Glycopyrronium (the active moiety of glycopyrronium bromide, also referred to as glycopyrrolate) is a LAMA which exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. Glycopyrronium is approved in many countries in multiple formulations for different indications, including 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 1361 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) European Public Assessment Report for Seebri Breezhaler, 2012]. In addition to the published data with Seebri Breezhaler (also referred to as NVA237), there is also 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 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 pre-operative 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 twice daily (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 United States (US) as an oral solution (Cuvposa®) which is indicated to reduce chronic severe drooling in patients aged three to16 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® Turbohaler®, 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.

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 2500 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 Pearl's GFF MDI

Pearl is developing GFF MDI, GP MDI, and FF MDI using its porous particle technology platform. This technology is based on spray dried porous particles comprised of distearoylphophatidylcholine and calcium chloride that are co-suspended with micronized active pharmaceutical ingredients (APIs) in a 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 technology also enables reproducible administration of very low doses of potent therapeutics.

1.5 Study Rationale

Published studies have shown that the complementary mechanisms of action of a LABA (formoterol fumarate) and a LAMA (tiotropium bromide) significantly improved bronchodilation in subjects with COPD compared with the individual agents [Celli 2014, Chapman 2014, Dahl 2014, Donohue 2013, Wedzicha 2014]. Currently, fixed-dose combinations of a LABA and LAMA are available for the treatment of COPD in various countries worldwide, including the US, the EU, Japan, the United Kingdom, etc.

Pearl is developing the combination product, GFF MDI (14.4/9.6 μg ex-actuator [dose delivered from the actuator, ie., mouthpiece, of the MDI]), as a BID maintenance bronchodilator treatment in subjects with COPD. In parallel, Pearl is also developing the individual products, GP MDI (14.4 μg ex-actuator, BID) and FF MDI (9.6 μg ex-actuator, BID) as maintenance bronchodilator treatments in subjects with COPD. These doses of GFF MDI (14.4/9.6 μg) and GP MDI (14.4 μg) administered in this study in healthy Japanese subjects are doses being tested in global Phase III studies to support the approval of GFF MDI and GP MDI.

The purpose of this study is to characterize the pharmacokinetic (PK) profile of two doses of GFF MDI and GP MDI in adult Japanese healthy subjects using the defined doses (14.4/9.6 μg and 14.4 μg, respectively) and 2-fold higher doses of GFF MDI and GP MDI (28.8/9.6 μg and 28.8 μg, respectively).

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to describe the PK profile of single administration of two doses of GFF MDI and two doses of GP MDI in adult Japanese healthy subjects.

2.2 Secondary Objective

The secondary objective of the study is to assess the safety of two doses of GFF MDI and two doses of GP MDI in adult Japanese healthy subjects.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

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

3.2 Safety Endpoints

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

3.3 Pharmacokinetic Endpoints

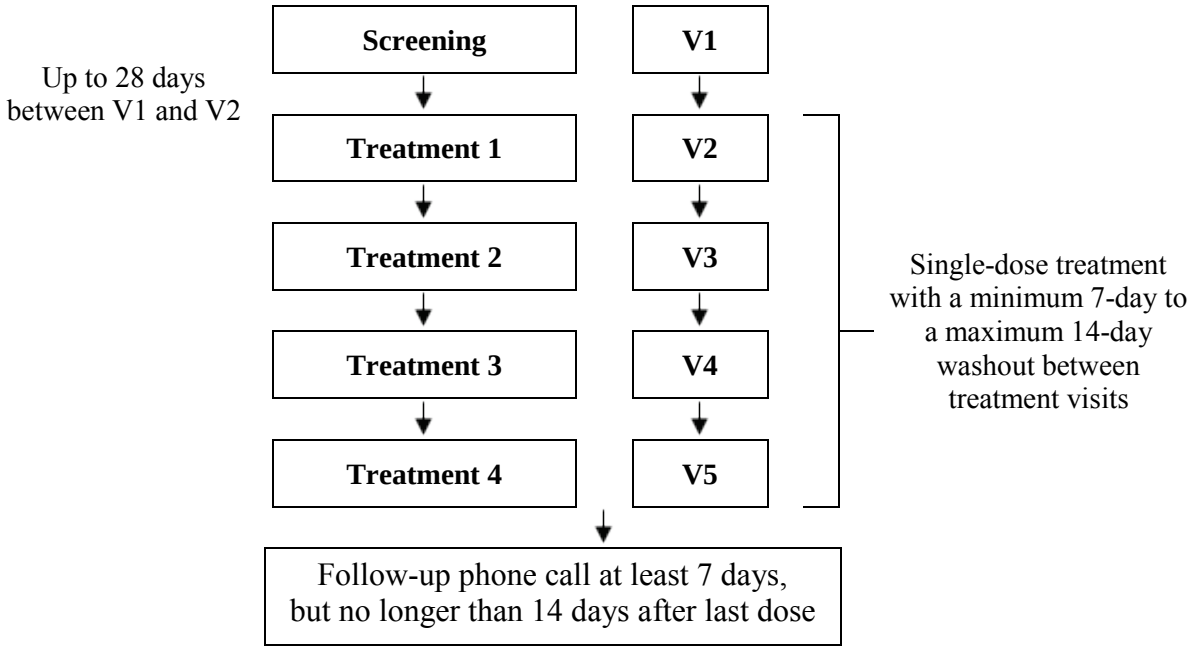
The PK of from GFF MDI and GP MDI will be assessed and compared using plasma concentrations of glycopyrronium and formoterol. Timepoints for PK blood sample collection during each of the four single-dose Treatment Periods will be at 30 minutes prior to dosing and then at 2, 6, 20, and 40 minutes post-dose and 1, 2, 4, 8, 10, 12, 16, and 24 hours post-dose (see Table 8-2). Pharmacokinetic parameters at all doses will include maximum plasma concentration (C_{max}), area under the curve from 0 to 12 hours (AUC_{0-12}), area under the curve from 0 to time of the last measurable plasma concentration (AUC_{0-t}), area under the curve from 0 extrapolated to infinity ($AUC_{0-\infty}$), time to maximum plasma concentration (t_{max}), apparent terminal elimination half-life ($t_{½}$), apparent total body clearance (CL/F), apparent volume of distribution (Vd/F), and termination elimination rate constant (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, Phase I study with a randomized, double-blind, four-period, four-treatment, cross-over design to assess the safety and PK of two doses of GFF MDI and two doses of GP MDI in healthy Japanese subjects. The overall study design is summarized and illustrated in Figure 4-1.

Figure 4-1. Study Design



Subjects who provide informed consent, undergo screening procedures, and qualify for the study will be randomized to one of four treatment sequences. Each treatment sequence will contain GFF MDI 28.8/9.6 µg, GFF MDI 14.4/9.6 µg, GP MDI 28.8 µg, and GP MDI 14.4 µg. At the target of 24 subjects randomized, each of the four sequences will be used six times. If all subjects complete the study, the design is balanced for both period and first-order carryover effects.

Each inpatient treatment session will be separated by a minimum outpatient Washout Period of 7 days to a maximum of 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 clinic.

Safety data will be closely monitored and baseline and post-dosing serial blood draws (Section 7.9) for PK analysis (see Table 8-2) will be obtained during each inpatient Treatment Period. After all scheduled assessments are completed and all available safety

data have been reviewed by the Principal Investigator, subjects will be discharged from the clinic. Following the first Treatment Period, subjects will return to the clinic the following week for their next Treatment Period until all four Treatment Periods have been completed. The Washout Period between treatment periods will consist of a minimum of 7 days to a maximum of 14 days between doses. Other safety assessments will be obtained as listed in Table 8-2. A follow-up phone call will be conducted at least 7 days, but no longer than 14 days after completion of the last dose date on Treatment Period 4.

4.2 Study Duration and Dates

This study will include a Screening Period of up to 28 days and four single-dose Treatment Periods separated by a minimum Washout Period of 7 days to a maximum of 14 days for added scheduling flexibility. A follow-up phone call will be conducted at least 7 days but no longer than 14 days after completion of the last dose date on Treatment Period 4. The planned participation in the study is between 33 and 98 days.

5 STUDY POPULATION SELECTION

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

5.1 Inclusion Criteria

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

1. Signed and dated Institutional Review Board/ Independent Ethics Committee (IRB/IEC)-approved Informed Consent form (ICF) before any protocol-specific screening procedures are performed.
2. Male and female first generation Japanese subjects 18 to 45 years, inclusive:
   - *First generation subjects who were born in Japan to two parents and four grandparents also born in Japan of full Japanese descent*
   - *Subjects must be expatriate of Japan residing outside of Japan for less than 5 years*
   - *Subjects must have a valid Japanese passport*
   - *Subjects who have a body weight >50 kg (110 lbs) and body mass index between 18.0 and 30.0 kg/m^2, 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 7 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. 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 7 days after the Final Visit as a safety precaution. Females of non-childbearing potential, defined as surgically sterile (status post-hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months, do not require contraception during the study. Post-menopausal must be confirmed by a serum follicle-stimulating hormone (FSH) test at Screening and the reason must be documented in the medical history electronic Case Report form (eCRF).
6. 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.

7. 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.

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 four Treatment Periods.
3. Subjects with clinically significant neurologic, cardiovascular, hepatic, renal, endocrinologic, pulmonary, hematological, psychiatric, or other medical illness that would interfere with participation in this study.
4. Subjects with a history of ECG abnormalities including PR >220 msec; QRS complex >110 msec; QT corrected for heart rate with Fridericia's formula (QTcF) >429 msec and QTcF >436 msec in males and females, respectively based on normal population data in the Japanese population [Funada, 2008]; 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 (ie. 12 lead ECGs performed at Screening or baseline [pre-dose on Day 1 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 study site staff.
7. Subjects who have cancer that has not been in complete remission for at least 5 years.
8. Supine BP >140/90 mmHg or resting HR ≥100 bpm at Screening, baseline (pre-dose on Day 1 of the first Treatment Period).
9. Male subjects with symptomatic prostatic hypertrophy that is clinically significant in the opinion of the Investigator.
10. Male subjects with a trans-urethral resection of the prostate or full resection of the prostate within 6 months prior to Screening.

11. Subjects with bladder neck obstruction or urinary retention that is clinically significant in the opinion of the Investigator.
12. Subjects with a diagnosis of glaucoma that in the opinion of the Investigator has not been adequately treated. All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective β-blockers such as betaxolol, carteolol, levobunolol, metipranolol, 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 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 Screening 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 study drug administration.
17. 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.
18. Blood collection of greater than 500 mL within 56 days prior to Screening.
19. Subjects with pre-existing anemia and/or iron deficiency anemia **Note:** Subjects with anemia (defined as hemoglobin 13.8-16.6 g/dL and 11.3-15.5 g/dL for males and females, respectively, and hematocrit 40.2%-49.4% and 34.4%-45.6% for males and females, respectively [Yatomi, 2013]).
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 4 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 4 weeks of drug administration.
25. Any other condition and/or situation that causes the Investigator to deem a subject unsuitable for the study (eg., due to expected study drug non-compliance, inability to medically tolerate the study procedures, or a subject's unwillingness to comply with study-related procedures).
26. Subjects with abnormal-glomerular filtration rate (GFR; estimated GFR <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 Screening. Only subjects continuing to meet entry inclusion/exclusion criteria at Treatment Period 1 will be assigned a unique subject randomization number.

5.4 Prior, Concomitant, and Prohibited Medications

Investigational therapies are not permitted within 30 days or five half-lives (whichever is longer) prior to study drug administration. 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. 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 ICF will be documented as prior study drugs 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 to whenever the subject discontinues the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented.

In addition to Exclusion Criterion #14 (subjects are excluded if a history of smoking or use of nicotine-containing products within 3 months of Screening by self-reporting), the use of electronic cigarettes within 3 months of Screening is also exclusionary.

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.

5.6 Removal of Subjects from the Study 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 an adverse event

- 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.

5.7 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. The reason should be communicated in writing to Pearl.

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

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. The Pearl products (GFF MDI and GP MDI) are identical in form and function and indistinguishable from each other. The characteristics of the two GFF MDI doses and the two GP MDI doses that will be administered during the study are provided in Table 6-1.

An unblinded pharmacist at the study site will be provided with a written randomization scheme for allocation of subjects to one of four treatment sequences and to manage the distribution of clinical supplies. The four treatment sequences are listed below, where A, B, C, and D each represent one of the four treatments by random selection. Six of the planned 24 subjects will be included in each treatment sequence. Should all subjects complete the study, the design is balanced for period and first-order carryover effects.

Sequence 1: ABCD

Sequence 2: BDAC

Sequence 3: CADB

Sequence 4: DCBA

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 GFF MDI 28.8/9.6 µg, GFF MDI 14.4/9.6 µg, GP MDI 28.8 µg, and GP MDI 14.4 µg by random assignment to one of four 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 GFF MDI active drug substances are glycopyrronium and formoterol fumarate and the active drug substance of the GP MDI is glycopyrronium.

Investigational materials will be provided by Pearl as summarized in Table 6-1.

Table 6-1. Product Descriptions

Product Name & Dose	Product Strength	Dosage Form	Administration
GFF MDI 28.8/9.6 µg ex-actuator	14.4/4.8 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
GP MDI 28.8 µg ex-actuator	14.4 µg/actuation	MDI	Taken as 2 inhalations
GP MDI 14.4 µg ex-actuator	7.2 µg/actuation	MDI	Taken as 2 inhalations

Abbreviations: GFF MDI=Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; GP MDI=glycopyrronium 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 four treatment sequences. The treatment and study visit schedule is illustrated in Figure 4-1 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 the four treatments.

GFF MDI and GP 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.

6.5 Unblinding Procedures

Pearl 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 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

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

Clinical supplies for this study will be provided to the study site pharmacy by [redacted]. The clinical supplies storage area at the study site must be monitored by the study 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 1.

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 drug should be handled in accordance with Good Pharmacy Practices. The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned to [redacted].

The study site should check with the Pearl 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 IRB/IEC. 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 28 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 personal health history, family health history, history of hospitalization, and history of surgeries.

7.4 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.

7.5 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

7.6 Vital Signs

Vital sign determinations, including BP, HR, 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 1 hour prior to administration of study drug and 30 minutes, 2 hours, and 12 hours post-administration of study drug (see Table 8-2).

7.7 Electrocardiography

Twelve-lead ECGs will be recorded at Screening, and on each clinic admission day (Day -1) of each Treatment Period (baseline represents pre-dose on Day 1 of the first Treatment Period). On each treatment day (Day 1), 12-lead ECGs will be obtained within 1 hour prior to dosing and at 30 minutes and 2 and 12 hours post-dosing (see Table 8-2). 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.

7.8 Clinical Laboratory Tests

7.8.1 Laboratory Parameters

Laboratory testing (hematology with differential, clinical chemistry, and urinalysis) will be performed using standard methods. Blood and urine samples for the clinical laboratory tests listed in Table 7-1 will be collected at Screening and on the day of clinic admission (Day -1 of each Treatment Period). Blood sample volumes will meet the laboratory's specification. Clinical chemistry and hematology samples will be collected during each of the four single-dose Treatment Periods at 30 minutes prior to dosing and then at 2, 6, 20, and 40 minutes post-dose and 1, 2, 4, 8, 10, 12, 16, and 24 hours post-dose. In addition, blood will be drawn for glucose and potassium level determinations within 1 hour prior to dosing and at 30 minutes and 2 and 4 hours post administration of study drug on Day 1 (see Table 8-2). 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 7-1. List of Laboratory Tests

Hematology	Clinical Chemistry	
Hematocrit [a]	Creatinine [b]	Bilirubin (direct)
Hemoglobin	Potassium (K+) [c]	Aspartate aminotransferase (AST)
Platelet count	Sodium (Na+)	Alanine aminotransferase (ALT)
Red blood cell (RBC) count	Chloride (Cl-)	Gamma-glutamyltransferase (GGT)
WBC count	Magnesium (Mg++)	Alkaline phosphatase
WBC differential	Calcium	Total Protein
Mean corpuscular volume (MCV)	Inorganic phosphate	Albumin
Mean cell hemoglobin (MCH)	Glucose [c]	
MCH concentration (MCHC)	Urea	
	Bilirubin (Total)	
Urinalysis: Macroscopic examination routinely including specific gravity, pH, protein, glucose, ketones, blood, and urobilinogen. A microscopic examination will be performed if warranted based on macroscopic results.		
Urine drug screen: A urine sample will be collected and analyzed (positive or negative) for drugs of abuse including amphetamine, opiate, cocaine, barbiturates, benzodiazepines, and marijuana [tetrahydrocannabinol].		
Breathalyzer Test: A breathalyzer test will be performed for the presence of alcohol (positive or negative).		
Serology: Testing for HbsAg, Hepatitis C antibody and HIV will be performed at Screening only. Results of each serology test will be reported as either positive or negative.		
For females who are not post-menopausal: A serum hCG test at Screening and urine hCG test at admission for each of the four Treatment Periods.		
For females of non-childbearing potential: A serum hCG test at Screening 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.		

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

[a] Packed cell volume
[b] Serum creatinine value will be used to calculate eGFR using CKD-EPI.
[c] Additionally, within 1 hour prior to dosing and at 30 minutes, 2 hours and 4 hours post-dose of each Treatment Period

7.8.2 Sample Collection, Storage, and Shipping

Detailed instructions for laboratory sample collection, processing, and shipping instructions will be provided in the [redacted] laboratory manual. Approximately 400 mL of blood will be collected per subject during the study.

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

7.9 Pharmacokinetic Assessments

Pharmacokinetic sampling will occur in conjunction with Treatment Periods 1, 2, 3, and 4.

Approximately 5 mL of whole blood will be collected at 30 minutes prior to dosing and then at 2, 6, 20, and 40 minutes post-dose and 1, 2, 4, 8, 10, 12, 16, and 24 hours post-dose. Samples will be collected via an indwelling IV 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 ≤-60 C. Refer to Appendix 2 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 glycopyrronium and formoterol will be determined using validated High Performance Liquid Chromatography tandem Mass Spectrometry methodology. Instructions for sample handling, storage, and shipping will be provided in the [redacted] laboratory manual.

Sample collections will be scheduled for the nominal timepoint and actual collection times recorded in the source documents (see Table 8-2).

7.10 Safety Assessments

7.10.1 Adverse Events Assessments

7.10.1.1 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. In addition, certain AEs (as described in Section 7.10.1.8) are classified as "serious" and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as an SAE to Pearl or its designee.

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

Adverse events 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. If this data is collected after the study database is locked, it will be reported to Pearl, but will not be included in the study database.

7.10.1.2 Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonisation (ICH) and the US Code of Federal Regulations (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 (eg., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (eg., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Adverse events include, but are not limited to:

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

An AE does not include:

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

7.10.1.3 Pre-Randomization Adverse Events

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

7.10.1.4 Treatment-Emergent Adverse Events

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

7.10.1.5 Severity

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

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

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

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

7.10.1.6 Relationship

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

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

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

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

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

7.10.1.7 Clinical Laboratory Adverse Events

Many laboratory abnormalities observed during the course of a study will be included under a reported AE describing a clinical syndrome (eg., elevated blood urea nitrogen and creatinine in the setting of an AE of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). In such cases, the laboratory abnormality itself (eg., elevated creatinine in a setting of renal failure) does not need to be recorded as an AE. However,

isolated laboratory abnormalities should be reported as AEs if they are considered to be clinically significant by the Investigator.

Criteria for a "clinically significant" laboratory abnormality are:

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

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

7.10.1.8 Serious Adverse Events

DEFINITION

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

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

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered 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.

REPORTING SERIOUS ADVERSE EVENTS

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for AE identification, documentation, grading, assignment of causality, and prompt notification of SAEs to the Pearl's Medical Monitor or designee. All SAEs must be reported to Pearl no later than 24 hours after the Investigator recognizes/classifies the event as an SAE. At a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report using the appropriate form (eg., SAE Report Form). After the initial report, as necessary, the Investigator must provide any additional information on an SAE to the Medical Monitor within 2 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.

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

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

7.10.1.9 Supplemental Investigation of Serious Adverse Events

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

7.10.1.10 Post Study Follow Up of Adverse Events

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

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

7.10.1.11 Notification of Post Study Serious Adverse Events

Investigators are not obligated to actively follow subjects after the completion of the study. However, if the 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, whether or not the event is

attributable to study drug. All SAEs must be reported to Pearl no later than 24 hours after the Investigator recognizes/classifies the event as an SAE.

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

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

7.10.1.13 Health Authority Safety Reports

Pearl 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 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-sponsored clinical studies. Safety reports must be submitted to the appropriate IRB/IEC as soon as possible. Documentation of the submission to the IRB/IEC must be retained for each safety report.

7.10.2 Overdose

An overdose is defined as a dose greater than the highest dose level of each study drug evaluated in this study as described in Section 6.3 (Product Descriptions), which results in clinical signs and symptoms. In the event of an overdose of study drug, the Investigator should use clinical judgment in treating the overdose and contact the 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 for GFF MDI and GP MDI.

7.10.3 Pregnancy

Any pregnancy that occurs from Screening until study completion must be reported to Pearl. To ensure subject safety, each pregnancy must be reported to Pearl within 14 days of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child.

8 STUDY ACTIVITIES

A time and events schedule is provided in Table 8-1 and a schedule of inpatient period assessments is provided in Table 8-2.

Table 8-1. Study Visit Schedule

Procedure	Screening From Day -28	Inpatient Treatment Periods 1 Through 4		Follow Up Phone Call
		Day -1	Day 1	7 Days after last dose period (but no longer than 14 days)
Informed Consent	X			
Medical History	X	X		X
Demographics	X			
Physical Examination	X		X[a]	
Vital Signs	X[b]	X[b]	X[b]	
Eligibility Review	X	X		
Placebo MDI Usage Demonstration/Practice[c]	X	X	X	
12-lead ECG	X[b]	X[b]	X[b]	
Clinical Laboratory Testing	X[d]	X[d]	X[e, f]	
Adverse Events		X[g]	X	X
Concomitant Medications	X	X	X	X
Urine Drug Screen	X	X		
Alcohol Breathalyzer	X	X		
Pregnancy Test (women only)	X[h, i]	X[h]		
Serology: (HIV, HbsAg, Hep C)	X			
PK Assessment			X[b]	
Study Drug Administration			X[b]	
Inpatient Discharge			X[j]	

Abbreviations: ECG=electrocardiogram; HbsAg=hepatitis B surface antigen; Hep C=hepatitis C; HIV=human immunodeficiency virus; MDI=metered dose inhaler; PK=pharmacokinetic

Note: Following the first treatment period, subjects will return to the clinic the following week, for their next treatment period until all four treatment periods have been completed. The Washout Period between treatment periods will consist of a minimum of 7 days to a maximum 14 days between doses.

[a] Completed prior to discharge on Treatment Period 4 only, excluding height and weight.

[b] See the Schedule for Inpatient Period Assessments (Table 8-2) for detail regarding times and events for the Screening and baseline 12-lead ECG, vital signs, drug administration, and PK assessments during Treatment Periods 1 to 4.

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

[d] Urinalysis to be performed at Screening and Day -1 of each Treatment Period.

[e] Glucose, and Potassium ONLY - done within 1 hour prior to dosing and at 30 minutes and 2 and 4 hours post-dose

[f] Clinical chemistry and hematology at 12 hours post-dose.

[g] AEs will be collected from the time of the first dose of study drug.

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

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

[j] After all scheduled assessments are complete and all available safety data have been reviewed by the Investigator

Table 8-2. Schedule of Inpatient Period Assessments

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**	**16 hr**	**24 hr**
PK Blood Draw	X		X	X	X		X	X	X	X	X	X	X	X	X
Administration of Study Drug[a]		X													
12-lead ECG[b]	X[c]					X			X				X		
Clinical Laboratory Tests	X[d]					X[d]			X[d]	X[d]			X[e]		
Vital Signs	X[c]					X			X				X		
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X	X		

Abbreviations: ECG=electrocardiogram; hr=hour; min=minutes; PK=pharmacokinetics

[a] Following the first treatment period, subjects will return to the clinic the following week, for their next treatment period until all four treatment periods have been completed. The Washout Period between treatment periods will consist of a minimum of 7 days to a maximum of 14 days between doses.

[b] Twelve-lead ECGs will be recorded at Screening, on Day -1of Treatment Period 1 to confirm eligibility, within 1 hour prior to dosing and as scheduled above. Completed within ±10 minutes of timepoint.

[c] Within 1 hour of dosing

[d] Glucose and potassium level determinations only within 1 hour prior to dosing and at 30 minutes and 2 and 4 hours post administration of study drug.

[e] Complete clinical laboratory testing – clinical chemistry and hematology

8.1 Screening Period (Up to 28 Days Prior to Randomization)

The following procedures and assessments will be performed during Screening 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 (including urinalysis)
- Urine drug testing
- Alcohol breathalyzer test
- Serum pregnancy test (women only; for all women of childbearing potential and non-childbearing potential)
- Follicle-stimulating hormone test for women of non-childbearing potential
- Serology (HIV, HBsAg, and hepatitis C)
- Document concomitant medications

8.2 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, will be documented in the eCRF and/or source documents:

- Randomization and treatment assignment
- Relevant medical history
- Vital signs
- Review of eligibility criteria
- Placebo MDI usage demonstration and practice
- 12-lead ECG
- Collect blood and urine samples for clinical laboratory testing
- Urine drug testing
- Alcohol breathalyzer test
- Urine pregnancy test for all women (childbearing and non-childbearing potential)
- Document concomitant medications

8.3 Treatment Period 1 (Day 1)

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

- Placebo MDI usage demonstration and practice
- Pre- and post-dose documentation of vital signs per Table 8-2
- Administration of study drug (see Appendix 1 for details regarding study drug dispensing and administration)
  Note: Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.
- Collect pre- and post-dose PK samples per Table 8-2
- Collect blood samples for clinical laboratory testing (glucose and potassium only) per Table 8-2
- Perform 12-lead ECG per Table 8-2
- Documentation of AEs (Note: AEs that occur prior to dosing will be recorded as Medical History unless the event meets the definition of an SAE as defined in Section 7.10.1.8)
- Documentation of concomitant medications
- After all scheduled assessments are complete and all available safety data has been reviewed by the Investigator, discharge from clinic upon completion of all protocol-specified procedures and complete a Washout Period of a minimum of 7 days to a maximum of 14 days between doses

8.4 Treatment Periods 2, 3, and 4

During these three Treatment Periods, subjects will be admitted to the clinic as inpatients on Day -1 and remain inpatients until completion of all protocol-specified procedures listed below: The results of the following procedures and assessments will be documented in the eCRF and/or source documents:

- Review of medical history
- Vital signs at clinic admission on Day -1
- Review eligibility criteria on Day -1
- Placebo MDI usage demonstration and practice on Day -1
- Perform 12-lead ECG on Day -1
- Collect blood and urine samples for clinical laboratory testing 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 8-2
- Administration of study drug on Day 1 (see Appendix 1 for details regarding study drug dispensing and administration)
  Note: Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.
- Collect pre- and post-dose PK samples on Day 1 per Table 8-2
- On Day 1, collect blood samples for clinical laboratory testing (glucose and potassium only) per Table 8-2
- Perform 12-lead ECG on Day 1 per Table 8-2
- Documentation of AEs on Day -1 and 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 Investigator, discharge from clinic and initiate a Washout Period of at least 7 calendar days and not exceeding 14 days between doses (between Treatments 2 and 3 and Treatments 3 and 4)

8.5 Follow-Up Phone Call

Upon completion of the study, a follow up phone call with each subject will be completed at least 7 days but no longer than 14 days from the last dose date. Subjects will be asked about any new or outstanding AEs, any new concomitant medication, and any changes to birth control method. This will be documented appropriately in the subject source documents and eCRFs.

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

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

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

Safety analyses will be performed on data from all subjects in the Safety Population. Adverse events, clinical laboratory evaluations, and other safety measures (eg., 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 of 24 randomized subjects is selected to provide approximately 20 completers. No formal criteria for the evaluation of PK were used to determine the sample size, but the chosen size is expected to provide reasonable estimates of the PK parameters in adult Japanese healthy subjects.

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 drug.
- 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 GFF MDI or GP MDI. For this population, data potentially affected by major protocol deviations will be removed (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 Screening, will be reported with the demographic information listed above.

9.5 Analysis of Pharmacokinetic Variables

Pharmacokinetic analysis will be performed using the PK population. Pharmacokinetic parameters at all doses will include C_{max}, t_{max}, $t_{½}$, AUC_{0-12}, AUC_{0-t}, $AUC_{0-\infty}$, 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 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 being selected. For AR(1), subject will be considered a random effect. For glycopyrronium 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.

9.6 Safety Analysis

Safety analysis will be performed using the Safety Population. The safety of GFF MDI and GP MDI will be assessed from physical examination findings, AE reporting including SAE reporting, vital signs (BP, HR, respiratory rate, and body temperature), clinical laboratory values (hematology, clinical chemistry, and urinalysis), and findings from 12-lead safety ECGs. The incidence of AEs and SAEs will be tabulated by treatment. Summary statistics of assessed laboratory values will be tabulated by treatment.

9.7 Interim Analysis

No interim analysis is planned for this study.

9.8 Randomization

Subjects will be randomized and assigned to one of the four treatment sequences shown below where A, B, C, and D represent each of the 4 treatment groups by a random determination:

Sequence 1: ABCD

Sequence 2: BDAC

Sequence 3: CADB

Sequence 4: DCBA

The randomization will not be stratified. If all subjects complete the study then the design is balanced for both period and first-order carryover effects.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

The study administration structure is provided in Table 10-1.

Table 10-1. Study Administrative Structure

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

10.2 Regulatory Authority Approval

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

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

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

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

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

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

10.4 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/IEC and Pearl prior to initiation of the study.

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

10.5 Confidentiality

10.5.1 Confidentiality of Data

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

10.5.2 Confidentiality of Subject/Patient Records

By signing this protocol, the Investigator agrees that Pearl (or representative), IRB/IEC, or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the 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. In addition, the Investigator agrees to treat all subject/patient data used and disclosed in connection with this study in accordance with all applicable privacy laws (ie., Health Insurance Portability and Accountability Act), rules, and regulations.

10.6 Quality Control and Assurance

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

10.7 Data Management

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

10.8 Study Monitoring

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

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

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

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

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

10.9 Retention of Data

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

10.10 Financial Disclosure

The Principal Investigator or sub-Investigators named on the Form FDA 1572 will need to complete a financial disclosure form prior to study initiation, at any time during the study execution if new information needs to be disclosed, and for 1 year after study completion.

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

10.11 Investigator's Final Report

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

10.12 Publication Policy

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

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

1. **Responsibility:** Each principal Investigator is responsible for the accuracy and completeness of all data from their site. Pearl (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.
2. **Authorship and Publication Committee:** Pearl, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE and ISMPP. It is anticipated that a publication committee will be formed to assume oversight of these activities. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
3. **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted at least 30 days prior to submission for publication or presentation to Pearl for review, approval, and to ensure consistency with the policy in this protocol. Pearl will have the right to request appropriate modification to correct facts and to represent its opinions, or the opinions of the publication committee, if these differ with the proposed publication.
4. **Confidentiality:** Investigators will conduct all interactions with Pearl and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as

future plans, results of nonclinical studies, or chemical formulae) may still need to remain confidential.

5. **Medical Journal Review:** Consistent with the intention of Pearl to publish the study in a fair and accurate manner, Pearl supports diligence in the publication review process of medical journals. Accordingly, upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, eg., protocol and amendments, data tabulations, etc. The journal and reviewers will need to make arrangements to maintain the confidentiality of such supplemental information, where relevant, and Pearl will make suitable arrangements to ensure that the identity of journal reviewers is kept confidential. Records will be maintained of reviewers and the respective documents and datasets that were reviewed by each of them.
6. **Reporting of Clinical Trials Results:** To provide transparency in the conduct and reporting of randomized clinical trials, Pearl reports clinical findings based on the guidance of The CONSORT (CONsolidated Standards of Reporting Trials) Statement [CONSORT, 2010] and a 25-item checklist which is intended to improve the reporting of a randomized controlled trial, facilitate reader understanding of the trial design, conduct, analysis and interpretation, and to support their ability to assess the validity of its results.
7. **Internet Clinical Trial Listing:** In addition, also consistent with the recommendations of the ICMJE, Pearl will make available appropriate information regarding the study via the internet. This will include registration and listing of the study on www.clinicaltrials.gov, the US National Institutes of Health listing of clinical trials.

11 REFERENCE LIST

Aalbers R, Ayres J, Backer V, et al. Formoterol in patients with chronic obstructive pulmonary disease: a randomized, controlled, 3-month trial. Eur Respir J. 2002; 9:936-43.

Anderson, GP. Formoterol: Pharmacology, molecular basis of agonism, and mechanism of long duration of a highly potent and selective β2 adrenoceptor agonist bronchodilator. Life Sciences. 1993;52(26):2145-60.

Berger WE, Nadel JA. Efficacy and safety of formoterol for the treatment of chronic obstructive pulmonary disease. Respir Med. 2008;102:173-88.

Campbell M, Eliraz A, Johansson G, et al. Formoterol for maintenance and as-needed treatment of chronic obstructive pulmonary disease. Respir Med. 2005;99:1511-20.

Campbell SC, Criner GJ, Levine BE, et al. Cardiac safety of formoterol 12 µg twice daily in patients with chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2007;20:571-79.

Chapman K, Bateman E, Gallagher N, Hu H, Banerji D. Once-daily QVA149 improves lung function, dyspnea, and health status independent of disease severity and prior medications: The SHINE Study [abstract]. Chest. 2014;145(3 Suppl):401A.

Celli B, Crater G, Kilbride S, et al. Once-daily umeclidnium/vilanterol 125/25 mcg in COPD: a randomized, controlled study. Chest. 2014;13-1579.

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

Dahl R, Greefhorst LA, Nowak D, et al. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164:778-84.

Dahl R, Jadayel D, Alagappan V, Chen H, Banerji D. Efficacy and safety of once-daily QVA149 compared with the free combination of its monocomponents: The BEACON Study [abstract]. Chest. 2014;145(3 Suppl):407A.

Dellamary LA, Tarara TE, Smith DJ, et al. Hollow porous particles in metered dose inhalers. Pharm Res. 2000;17(2):168-74.

Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. Respir Med. 2013;107(10):1538-46.

Funada A, Hayashi K, Ino H, et al. Assessment of QT intervals and prevalence of short QT syndrome in Japan. Clin Cardiol. 2008 Jun;31(6):270-4.

Global strategy for the diagnosis, management, and prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. http://www.goldcopd.org. Accessed 14 March 2014.

Hirst PH, Pitcairn GR, Weers JG, et al. In vivo lung deposition of hollow porous particles from a pressurized metered dose inhaler. Pharm Res. 2002;19(3):258-64.

Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c869. doi: 10.1136/bmj.c869

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

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

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;121:1058-69.

Wedzicha J, Ficker J, Niewohner D, Sandström T, Fowlertaylor A, Banerji D. Dual bronchodilation with once-daily QVA149 reduces exacerbations, improves lung function and health status versus glycopyrronium and tiotropium in severe-to-very severe COPD patients: The SPARK Study [abstract]. Chest. 2014;145(3 Suppl): 406A.

Yatomi Y. Reference Values. In: Yazaki Y, editor. Asakura Internal Medicine. 10th ed. Tokyo, Japan: Asakura Publishing; 2013. p. 3 Appendix.

Appendix 1 Administration of Study Drug

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

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.

GFF MDI and GP MDI Administration: A Pharmacy Manual containing GFF MDI and GP MDI dosage preparation and administration information will be provided to the study site. For each GFF MDI and GP 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 in the eCRF. The two GFF MDI treatments and two GP MDI treatments are:

- GFF MDI 28.8/9.6 µg
- GFF MDI 14.4/9.6 µg
- GP MDI 28.8 µg
- GP MDI 14.4 µg

The MDI dose delivery specifications for the four treatments are provided in Table A1-1.

Table A1-1. MDI Dose Delivery Specifications

Product Name & Dose	Product Strength	Dosage Form	Administration
GFF MDI 28.8/9.6 µg ex-actuator	14.4/4.8 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
GP MDI 28.8 µg ex-actuator	14.4 µg/actuation	MDI	Taken as 2 inhalations
GP MDI 14.4 µg ex-actuator	7.2 µg/actuation	MDI	Taken as 2 inhalations

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

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

The following study activities and assessments will be performed:

- Collect approximately 5 mL of blood into a single tube containing EDTA tripotassium (4×10^{3}M in phosphate buffered saline). Care should be taken to minimize hemolysis during sample collection.
- Place all tubes on wet ice immediately after collection.
- Centrifuge the blood within 30 minutes of collection at >1000 x g (~2500 rpm) for 10 to 15 minutes.
- Transfer approximately equal aliquots (Aliquot A and Aliquot B) of plasma into duplicate labeled polypropylene test tubes with a snap or screw cap. Care should be taken to minimize contamination with red blood cells (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 3 days prior to a holiday via priority overnight delivery.
- Ship Aliquot A samples first.
- Aliquot B samples should be retained frozen until receipt of Aliquot A samples is confirmed and then shipped according to instruction.

Shipping Address:

[redacted]

ATTENTION: Sample Management

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

Appendix 3 Sponsor Signatory

Study Title: A Phase I, Randomized, Double-Blind, Single-Dose, Four-Period, Four-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Two Doses of PT003 and Two Doses of PT001 in Japanese Healthy Subjects

Study Number: PT003010

Final Date: Version 1.0, [redacted]

Signature: [redacted] Date: [redacted]

Name: [redacted]

Title: [redacted]

Pearl Therapeutics Inc.

Appendix 4 Investigator's Agreement and Signature Page

Study Title: A Phase I, Randomized, Double-Blind, Single-Dose, Four-Period, Four-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Two Doses of PT003 and Two Doses of PT001 in Japanese Healthy Subjects

Study Number: PT003010 **Final Date:** Version 1.0, [redacted]

I agree:

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

Signature: [redacted] Date: [redacted]

Name: [redacted]

Affiliation: [redacted]

Clinical Trial Protocol: PT003010-01

Study Title:	A Phase I, Randomized, Double-Blind, Single-Dose, Four-Period, Four-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Two Doses of PT003 and Two Doses of PT001 in Japanese Healthy Subjects
Study Number:	PT003010-01
Study Phase:	Phase I
Product Name:	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; PT003, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler (GFF MDI) Glycopyrronium Inhalation Aerosol; PT001, Glycopyrrolate MDI (GP MDI)
IND Number:	107739
Investigators:	Single Center
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]

	Version Number	Date
Original Protocol	Version 1.0	[redacted]
Amendment 1	Version 2.0	[redacted]

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

Based on the points which required clarification in the Administrative Letters dated [redacted] and removal of a safety endpoint that was incorrectly listed in the protocol the following changes have been incorporated into Amendment 1 (Version 2.0) of the Study PT003010 protocol.

1. In the Synopsis, Section 3.2, and Section 9.6 the safety endpoints incorrectly listed respiratory rate and has been removed.

2. In Section 3.3 the word "from" has been removed from the statement *"The PK of from GFF MDI"* on page 3 and page 17 for grammatical reasons.

3. In Section 7.8.1 Laboratory Parameters section refers to clinical chemistry collection at what are actually each PK time point. The text has been revised to correctly read *"Laboratory testing (hematology with differential, clinical chemistry, and urinalysis) will be performed using standard methods. Blood and urine samples for the clinical laboratory tests listed in Table 7-1 will be collected at Screening and on the day of clinic admission (Day -1 of each Treatment Period). Blood sample volumes will meet the laboratory's specification. Blood for PK will be collected during each of the four single-dose Treatment Periods at 30 minutes prior to dosing and then at 2, 6, 20, and 40 minutes post-dose and 1, 2, 4, 8, 10, 12, 16, and 24 hours post-dose. In addition, blood will be drawn for glucose and potassium level determinations within 1 hour prior to dosing and at 30 minutes and 2 and 4 hours post administration of study drug on Day 1 (see Table 8-2). 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."*

4. In Table 7-1. List of Laboratory Tests serum iron and ferritin were added to the safety panel for accuracy.

5. In Table 8-2. Schedule of Inpatient Period Assessments AEs and concomitant medications have been added to the 16 and 24 hour time point to correctly reflect visit procedures.

6. In Table 8-2. Schedule of Inpatient Period Assessments Clinic Admission (Day -1) the bullet *"Randomization and treatment assignment"* has been removed as the procedure is for the Pharmacist to assign randomization numbers to subjects only after they meet all pre-dose eligibility on Day 1.

7. In Section 8.3 Treatment Period 1 (Day 1) the bullet *"Randomization and treatment assignment"* has been added, as the actual procedure is for the Pharmacist to assign randomization numbers to subjects only after they meet all pre-dose eligibility on Day 1.

8. In Section 8.3 the 5th bullet point erroneously stated: *"Collect blood samples for laboratory testing (glucose and potassium only)"* and has been revised to state: *"Collect blood samples for clinical laboratory testing per Table 8-2."*

9. In Section 8.3 the last bullet is inconsistent with the last bullet in Section 8.3 and has been updated to state: *"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 a minimum of 7 days to a maximum of 14 days between doses."*

10. In Section 10.4 the last paragraph has been updated to state: *"The Investigator or designee will be responsible for obtaining written informed consent from potential subjects prior to any study-specific screening and entry into the study."*

11. In Appendix 1 first sentence under the header **GFF MDI and GP MDI Administration,** which stated "*A Pharmacy Manual containing GFF MDI and GP MDI dosage preparation and administration information will be provided to the study site.*" has been deleted and replaced with the following: "*For each GFF MDI and GP 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 in the eCRF. The two GFF MDI treatments and two GP MDI treatments are:*

    GFF MDI 28.8/9.6 µg

    GFF MDI 14.4/9.6 µg

    GP MDI 28.8 µg

    GP MDI 14.4 µg"

12. In addition, the opportunity was taken to address other minor protocol inconsistencies and typographical errors and formatting corrections.

SYNOPSIS

Sponsor:
Pearl Therapeutics, Inc.
[redacted]

Name of Finished Product:

- Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; PT003, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler (GFF MDI)
- Glycopyrronium Inhalation Aerosol; PT001, Glycopyrrolate MDI (GP MDI)

Name of Active Ingredients:

- Glycopyrronium
- Formoterol fumarate

Study Title:
A Phase I, Randomized, Double-Blind, Single-Dose, Four-Period, Four-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Two Doses of Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI) and Two Doses of Glycopyrronium Inhalation Aerosol (GP MDI) in Japanese Healthy Subjects

Study Number:
PT003010-01

Study Phase: Phase I

Primary Objective:
The primary objective of the study is to describe the pharmacokinetic (PK) profile of single administration of two doses of GFF MDI and two doses of GP MDI in adult Japanese healthy subjects.

Secondary Objective:
The secondary objective of the study is to assess the safety of two doses of GFF MDI and two doses of GP MDI in adult Japanese healthy subjects.

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

- GFF MDI 28.8/9.6 µg
- GFF MDI 14.4/9.6 µg
- GP MDI 28.8 µg
- GP MDI 14.4 µg

Following determination of study eligibility, subjects will be randomized to one of four treatment sequences balanced for carryover and period effects. At the target of 24 subjects randomized, each sequence will be used six times. If all subjects complete the study, the design is balanced for both period and first-order carryover effects.

Study Population:

Twenty-four adult Japanese healthy male and female subjects are planned for randomization in the study. The sample size of 24 randomized subjects is selected to provide approximately 20 completers. Full inclusion and exclusion criteria are listed in Section 5.

Test Product, Dose, and Mode of Administration:

All dosing of the study drug will be by oral inhalation. The two doses of GFF MDI (28.8/9.6 µg and 14.4/9.6 µg) and the two doses of GP MDI (28.8 µg and 14.4 µg) will be administered on separate test days. The characteristics of the two GFF MDI doses and the two GP MDI doses that will be administered during the study are provided below:

Product Name & Dose	Product Strength	Dosage Form	Administration
GFF MDI 28.8/9.6 µg ex-actuator	14.4/4.8 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
GP MDI 28.8 µg ex-actuator	14.4 µg/actuation	MDI	Taken as 2 inhalations
GP MDI 14.4 µg ex-actuator	7.2 µg/actuation	MDI	Taken as 2 inhalations

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

Duration of Treatment:

This study will include a Screening Period of up to 28 days and four single-dose Treatment Periods separated by a minimum Washout Period of 7 days to a maximum of 14 days for added scheduling flexibility. The planned participation in the study is between 33 and 98 days.

Pharmacokinetic Assessments: The PK of GFF MDI and GP MDI will be assessed and compared using plasma concentrations of glycopyrronium and formoterol. Timepoints for PK blood sample collection during each of the four single-dose Treatment 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, 12, 16, and 24 hours post-dose. Pharmacokinetic parameters at all doses will include maximum plasma concentration (C_{max}), area under the curve from 0 to 12 hours (AUC_{0-12}), area under the curve from 0 to time of the last measurable plasma concentration (AUC_{0-t}), area under the curve from 0 extrapolated to infinity ($AUC_{0-\infty}$), time to maximum plasma concentration (t_{max}), apparent terminal elimination half-life ($t_{½}$), apparent total body clearance (CL/F), apparent volume of distribution (Vd/F), and terminal elimination rate constant (λ_z). Other PK parameters may be calculated, as appropriate.

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

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 drug. • 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 GFF MDI or GP MDI. For this population, data potentially affected by major protocol deviations will be removed (to be determined prior to unblinding). Summary statistics will be used to describe the PK parameters after treatment with GFF MDI or GP MDI. The sample size of 24 randomized subjects is selected to provide approximately 20 completers and reasonable estimates of the PK parameters in adult Japanese healthy subjects.
Date of Original Protocol: [redacted]
Date of Amendment 1: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ALT	Alanine Aminotransferase
API	Active Pharmaceutical Ingredients
AR(1)	First Order Auto Regressive
AST	Aspartate Aminotransferase
AUC_{0-12}	Area Under the Curve from 0 to 12 hours
AUC_{0-t}	Area Under the Curve from 0 to Time of the Last Measurable Plasma Concentration
$AUC_{0-\infty}$	Area Under the Curve from 0 Extrapolated to Infinity
BID	Bis In Die, Twice Daily
BP	Blood Pressure
CBC	Complete Blood Cell
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation (according to National Kidney Disease Education Program)
CL/F	Apparent Total Body Clearance
C_{max}	Maximum Plasma Concentration
COPD	Chronic Obstructive Pulmonary Disease
CV	Coefficient of variation
dL	Deciliter
DSPC	Distearoylphosphatidylcholine
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
eg.	Exempli Gratia, for example
EU	European Union
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration

FEV_1	Forced Expiratory Volume in One Second
FF MDI	Formoterol Fumarate Metered Dose Inhaler
FSH	Follicle-Stimulating Hormone
g	Gram
GCP	Good Clinical Practice
GFF MDI	Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler
GFR	Glomerular Filtration Rate
GMR	Geometric Mean Ratio
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP MDI	Glycopyrronium Metered Dose Inhaler
HbsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HFA	Hydrofluoroalkane
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroid
ICMJE	International Committee of Medical Journal Editors
ie.	Id Est, that is
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
ISMPP	International Society for Medical Publications Professionals
IV	Intravenous
LABA	Long-Acting β_2-Agonist
LAMA	Long-Acting Muscarinic Antagonist
λ_z	Terminal Elimination Rate Constant

MDI	Metered Dose Inhaler
µg	Microgram
µL	Microliter
mg	Milligram
mL	Milliliter
mmHg	Millimeter of Mercury
msec (ms)	Millisecond
PK	Pharmacokinetics
QD	Once Daily
QTcF	QT corrected for heart rate with Fridericia's formula
RBC	Red Blood Cell
REML	Restricted Maximum Likelihood
SABA	Short-Acting β_2-Agonist
SAE	Serious Adverse Event
[redacted]	[redacted]
SOP	Standard Operating Procedure
$t_{½}$	Apparent Terminal Elimination Half-life
[redacted]	[redacted]
TEAE	Treatment-emergent adverse event
TID	Three Times Daily
t_{max}	Time to Maximum Plasma Concentration
US	United States
Vd/F	Apparent Volume of Distribution
WBC	White Blood Cell

TRADEMARK INFORMATION

Trademarks not owned by Pearl Therapeutics, Inc.:

Aerolizer

Breezhaler

Cuvposa

Foradil

Oxis

Robinul

Seebri

Symbicort

Turbohaler

Ziploc

1 INTRODUCTION

Pearl Therapeutics, Inc. (hereafter referred to as Pearl) is developing a combination product, Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (PT003; hereafter referred to as glycopyrronium and formoterol fumarate metered dose inhaler [GFF MDI]), for the treatment of chronic obstructive pulmonary disease (COPD). In parallel, Pearl is also developing the individual product, Glycopyrronium Inhalation Aerosol (PT001; hereafter referred to as glycopyrronium metered dose inhaler [GP MDI]) for the treatment of COPD.

Glycopyrronium and formoterol fumarate are components (alone or in combination) of approved inhalation products for treatment of subjects with COPD and their safety and efficacy are well characterized. Clinical and non-clinical studies conducted with the Pearl dual combination product, GFF MDI and its individual components, glycopyrronium (GP) MDI and formoterol fumarate (FF) MDI support the evaluation of GFF MDI in this Phase I study in healthy subjects (Study PT003010). GFF MDI, GP MDI, and FF MDI are currently being evaluated in Phase III clinical studies in subjects with COPD.

1.1 Chronic Obstructive Pulmonary Disease

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

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are β_2-agonists, anticholinergics, and methylxanthines used as monotherapy or in combination. Treatment with long-acting bronchodilators is more convenient and more effective at producing maintained symptom relief than treatment with short-acting bronchodilators. Combining bronchodilators from different pharmacological classes may improve efficacy and decrease the risk of side effects compared with increasing the dose of a single bronchodilator [GOLD, 2014]. Long-acting β_2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) reduce bronchoconstriction through different mechanisms, and there is a long history of combination therapy for COPD with short-acting agents in these classes.

1.2 Glycopyrronium

Glycopyrronium (the active moiety of glycopyrronium bromide, also referred to as glycopyrrolate) is a LAMA which exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. Glycopyrronium is approved in many countries in multiple formulations for different indications, including 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 1361 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) European Public Assessment Report for Seebri Breezhaler, 2012]. In addition to the published data with Seebri Breezhaler (also referred to as NVA237), there is also 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 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 pre-operative 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 twice daily (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 United States (US) as an oral solution (Cuvposa®) which is indicated to reduce chronic severe drooling in patients aged three to16 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® Turbohaler®, 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 β_2 adrenoreceptors in the airways, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction.

Although formoterol fumarate is classified as a LABA, it has a rapid onset of action similar to short-acting β_2-agonists (SABAs). Formoterol fumarate is highly potent, displays high intrinsic activity, and can result in greater than 80% relaxation even under induced tone [Anderson, 1993]. Studies in 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 2500 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 Pearl's GFF MDI

Pearl is developing GFF MDI, GP MDI, and FF MDI using its porous particle technology platform. This technology is based on spray dried porous particles comprised of distearoylphophatidylcholine and calcium chloride that are co-suspended with micronized active pharmaceutical ingredients (APIs) in a 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 technology also enables reproducible administration of very low doses of potent therapeutics.

1.5 Study Rationale

Published studies have shown that the complementary mechanisms of action of a LABA (formoterol fumarate) and a LAMA (tiotropium bromide) significantly improved bronchodilation in subjects with COPD compared with the individual agents [Celli 2014, Chapman 2014, Dahl 2014, Donohue 2013, Wedzicha 2014]. Currently, fixed-dose combinations of a LABA and LAMA are available for the treatment of COPD in various countries worldwide, including the US, the EU, Japan, the United Kingdom, etc.

Pearl is developing the combination product, GFF MDI (14.4/9.6 μg ex-actuator [dose delivered from the actuator, ie., mouthpiece, of the MDI]), as a BID maintenance bronchodilator treatment in subjects with COPD. In parallel, Pearl is also developing the individual products, GP MDI (14.4 μg ex-actuator, BID) and FF MDI (9.6 μg ex-actuator, BID) as maintenance bronchodilator treatments in subjects with COPD. These doses of GFF MDI (14.4/9.6 μg) and GP MDI (14.4 μg) administered in this study in healthy Japanese subjects are doses being tested in global Phase III studies to support the approval of GFF MDI and GP MDI.

The purpose of this study is to characterize the pharmacokinetic (PK) profile of two doses of GFF MDI and GP MDI in adult Japanese healthy subjects using the defined doses (14.4/9.6 μg and 14.4 μg, respectively) and 2-fold higher doses of GFF MDI and GP MDI (28.8/9.6 μg and 28.8 μg, respectively).

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to describe the PK profile of single administration of two doses of GFF MDI and two doses of GP MDI in adult Japanese healthy subjects.

2.2 Secondary Objective

The secondary objective of the study is to assess the safety of two doses of GFF MDI and two doses of GP MDI in adult Japanese healthy subjects.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

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

3.2 Safety Endpoints

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

3.3 Pharmacokinetic Endpoints

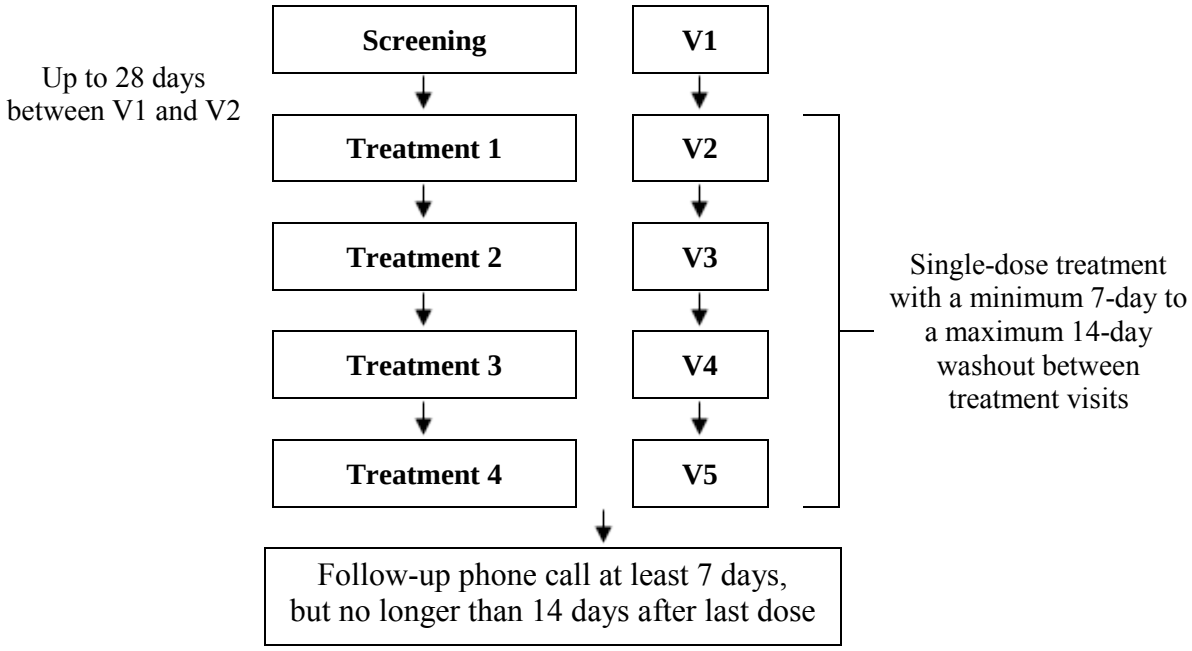
The PK of GFF MDI and GP MDI will be assessed and compared using plasma concentrations of glycopyrronium and formoterol. Timepoints for PK blood sample collection during each of the four single-dose Treatment Periods will be at 30 minutes prior to dosing and then at 2, 6, 20, and 40 minutes post-dose and 1, 2, 4, 8, 10, 12, 16, and 24 hours post-dose (see Table 8-2). Pharmacokinetic parameters at all doses will include maximum plasma concentration (C_{max}), area under the curve from 0 to 12 hours (AUC_{0-12}), area under the curve from 0 to time of the last measurable plasma concentration (AUC_{0-t}), area under the curve from 0 extrapolated to infinity ($AUC_{0-\infty}$), time to maximum plasma concentration (t_{max}), apparent terminal elimination half-life ($t_{½}$), apparent total body clearance (CL/F), apparent volume of distribution (Vd/F), and termination elimination rate constant (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, Phase I study with a randomized, double-blind, four-period, four-treatment, cross-over design to assess the safety and PK of two doses of GFF MDI and two doses of GP MDI in healthy Japanese subjects. The overall study design is summarized and illustrated in Figure 4-1.

Figure 4-1. Study Design



Subjects who provide informed consent, undergo screening procedures, and qualify for the study will be randomized to one of four treatment sequences. Each treatment sequence will contain GFF MDI 28.8/9.6 µg, GFF MDI 14.4/9.6 µg, GP MDI 28.8 µg, and GP MDI 14.4 µg. At the target of 24 subjects randomized, each of the four sequences will be used six times. If all subjects complete the study, the design is balanced for both period and first-order carryover effects.

Each inpatient treatment session will be separated by a minimum outpatient Washout Period of 7 days to a maximum of 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 clinic.

Safety data will be closely monitored and baseline and post-dosing serial blood draws (Section 7.9) for PK analysis (see Table 8-2) will be obtained during each inpatient Treatment Period. After all scheduled assessments are completed and all available safety

data have been reviewed by the Principal Investigator, subjects will be discharged from the clinic. Following the first Treatment Period, subjects will return to the clinic the following week for their next Treatment Period until all four Treatment Periods have been completed. The Washout Period between Treatment Periods will consist of a minimum of 7 days to a maximum of 14 days between doses. Other safety assessments will be obtained as listed in Table 8-2. A follow-up phone call will be conducted at least 7 days, but no longer than 14 days after completion of the last dose date on Treatment Period 4.

4.2 Study Duration and Dates

This study will include a Screening Period of up to 28 days and four single-dose Treatment Periods separated by a minimum Washout Period of 7 days to a maximum of 14 days for added scheduling flexibility. A follow-up phone call will be conducted at least 7 days but no longer than 14 days after completion of the last dose date on Treatment Period 4. The planned participation in the study is between 33 and 98 days.

5 STUDY POPULATION SELECTION

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

5.1 Inclusion Criteria

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

1. Signed and dated Institutional Review Board/ Independent Ethics Committee (IRB/IEC)-approved Informed Consent form (ICF) before any protocol-specific screening procedures are performed.
2. Male and female first generation Japanese subjects 18 to 45 years, inclusive:
   - *First generation subjects who were born in Japan to two parents and four grandparents also born in Japan of full Japanese descent*
   - *Subjects must be expatriate of Japan residing outside of Japan for less than 5 years*
   - *Subjects must have a valid Japanese passport*
   - *Subjects who have a body weight >50 kg (110 lbs) and body mass index between 18.0 and 30.0 kg/m^2, 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 7 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. 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 7 days after the Final Visit as a safety precaution. Females of non-childbearing potential, defined as surgically sterile (status post-hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months, do not require contraception during the study. Post-menopausal must be confirmed by a serum follicle-stimulating hormone (FSH) test at Screening and the reason must be documented in the medical history electronic Case Report form (eCRF).
6. 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.

7. 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.

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 four Treatment Periods.
3. Subjects with clinically significant neurologic, cardiovascular, hepatic, renal, endocrinologic, pulmonary, hematological, psychiatric, or other medical illness that would interfere with participation in this study.
4. Subjects with a history of ECG abnormalities including PR >220 msec; QRS complex >110 msec; QT corrected for heart rate with Fridericia's formula (QTcF) >429 msec and QTcF >436 msec in males and females, respectively based on normal population data in the Japanese population [Funada, 2008]; 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 (ie. 12 lead ECGs performed at Screening or baseline [pre-dose on Day 1 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 study site staff.
7. Subjects who have cancer that has not been in complete remission for at least 5 years.
8. Supine BP >140/90 mmHg or resting HR ≥100 bpm at Screening, baseline (pre-dose on Day 1 of the first Treatment Period).
9. Male subjects with symptomatic prostatic hypertrophy that is clinically significant in the opinion of the Investigator.
10. Male subjects with a trans-urethral resection of the prostate or full resection of the prostate within 6 months prior to Screening.

11. Subjects with bladder neck obstruction or urinary retention that is clinically significant in the opinion of the Investigator.
12. Subjects with a diagnosis of glaucoma that in the opinion of the Investigator has not been adequately treated. All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective β-blockers such as betaxolol, carteolol, levobunolol, metipranolol, 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 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 Screening 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 study drug administration.
17. 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.
18. Blood collection of greater than 500 mL within 56 days prior to Screening.
19. Subjects with pre-existing anemia and/or iron deficiency anemia **Note:** Subjects with anemia (defined as hemoglobin 13.8-16.6 g/dL and 11.3-15.5 g/dL for males and females, respectively, and hematocrit 40.2%-49.4% and 34.4%-45.6% for males and females, respectively [Yatomi, 2013]).
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 4 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 4 weeks of drug administration.
25. Any other condition and/or situation that causes the Investigator to deem a subject unsuitable for the study (eg., due to expected study drug non-compliance, inability to medically tolerate the study procedures, or a subject's unwillingness to comply with study-related procedures).
26. Subjects with abnormal-glomerular filtration rate (GFR; estimated GFR <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 Screening. Only subjects continuing to meet entry inclusion/exclusion criteria at Treatment Period 1 will be assigned a unique subject randomization number.

5.4 Prior, Concomitant, and Prohibited Medications

Investigational therapies are not permitted within 30 days or five half-lives (whichever is longer) prior to study drug administration. 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. 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 ICF will be documented as prior study drugs 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 to whenever the subject discontinues the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented.

In addition to Exclusion Criterion #14 (subjects are excluded if a history of smoking or use of nicotine-containing products within 3 months of Screening by self-reporting), the use of electronic cigarettes within 3 months of Screening is also exclusionary.

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.

5.6 Removal of Subjects from the Study 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 an adverse event

- 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.

5.7 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. The reason should be communicated in writing to Pearl.

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

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. The Pearl products (GFF MDI and GP MDI) are identical in form and function and indistinguishable from each other. The characteristics of the two GFF MDI doses and the two GP MDI doses that will be administered during the study are provided in Table 6-1.

An unblinded pharmacist at the study site will be provided with a written randomization scheme for allocation of subjects to one of four treatment sequences and to manage the distribution of clinical supplies. The four treatment sequences are listed below, where A, B, C, and D each represent one of the four treatments by random selection. Six of the planned 24 subjects will be included in each treatment sequence. Should all subjects complete the study, the design is balanced for period and first-order carryover effects.

Sequence 1: ABCD

Sequence 2: BDAC

Sequence 3: CADB

Sequence 4: DCBA

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 GFF MDI 28.8/9.6 µg, GFF MDI 14.4/9.6 µg, GP MDI 28.8 µg, and GP MDI 14.4 µg by random assignment to one of four 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 GFF MDI active drug substances are glycopyrronium and formoterol fumarate and the active drug substance of the GP MDI is glycopyrronium.

Investigational materials will be provided by Pearl as summarized in Table 6-1.

Table 6-1. Product Descriptions

Product Name & Dose	Product Strength	Dosage Form	Administration
GFF MDI 28.8/9.6 µg ex-actuator	14.4/4.8 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
GP MDI 28.8 µg ex-actuator	14.4 µg/actuation	MDI	Taken as 2 inhalations
GP MDI 14.4 µg ex-actuator	7.2 µg/actuation	MDI	Taken as 2 inhalations

Abbreviations: GFF MDI=Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; GP MDI=glycopyrronium 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 four treatment sequences. The treatment and study visit schedule is illustrated in Figure 4-1 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 the four treatments.

GFF MDI and GP 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.

6.5 Unblinding Procedures

Pearl 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 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

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

Clinical supplies for this study will be provided to the study site pharmacy by [redacted]. The clinical supplies storage area at the study site must be monitored by the study 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 1.

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 drug should be handled in accordance with Good Pharmacy Practices. The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned to [redacted].

The study site should check with the Pearl 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 IRB/IEC. 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 28 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 personal health history, family health history, history of hospitalization, and history of surgeries.

7.4 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.

7.5 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

7.6 Vital Signs

Vital sign determinations, including BP, HR, 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 1 hour prior to administration of study drug and 30 minutes, 2 hours, and 12 hours post-administration of study drug (see Table 8-2).

7.7 Electrocardiography

Twelve-lead ECGs will be recorded at Screening, and on each clinic admission day (Day -1) of each Treatment Period (baseline represents pre-dose on Day 1 of the first Treatment Period). On each treatment day (Day 1), 12-lead ECGs will be obtained within 1 hour prior to dosing and at 30 minutes and 2 and 12 hours post-dosing (see Table 8-2). 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.

7.8 Clinical Laboratory Tests

7.8.1 Laboratory Parameters

Laboratory testing (hematology with differential, clinical chemistry, and urinalysis) will be performed using standard methods. Blood and urine samples for the clinical laboratory tests listed in Table 7-1 will be collected at Screening and on the day of clinic admission (Day -1 of each Treatment Period). Blood sample volumes will meet the laboratory's specification. Blood for PK will be collected during each of the four single-dose Treatment Periods at 30 minutes prior to dosing and then at 2, 6, 20, and 40 minutes post-dose and 1, 2, 4, 8, 10, 12, 16, and 24 hours post-dose. In addition, blood will be drawn for glucose and potassium level determinations within 1 hour prior to dosing and at 30 minutes and 2 and 4 hours post administration of study drug on Day 1 (see Table 8-2). 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 7-1. List of Laboratory Tests

Hematology	Clinical Chemistry	
Hematocrit [a] Hemoglobin Platelet count Red blood cell (RBC) count WBC count WBC differential Mean corpuscular volume (MCV) Mean cell hemoglobin (MCH) MCH concentration (MCHC)	Creatinine [b] Potassium (K+) [c] Sodium (Na+) Chloride (Cl-) Magnesium (Mg++) Calcium Serum iron Ferritin Inorganic phosphate Glucose [c] Urea Bilirubin (Total)	Bilirubin (direct) Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-glutamyltransferase (GGT) Alkaline phosphatase Total Protein Albumin
Urinalysis: Macroscopic examination routinely including specific gravity, pH, protein, glucose, ketones, blood, and urobilinogen. A microscopic examination will be performed if warranted based on macroscopic results.		
Urine drug screen: A urine sample will be collected and analyzed (positive or negative) for drugs of abuse including amphetamine, opiate, cocaine, barbiturates, benzodiazepines, and marijuana [tetrahydrocannabinol].		
Breathalyzer Test: A breathalyzer test will be performed for the presence of alcohol (positive or negative).		
Serology: Testing for HbsAg, Hepatitis C antibody and HIV will be performed at Screening only. Results of each serology test will be reported as either positive or negative.		
For females who are not post-menopausal: A serum hCG test at Screening and urine hCG test at admission for each of the four Treatment Periods.		
For females of non-childbearing potential: A serum hCG test at Screening 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.		

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

[a] Packed cell volume
[b] Serum creatinine value will be used to calculate eGFR using CKD-EPI.
[c] Additionally, within 1 hour prior to dosing and at 30 minutes, 2 hours and 4 hours post-dose of each Treatment Period

7.8.2 Sample Collection, Storage, and Shipping

Detailed instructions for laboratory sample collection, processing, and shipping instructions will be provided in the [redacted] laboratory manual. Approximately 400 mL of blood will be collected per subject during the study.

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

7.9 Pharmacokinetic Assessments

Pharmacokinetic sampling will occur in conjunction with Treatment Periods 1, 2, 3, and 4.

Approximately 5 mL of whole blood will be collected at 30 minutes prior to dosing and then at 2, 6, 20, and 40 minutes post-dose and 1, 2, 4, 8, 10, 12, 16, and 24 hours post-dose. Samples will be collected via an indwelling IV 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 ≤-60 C. Refer to Appendix 2 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 glycopyrronium and formoterol will be determined using validated High Performance Liquid Chromatography tandem Mass Spectrometry methodology. Instructions for sample handling, storage, and shipping will be provided in the [redacted] laboratory manual.

Sample collections will be scheduled for the nominal timepoint and actual collection times recorded in the source documents (see Table 8-2).

7.10 Safety Assessments

7.10.1 Adverse Events Assessments

7.10.1.1 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. In addition, certain AEs (as described in Section 7.10.1.8) are classified as "serious" and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as an SAE to Pearl or its designee.

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

Adverse events 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. If this data is collected after the study database is locked, it will be reported to Pearl, but will not be included in the study database.

7.10.1.2 Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonisation (ICH) and the US Code of Federal Regulations (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 (eg., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (eg., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Adverse events include, but are not limited to:

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

An AE does not include:

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

7.10.1.3 Pre-Randomization Adverse Events

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

7.10.1.4 Treatment-Emergent Adverse Events

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

7.10.1.5 Severity

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

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

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

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

7.10.1.6 Relationship

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

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

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

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

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

7.10.1.7 Clinical Laboratory Adverse Events

Many laboratory abnormalities observed during the course of a study will be included under a reported AE describing a clinical syndrome (eg., elevated blood urea nitrogen and creatinine in the setting of an AE of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). In such cases, the laboratory abnormality itself (eg., elevated creatinine in a setting of renal failure) does not need to be recorded as an AE. However,

isolated laboratory abnormalities should be reported as AEs if they are considered to be clinically significant by the Investigator.

Criteria for a "clinically significant" laboratory abnormality are:

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

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

7.10.1.8 Serious Adverse Events

DEFINITION

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

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

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered 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.

REPORTING SERIOUS ADVERSE EVENTS

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for AE identification, documentation, grading, assignment of causality, and prompt notification of SAEs to the Pearl's Medical Monitor or designee. All SAEs must be reported to Pearl no later than 24 hours after the Investigator recognizes/classifies the event as an SAE. At a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report using the appropriate form (eg., SAE Report Form). After the initial report, as necessary, the Investigator must provide any additional information on an SAE to the Medical Monitor within 2 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.

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

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

7.10.1.9 Supplemental Investigation of Serious Adverse Events

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

7.10.1.10 Post Study Follow Up of Adverse Events

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

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

7.10.1.11 Notification of Post Study Serious Adverse Events

Investigators are not obligated to actively follow subjects after the completion of the study. However, if the 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, whether or not the event is attributable to study drug. All SAEs must be reported to Pearl no later than 24 hours after the Investigator recognizes/classifies the event as an SAE.

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

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

7.10.1.13 Health Authority Safety Reports

Pearl 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 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-sponsored clinical studies. Safety reports must be submitted to the appropriate IRB/IEC as soon as possible. Documentation of the submission to the IRB/IEC must be retained for each safety report.

7.10.2 Overdose

An overdose is defined as a dose greater than the highest dose level of each study drug evaluated in this study as described in Section 6.3 (Product Descriptions), which results in clinical signs and symptoms. In the event of an overdose of study drug, the Investigator should use clinical judgment in treating the overdose and contact the 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 for GFF MDI and GP MDI.

7.10.3 Pregnancy

Any pregnancy that occurs from Screening until study completion must be reported to Pearl. To ensure subject safety, each pregnancy must be reported to Pearl within 14 days of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child.

8 STUDY ACTIVITIES

A time and events schedule is provided in Table 8-1 and a schedule of inpatient period assessments is provided in Table 8-2.

Table 8-1. Study Visit Schedule

Procedure	Screening From Day -28	Inpatient Treatment Periods 1 Through 4		Follow Up Phone Call
		Day -1	Day 1	7 Days after last dose period (but no longer than 14 days)
Informed Consent	X			
Medical History	X	X		X
Demographics	X			
Physical Examination	X		X[a]	
Vital Signs	X[b]	X[b]	X[b]	
Eligibility Review	X	X		
Placebo MDI Usage Demonstration/Practice[c]	X	X	X	
12-lead ECG	X[b]	X[b]	X[b]	
Clinical Laboratory Testing	X[d]	X[d]	X[e, f]	
Adverse Events		X[g]	X	X
Concomitant Medications	X	X	X	X
Urine Drug Screen	X	X		
Alcohol Breathalyzer	X	X		
Pregnancy Test (women only)	X[h, i]	X[h]		
Serology: (HIV, HbsAg, Hep C)	X			
PK Assessment			X[b]	
Study Drug Administration			X[b]	
Inpatient Discharge			X[j]	

Abbreviations: ECG=electrocardiogram; HbsAg=hepatitis B surface antigen; Hep C=hepatitis C; HIV=human immunodeficiency virus; MDI=metered dose inhaler; PK=pharmacokinetic

Note: Following the first Treatment Period, subjects will return to the clinic the following week, for their next Treatment Period until all four Treatment Periods have been completed. The Washout Period between Treatment Periods will consist of a minimum of 7 days to a maximum 14 days between doses.

[a] Completed prior to discharge on Treatment Period 4 only, excluding height and weight.

[b] See the Schedule for Inpatient Period Assessments (Table 8-2) for detail regarding times and events for the Screening and baseline 12-lead ECG, vital signs, drug administration, and PK assessments during Treatment Periods 1 to 4.

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

[d] Urinalysis to be performed at Screening and Day -1 of each Treatment Period.

[e] Glucose, and Potassium ONLY - done within 1 hour prior to dosing and at 30 minutes and 2 and 4 hours post-dose

[f] Clinical chemistry and hematology at 12 hours post-dose.

[g] AEs will be collected from the time of the first dose of study drug.

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

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

[j] After all scheduled assessments are complete and all available safety data have been reviewed by the Investigator

Table 8-2. Schedule of Inpatient Period Assessments

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**	**16 hr**	**24 hr**
PK Blood Draw	X		X	X	X		X	X	X	X	X	X	X	X	X
Administration of Study Drug[a]		X[f]													
12-lead ECG[b]	X[c]					X			X				X		
Clinical Laboratory Tests	X[d]					X[d]			X[d]	X[d]			X[e]		
Vital Signs	X[c]					X			X				X		
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ECG=electrocardiogram; hr=hour; min=minutes; PK=pharmacokinetics

[a] Following the first Treatment Period, subjects will return to the clinic the following week, for their next Treatment Period until all four Treatment Periods have been completed. The Washout Period between Treatment Periods will consist of a minimum of 7 days to a maximum of 14 days between doses.

[b] Twelve-lead ECGs will be recorded at Screening, on Day -1of Treatment Period 1 to confirm eligibility, within 1 hour prior to dosing and as scheduled above. Completed within ±10 minutes of timepoint.

[c] Within 1 hour of dosing

[d] Glucose and potassium level determinations only within 1 hour prior to dosing and at 30 minutes and 2 and 4 hours post administration of study drug.

[e] Complete clinical laboratory testing – clinical chemistry and hematology

[f] Study drug administration on Day 1 only

8.1 Screening Period (Up to 28 Days Prior to Randomization)

The following procedures and assessments will be performed during Screening 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 (including urinalysis)
- Urine drug testing
- Alcohol breathalyzer test
- Serum pregnancy test (women only; for all women of childbearing potential and non-childbearing potential)
- Follicle-stimulating hormone test for women of non-childbearing potential
- Serology (HIV, HBsAg, and hepatitis C)
- Document concomitant medications

8.2 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, will be documented in the eCRF and/or source documents:

- Relevant medical history
- Vital signs
- Review of eligibility criteria
- Placebo MDI usage demonstration and practice
- 12-lead ECG
- Collect blood and urine samples for clinical laboratory testing
- Urine drug testing
- Alcohol breathalyzer test
- Urine pregnancy test for all women (childbearing and non-childbearing potential)
- Document concomitant medications

8.3 Treatment Period 1 (Day 1)

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

- Randomization and treatment assignment
- Placebo MDI usage demonstration and practice
- Pre- and post-dose documentation of vital signs per Table 8-2
- Administration of study drug (see Appendix 1 for details regarding study drug dispensing and administration)
  Note: Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.
- Collect pre- and post-dose PK samples per Table 8-2
- Collect blood samples for clinical laboratory testing per Table 8-2
- Perform 12-lead ECG per Table 8-2
- Documentation of AEs (Note: AEs that occur prior to dosing will be recorded as Medical History unless the event meets the definition of an SAE as defined in Section 7.10.1.8)
- Documentation of concomitant medications
- After all scheduled assessments are complete and all available safety data has been reviewed by the Investigator, discharge from clinic upon completion of all protocol-specified procedures and complete a Washout Period of a minimum of 7 days to a maximum of 14 days between doses

8.4 Treatment Periods 2, 3, and 4

During these three Treatment Periods, subjects will be admitted to the clinic as inpatients on Day -1 and remain inpatients until completion of all protocol-specified procedures listed below: The results of the following procedures and assessments will be documented in the eCRF and/or source documents:

- Review of medical history
- Vital signs at clinic admission on Day -1
- Review eligibility criteria on Day -1
- Placebo MDI usage demonstration and practice on Day -1
- Perform 12-lead ECG on Day -1
- Collect blood and urine samples for clinical laboratory testing 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 8-2
- Administration of study drug on Day 1 (see Appendix 1 for details regarding study drug dispensing and administration)
  Note: Subjects will wear a surgical mask approximately 30 minutes before and 30 minutes after dosing to prevent possible cross contamination.
- Collect pre- and post-dose PK samples on Day 1 per Table 8-2
- On Day 1, collect blood samples for clinical laboratory testing (glucose and potassium only) per Table 8-2
- Perform 12-lead ECG on Day 1 per Table 8-2
- Documentation of AEs on Day -1 and 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 Investigator, discharge from clinic upon completion of all protocol-specified procedures and complete a Washout Period of a minimum of 7 days to a maximum of 14 days between doses.

8.5 Follow-Up Phone Call

Upon completion of the study, a follow up phone call with each subject will be completed at least 7 days but no longer than 14 days from the last dose date. Subjects will be asked about any new or outstanding AEs, any new concomitant medication, and any changes to birth control method. This will be documented appropriately in the subject source documents and eCRFs.

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

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

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

Safety analyses will be performed on data from all subjects in the Safety Population. Adverse events, clinical laboratory evaluations, and other safety measures (eg., 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 of 24 randomized subjects is selected to provide approximately 20 completers. No formal criteria for the evaluation of PK were used to determine the sample size, but the chosen size is expected to provide reasonable estimates of the PK parameters in adult Japanese healthy subjects.

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 drug.
- 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 GFF MDI or GP MDI. For this population, data potentially affected by major protocol deviations will be removed (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 Screening, will be reported with the demographic information listed above.

9.5 Analysis of Pharmacokinetic Variables

Pharmacokinetic analysis will be performed using the PK population. Pharmacokinetic parameters at all doses will include C_{max}, t_{max}, $t_{½}$, AUC_{0-12}, AUC_{0-t}, $AUC_{0-\infty}$, 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 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 being selected. For AR(1), subject will be considered a random effect. For glycopyrronium 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.

9.6 Safety Analysis

Safety analysis will be performed using the Safety Population. The safety of GFF MDI and GP MDI will be assessed from physical examination findings, AE reporting including SAE reporting, vital signs (BP, HR, and body temperature), clinical laboratory values (hematology, clinical chemistry, and urinalysis), and findings from 12-lead safety ECGs. The incidence of AEs and SAEs will be tabulated by treatment. Summary statistics of assessed laboratory values will be tabulated by treatment.

9.7 Interim Analysis

No interim analysis is planned for this study.

9.8 Randomization

Subjects will be randomized and assigned to one of the four treatment sequences shown below where A, B, C, and D represent each of the 4 treatment groups by a random determination:

Sequence 1: ABCD

Sequence 2: BDAC

Sequence 3: CADB

Sequence 4: DCBA

The randomization will not be stratified. If all subjects complete the study then the design is balanced for both period and first-order carryover effects.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

The study administration structure is provided in Table 10-1.

Table 10-1. Study Administrative Structure

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

10.2 Regulatory Authority Approval

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

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

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

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

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

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

10.4 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/IEC and Pearl prior to initiation of the study.

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

10.5.2 Confidentiality of Subject/Patient Records

By signing this protocol, the Investigator agrees that Pearl (or representative), IRB/IEC, or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the 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. In addition, the Investigator agrees to treat all subject/patient data used and disclosed in connection with this study in accordance with all applicable privacy laws (ie., Health Insurance Portability and Accountability Act), rules, and regulations.

10.6 Quality Control and Assurance

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

10.7 Data Management

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

10.8 Study Monitoring

In accordance with applicable regulations, GCP, and Pearl procedures, clinical monitors will contact the study site prior to subject randomization to review the protocol and data collection procedures with study site staff. In addition, the monitor will periodically contact the study site, including conducting on-site visits. The extent, nature, and frequency of

on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrollment rate.

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

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

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

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

10.9 Retention of Data

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

10.10 Financial Disclosure

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

10.11 Investigator's Final Report

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

10.12 Publication Policy

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

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

1. **Responsibility:** Each principal Investigator is responsible for the accuracy and completeness of all data from their site. Pearl (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.
2. **Authorship and Publication Committee:** Pearl, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE and ISMPP. It is anticipated that a publication committee will be formed to assume oversight of these activities. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
3. **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted at least 30 days prior to submission for publication or presentation to Pearl for review, approval, and to ensure consistency with the policy in this protocol. Pearl will have the right to request appropriate modification to correct facts and to represent its

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

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

11 REFERENCE LIST

Aalbers R, Ayres J, Backer V, et al. Formoterol in patients with chronic obstructive pulmonary disease: a randomized, controlled, 3-month trial. Eur Respir J. 2002; 9:936-43.

Anderson, GP. Formoterol: Pharmacology, molecular basis of agonism, and mechanism of long duration of a highly potent and selective β_2 adrenoceptor agonist bronchodilator. Life Sciences. 1993;52(26):2145-60.

Berger WE, Nadel JA. Efficacy and safety of formoterol for the treatment of chronic obstructive pulmonary disease. Respir Med. 2008;102:173-88.

Campbell M, Eliraz A, Johansson G, et al. Formoterol for maintenance and as-needed treatment of chronic obstructive pulmonary disease. Respir Med. 2005;99:1511-20.

Campbell SC, Criner GJ, Levine BE, et al. Cardiac safety of formoterol 12 µg twice daily in patients with chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2007;20:571-79.

Chapman K, Bateman E, Gallagher N, Hu H, Banerji D. Once-daily QVA149 improves lung function, dyspnea, and health status independent of disease severity and prior medications: The SHINE Study [abstract]. Chest. 2014;145(3 Suppl):401A.

Celli B, Crater G, Kilbride S, et al. Once-daily umeclidnium/vilanterol 125/25 mcg in COPD: a randomized, controlled study. Chest. 2014;13-1579.

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

Dahl R, Greefhorst LA, Nowak D, et al. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164:778-84.

Dahl R, Jadayel D, Alagappan V, Chen H, Banerji D. Efficacy and safety of once-daily QVA149 compared with the free combination of its monocomponents: The BEACON Study [abstract]. Chest. 2014;145(3 Suppl):407A.

Dellamary LA, Tarara TE, Smith DJ, et al. Hollow porous particles in metered dose inhalers. Pharm Res. 2000;17(2):168-74.

Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. Respir Med. 2013;107(10):1538-46.

Funada A, Hayashi K, Ino H, et al. Assessment of QT intervals and prevalence of short QT syndrome in Japan. Clin Cardiol. 2008 Jun;31(6):270-4.

Global strategy for the diagnosis, management, and prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. http://www.goldcopd.org. Accessed 14 March 2014.

Hirst PH, Pitcairn GR, Weers JG, et al. In vivo lung deposition of hollow porous particles from a pressurized metered dose inhaler. Pharm Res. 2002;19(3):258-64.

Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c869. doi: 10.1136/bmj.c869

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

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

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;121:1058-69.

Wedzicha J, Ficker J, Niewohner D, Sandström T, Fowlertaylor A, Banerji D. Dual bronchodilation with once-daily QVA149 reduces exacerbations, improves lung function and health status versus glycopyrronium and tiotropium in severe-to-very severe COPD patients: The SPARK Study [abstract]. Chest. 2014;145(3 Suppl): 406A.

Yatomi Y. Reference Values. In: Yazaki Y, editor. Asakura Internal Medicine. 10th ed. Tokyo, Japan: Asakura Publishing; 2013. p. 3 Appendix.

Appendix 1 Administration of Study Drug

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

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.

GFF MDI and GP MDI Administration: For each GFF MDI and GP 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 in the eCRF. The two GFF MDI treatments and two GP MDI treatments are:

- GFF MDI 28.8/9.6 µg
- GFF MDI 14.4/9.6 µg
- GP MDI 28.8 µg
- GP MDI 14.4 µg

The MDI dose delivery specifications for the four treatments are provided in Table A1-1.

Table A1-1. MDI Dose Delivery Specifications

Product Name & Dose	Product Strength	Dosage Form	Administration
GFF MDI 28.8/9.6 µg ex-actuator	14.4/4.8 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
GP MDI 28.8 µg ex-actuator	14.4 µg/actuation	MDI	Taken as 2 inhalations
GP MDI 14.4 µg ex-actuator	7.2 µg/actuation	MDI	Taken as 2 inhalations

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

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

The following study activities and assessments will be performed:

- Collect approximately 5 mL of blood into a single tube containing EDTA tripotassium (4×10^{3}M in phosphate buffered saline). Care should be taken to minimize hemolysis during sample collection.
- Place all tubes on wet ice immediately after collection.
- Centrifuge the blood within 30 minutes of collection at >1000 x g (~2500 rpm) for 10 to 15 minutes.
- Transfer approximately equal aliquots (Aliquot A and Aliquot B) of plasma into duplicate labeled polypropylene test tubes with a snap or screw cap. Care should be taken to minimize contamination with red blood cells (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 3 days prior to a holiday via priority overnight delivery.
- Ship Aliquot A samples first.
- Aliquot B samples should be retained frozen until receipt of Aliquot A samples is confirmed and then shipped according to instruction.

Shipping Address:

[redacted]

ATTENTION: Sample Management

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

Appendix 3 Sponsor Signatory

Study Title: A Phase I, Randomized, Double-Blind, Single-Dose, Four-Period, Four-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Two Doses of PT003 and Two Doses of PT001 in Japanese Healthy Subjects

Study Number: PT003010-01

Final Date: Version 2.0, [redacted]

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

Name: [redacted]

Title: [redacted]
Pearl Therapeutics Inc.

Appendix 4 Investigator's Agreement and Signature Page

Study Title: A Phase I, Randomized, Double-Blind, Single-Dose, Four-Period, Four-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Two Doses of PT003 and Two Doses of PT001 in Japanese Healthy Subjects

Study Number: PT003010-01 **Final Date:** Version 2.0, [redacted]

I agree:

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

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

Name:_[redacted]_____

Affiliation: [redacted]