Clinical Trial Protocol: PT001004-01

Study Title: A Randomized, Double-Blind, Chronic Dosing (7-Day), Four-Period, Four-Treatment, Placebo-Controlled, Cross-Over, Multi-Center Study to Assess the Efficacy and Safety of Three Doses of PT001 in Japanese Subjects With Moderate to Severe COPD

Study Number: PT001004-01

Study Phase: IIb

Product Name: Glycopyrronium Inhalation Aerosol; PT001

Indication: Chronic Obstructive Pulmonary Disease

Investigators: Multi-center

Sponsor: Pearl Therapeutics, Inc.

Sponsor Contact: [redacted]

Pearl Therapeutics, Inc.

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

Confidentiality Statement

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

The amended study protocol, PT001004-01 (Version 2.0) includes the following revisions:

- Clarification was made to the administration of short-acting bronchodilator (ipratropium bromide) during the screening and washout periods, to read "*as directed by the Investigator (at least one inhalation BID should be administered, see footnote c of* Table 5-1*) or in accordance with the local package insert*". This change is reflected in Sections 4.1, 5.4.1, and 5.4.2, and in Table 5-1.
- Clarification was made to the administration of salbutamol sulfate to better communicate that "*...subjects will be permitted to use salbutamol sulfate as needed for relief of COPD symptoms. The dosage of salbutamol sulfate should be within the description of the local package insert"*. This change is reflected in Sections 4.1, 5.4.1, and 5.4.2, and in Table 5-1.
- Clarification was provided in Section 5.2. The third bullet of Exclusion criterion 2h was deleted because FEV_1 Baseline Stability cannot be assessed as a screening test.
- Clarification was made to Exclusion criterion 3b, which was revised to read: "*Clinically significant abnormal ECG: Subjects who have a clinically significant abnormal 12-lead ECG*". The clinically significant abnormal ECGs are described in the bullet below this statement.
- A revision was made to the maximum allowable total daily dosage of theophylline, which now reads 400 mg/day maximum total daily dose. This change is reflected in Table 5-2.
- Clarification was provided at which visits subjects must refrain from xanthine-containing foods and beverages, and smoking. This is provided in Section 5.5.
- The clinical laboratory parameters were corrected to delete urea. Urea is not included in these parameters. This change is reflected in Table 7-1.
- Clarification was provided in Table 8-1 regarding the prioritization of spirometry measurements. In Table 8-2, clarification was provided regarding the Visits at which FEV_1 Baseline Stability Criteria must be within the pre-specified criteria in comparison with the Randomization Visit.
- Other minor protocol inconsistencies, clarifications, and typographical errors were also addressed through-out the document. None of the changes compromise subject safety or the intent of the original study design.

SYNOPSIS

Sponsor:

Pearl Therapeutics, Inc.
[redacted]

Names of Investigational Product:

Glycopyrronium Inhalation Aerosol; Glycopyrronium (GP) Metered Dose Inhaler (MDI); PT001

Name of Active Ingredients:

Glycopyrronium

Study Title:

A Randomized, Double-Blind, Chronic-Dosing (7-Day), Four-Period, Four-Treatment, Placebo-Controlled, Cross-Over, Multi-Center Study to Assess the Efficacy and Safety of Three Doses of PT001 in Japanese Subjects With Moderate to Severe COPD

Study Number: PT001004-01

Study Phase: IIb

Primary Objective:

The primary objective of this study is to assess the efficacy of GP MDI relative to Placebo as measured by lung function assessments in Japanese subjects with moderate to severe chronic obstructive pulmonary disease (COPD) across a dose range of 28.8, 14.4, and 7.2 µg ex-actuator, administered twice daily (BID).

Secondary Objective:

The secondary objective of the study is to evaluate the relationship between doses and responses for GP MDI in Japanese subjects with moderate to severe COPD.

Safety Objective:

The safety objective of this study is to evaluate the safety of GP MDI (28.8, 14.4, and 7.2 µg ex-actuator, BID) in Japanese subjects with moderate to severe COPD compared with Placebo.

Study Design:

This is a randomized, double-blind, chronic-dosing (7-day), four-period, four-treatment, placebo-controlled, cross-over, multi-center study to assess the efficacy and safety of three doses of GP MDI (28.8, 14.4, and 7.2 µg ex-actuator, BID) in Japanese subjects with moderate to severe COPD.

This multi-center study will be conducted at approximately 25 sites in Japan. Across these sites, it is planned that approximately 60 subjects with moderate to severe COPD will be randomized to one of four treatment sequences to provide approximately 50 subjects to complete the study. If all subjects complete, then each sequence will be used 15 times, and the design will be balanced for period and first-order carry-over effects.

Study Population:

Approximately 60 Japanese subjects with moderate to severe COPD will be randomized into the study to provide approximately 50 subjects to complete the study.

Study Drug, Dose, and Mode of Administration:

Study drugs will be provided as summarized in the table below.

Descriptions of Study Drugs

Name and Dose of Study Drug	Strength of Study Drug	Dosage Form	Administration
GP MDI 28.8 µg ex-actuator	GP MDI 14.4 µg per actuation	MDI	Taken as two inhalations, BID
GP MDI 14.4 µg ex-actuator	GP MDI 7.2 µg per actuation	MDI	Taken as two inhalations, BID
GP MDI 7.2 µg ex-actuator	GP MDI 3.6 µg per actuation	MDI	Taken as two inhalations, BID
Placebo	Formulation does not contain active ingredient	MDI	Taken as two inhalations, BID

Abbreviations: BID=twice daily; GP MDI=glycopyrronium metered dose inhaler; MDI=metered dose inhaler; µg=micrograms

Note: All study drugs will be administered by oral inhalation.

Duration of Treatment:

Each subject will receive 4 separate study treatments, scheduled as four, 7-day Treatment Periods, for a total treatment duration of 28 days.

A Washout Period of 5 to 21 days will occur between each Treatment Period.

Participation in this study will take approximately 12-19 weeks for each individual subject.

Duration of Study:

This study is conducted from [redacted] (obtaining consent from first subject) to [redacted] (last subject last visit) (planned)

Efficacy Assessments:

The first day of treatment in each Treatment Period is Day 1. Following 7 days of treatment in each Treatment Period, the last day of treatment in each Treatment Period is considered Day 8. Therefore, assessments collected on Day 8 (Visits 3, 5, 7, and 9) will occur following 7 days of treatment.

Primary Efficacy Endpoint:

- Change from baseline in morning pre-dose trough forced expiratory volume in 1 second (FEV_1) on Day 8

Secondary Efficacy Endpoints:

- FEV_1 area under the curve from 0 to 2 hours (AUC_{0-2}) on Day 1 and Day 8
- Peak change from baseline in FEV_1 on Day 1 and Day 8
- Forced vital capacity (FVC) AUC_{0-2} on Day 8

Other Efficacy Endpoints:

The other efficacy endpoints of this study are as follows:

- Change from baseline in FEV_1 at each post-dose timepoint on Day 1 and Day 8
- Change from baseline in morning pre-dose trough FVC on Day 8
- FVC AUC_{0-2} on Day 1
- Peak change from baseline in FVC on Day 1 and Day 8
- Change from baseline in FVC at each post-dose timepoint on Day 1 and Day 8
- Change from baseline in morning pre-dose trough peak expiratory flow rate (PEFR) on Day 8
- PEFR AUC_{0-2} on Day 1 and Day 8
- Peak change from baseline in PEFR on Day 1 and Day 8
- Change from baseline in PEFR at each post-dose timepoint on Day 1 and Day 8
- Change from baseline in average daily use of rescue salbutamol sulfate over the Treatment Period

Safety Assessments:
The safety assessments include electrocardiograms (ECGs), vital sign measurements, clinical laboratory tests, physical examination findings, and adverse events (AEs).

Exploratory Assessment (Metabolite Assay):

Blood plasma will be collected from all subjects at a pre-specified, single timepoint in a randomized manner at 15 minutes, 30 minutes, 1 hour, or 2 hours post-dose on Day 8 of each Treatment Period. Contingent upon the results of the in vitro characterization, the plasma samples may be analyzed to characterize any potential metabolites of glycopyrronium, or will be destroyed.

Statistical Methods:

Sample Size Determination:

Power calculations are based on the properties of the primary endpoint, the change from baseline in morning pre-dose trough FEV_1 on Day 8. Estimates of within-subject standard deviation (SD) were obtained from previous studies. A within-subject SD of 130 mL is assumed. Under the further assumption of 15% dropout and 60 randomized subjects, the study is approximately 80% powered to demonstrate a difference between any two treatments of 75 mL using a two-sided alpha level of 0.05.

Primary Efficacy Analyses:

The primary efficacy analysis involves the comparison of the primary efficacy endpoint (change from baseline in morning pre-dose trough FEV_1 at Day 8) for each GP MDI dose with Placebo. In addition, comparisons among the GP MDI doses will be conducted as supportive analyses. Efficacy analyses will be conducted using mixed model repeated measures with baseline FEV_1, the response to ipratropium bromide at Screening (Visit 1),

and treatment as covariates. Within-subject correlation will be modeled by treating subject as a random effect. The model will not include treatment sequence unless those terms are determined to be important ($p<0.10$).

For the primary efficacy objective, the family-wise Type I error will not be controlled for multiplicity. As the aim of the study is to describe the dose-ranging profile of GP MDI, all doses of GP MDI will be tested relative to Placebo. The totality of the data will be used to select an appropriate dose.

Safety analyses:

The evaluation of safety will be based on descriptive statistics, per treatment group, of vital signs, 12 lead ECG (including QTcF), clinical laboratory measurements, number, frequency, severity, and intensity of AEs, and number of subjects withdrawn from the study due to drug-related AEs.

Date of Original Approved Protocol: [redacted]

Date of Protocol Amendment 1: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AR(1)	Autoregressive Order 1
ATS	American Thoracic Society
AUC	Area Under the Curve
AUC_{0-2}	Area Under the Curve from 0 to 2 hours
BID	Bis In Die, Twice Daily
BMP	Basic Metabolic Panel
BP	Blood Pressure
bpm	Beats Per Minute
BTPS	Body Temperature and Pressure Saturated
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMP	Comprehensive Metabolic Panel
CONSORT	CONsolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computed Tomography
DBP	Diastolic Blood Pressure
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
e.g.	Exempli Gratia, For Example
ERS	European Respiratory Society
etc.	Et Cetera, and So Forth
EV	Back Extrapolation Volume
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second

FF MDI	Formoterol Fumarate Metered Dose Inhaler
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GFF MDI	Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler
GLP	Good Laboratory Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	Glycopyrronium
GP MDI	Glycopyrronium Metered Dose Inhaler
HCG	Human Chorionic Gonadotropin
HFA	Hydrofluoroalkane
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
ID	Identification
i.e.	Id Est, That Is
IRB	Institutional Review Board
ISMPP	International Society for Medical Publications Professionals
ITT	Intent-To-Treat
IWRS	Interactive Web Response System
JRS	Japanese Respiratory Society
L	Liter
LABA	Long-Acting β_2-Agonist
LAMA	Long-Acting Muscarinic Antagonist
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat

mL	Milliliter
msec (ms)	Millisecond
OTC	Over-the-Counter
PEFR	Peak Expiratory Flow Rate
PFT	Pulmonary Function Test
PIN	Personal Identification Number
PMDA	Pharmaceuticals and Medical Devices Agency
PRN	Pro Re Nata, As Needed
QID	Quarter In Die; Four Times Daily
QTcF	QT Corrected Using Fridericia's Formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
US	United States
VC	Vital Capacity

TRADEMARK INFORMATION

Trademarks not owned by Pearl Therapeutics, Inc.:

[redacted]

1 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality at a global level and recent statistics suggest it will become more prevalent as smoking frequencies rise and the population ages [Calverley, 2003; Feenstra, 2001; Ferrer, 1997; Murray, 1997; Sullivan, 2000]. In a systemic review and meta-analysis by Halbert and colleagues, the prevalence of physiologically defined COPD in adults aged ≥40 years was observed to be 9% to 10% [Halbert, 2006; Halbert, 2003]. In Japan, prevalence of COPD was reported as at least 8.6% in adults aged ≥40 years [Fang, 2011; Fukuchi, 2004]. The causes behind COPD are multi-factorial, where various risk factors and environmental stimuli have been identified and include smoking, air pollution, and occupational hazards. Hence, COPD is not only a smoker's disease with familial origins, but one that worsens with age.

Chronic obstructive pulmonary disease is progressive in nature and only partially reversible at a functional level. This disease is characterized by premature loss of ventilatory function as determined by a decline in forced expiratory volume in 1 second (FEV_1) of exhalation. Pathological inflammatory changes are characterized by elevations in activated macrophages, neutrophils, elastases, and CD8 lymphocytes. These molecular and cellular changes cause the destruction of small airways and surrounding alveoli. As expiratory airflow (FEV_1 or forced vital capacity [FVC]) is a function of pressure against resistance, airflow in COPD is diminished due to a loss of elastic recoil and airway constriction. Exacerbations and co-morbidities contribute to the overall severity in individual subjects. Pharmacologic therapy in COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance [Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2014; Japanese Respiratory Society (JRS), 2013]. The diagnostic criteria and treatment approaches as described in the JRS Guideline for the Diagnosis and Treatment of COPD, 4th edition, 2013, are consistent with GOLD, 2014.

Bronchodilator medications are central to symptom management in 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.

Glycopyrronium (GP) is an anticholinergic drug that is marketed in the United States (US) in both oral and parenteral formulations. Glycopyrronium is a quaternary ammonium derivative that when inhaled results in minimal mucosal absorption and systemic side effects. Glycopyrronium is approved for respiratory inhalation capsule in Japan for the treatment of COPD. In addition, another anticholinergic drug, tiotropium bromide, is licensed in Japan as inhalation capsule and soft mist. It has been shown to reduce the rate of COPD exacerbations and to improve the effectiveness of pulmonary rehabilitation [Niewoehner, 2005; Casaburi, 2005].

Pearl Therapeutics, Inc. (hereafter referred to as Pearl) has licensed and developed a particle engineering technology that utilizes porous particles for pulmonary drug delivery via metered

dose inhalers (MDIs). This technology is based on spray-dried porous particles comprised of distearoylphosphatidylcholine and calcium chloride that are co-suspended with crystalline active drug substances and formulated into suspension-based hydrofluoroalkane (HFA) MDIs. Pearl is developing a broad range of MDI-based inhalation products using its porous particle technology platform.

Note: Ipratropium bromide and salbutamol sulfate will be locally sourced as a comparable product with the same active pharmaceutical ingredients. For clarity and consistency within this protocol, these products will be referred to as indicated above.

1.1 Study Rationale

The primary objective of this study is to assess the efficacy of GP MDI relative to Placebo, as measured by lung function, in Japanese subjects with moderate to severe COPD across a dose range of 28.8, 14.4, and 7.2 µg ex-actuator (BID).

Pearl Therapeutics has recently changed the naming convention for GP MDI to make reference to the active moiety – glycopyrronium – instead of the bromide salt form previously used (glycopyrronium bromide, also known as glycopyrrolate). There have been no changes made to formulation of GP MDI, just a change in how the strength/dose is expressed. All references to strengths/doses of GP MDI in this protocol are based on the mass of glycopyrronium. In all prior clinical studies, Pearl Therapeutics expressed the strengths/doses of GP MDI based on the mass of glycopyrrolate (glycopyrronium bromide), which is the bromide salt form of the active material.

The efficacy and safety of GP MDI has been evaluated in Western subjects across a 240-fold range of doses from 144 µg down to 0.6 µg (115 µg down to 0.5 µg expressed as glycopyrronium). The lower end of the dose-response curve has been adequately characterized in two chronic-dose, dose-ranging studies (Studies PT001002 and PT001003), and the findings from these two studies and the previous Phase II studies supported the evaluation of GP MDI 18 µg (14.4 µg expressed as glycopyrronium) BID in Phase III clinical studies. To ensure the appropriateness of the doses selected for the combination product, eight different doses of the combination have been evaluated; including a 60-fold range of glycopyrrolate doses from 72 µg down to 1.2 µg (58 µg down to 1 µg expressed as glycopyrronium) administered in combination with formoterol fumarate 9.6 µg. The results from the final Phase II dose-ranging study with glycopyrronium and formoterol fumarate metered dose inhaler (GFF MDI; Study PT003005) provided assurance that the dose of GP MDI to be evaluated alone was the appropriate dose of glycopyrronium to use in the combination product as it provided meaningful benefit when added to formoterol fumarate 9.6 µg (GFF MDI 18/9.6 µg [14.4/9.6 µg expressed as glycopyrronium]), with a safety profile that appears similar to the individual agents. A summary of the integrated efficacy and safety data from the six Phase II chronic dosing studies with GFF MDI, GP MDI, and formoterol fumarate metered dose inhaler (FF MDI) is provided in the Investigator's Brochure (IB) for GFF MDI, GP MDI, and FF MDI.

The European Medicines Agency and Health Canada have previously agreed with the approach for Phase III dose selection of GP MDI and GFF MDI and the Food and Drug Administration (FDA) has agreed with the evaluation of 18 µg glycopyrrolate (14.4 µg of glycopyrronium) administered BID in GP MDI and GFF MDI for the Phase III clinical studies.

Based on these findings in Western subjects, Study PT001004 will confirm that the doses studied are appropriate for the Japanese population by assessing the safety and efficacy in Japanese subjects, in doses ranging from GP MDI 28.8 µg BID down to GP MDI 7.2 µg BID in Japanese subjects with moderate to severe COPD.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the efficacy of GP MDI relative to Placebo as measured by lung function assessments in Japanese subjects with moderate to severe COPD across a dose range of 28.8, 14.4, and 7.2 μg ex-actuator (BID).

2.2 Secondary Objective

The secondary objective of the study is to evaluate relationship between doses and responses for GP MDI in Japanese subjects with moderate to severe COPD.

2.3 Safety Objective

The safety objective is to evaluate the safety of GP MDI (28.8, 14.4, and 7.2 μg ex-actuator, BID) in Japanese subjects with moderate to severe COPD compared with Placebo.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

The first day of treatment in each Treatment Period is Day 1. Following 7 days of treatment in each period, the last day of treatment in each Treatment Period is considered Day 8. Therefore, assessments collected on Day 8 (Visits 3, 5, 7, and 9) will occur following 7 days of treatment.

3.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is:

- Change from baseline in morning pre-dose trough FEV_1 on Day 8

3.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are as follows:

- FEV_1 area under the curve from 0 to 2 hours (AUC_{0-2}) on Day 1 and Day 8
- Peak change from baseline in FEV_1 on Day 1 and Day 8
- FVC AUC_{0-2} on Day 8

3.1.3 Other Efficacy Endpoints

The other efficacy endpoints of this study are as follows:

- Change from baseline in FEV_1 at each post-dose timepoint on Day 1 and Day 8
- Change from baseline in morning pre-dose trough FVC on Day 8
- FVC AUC_{0-2} on Day 1
- Peak change from baseline in FVC on Day 1 and Day 8
- Change from baseline in FVC at each post-dose timepoint on Day 1 and Day 8
- Change from baseline in morning pre-dose trough peak expiratory flow rate (PEFR) on Day 8
- PEFR AUC_{0-2} on Day 1 and Day 8
- Peak change from baseline in PEFR on Day 1 and Day 8
- Change from baseline in PEFR at each post-dose timepoint on Day 1 and Day 8
- Change from baseline in average daily use of rescue salbutamol sulfate over the Treatment Period

3.2 Safety Endpoints

The safety assessments include electrocardiograms (ECGs), vital sign measurements, clinical laboratory tests, physical examination findings, and adverse events (AEs).

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind, chronic-dosing (7-day), four-period, four-treatment, placebo-controlled, cross-over, multi-center study to assess the efficacy and safety of three doses of GP MDI (28.8, 14.4, and 7.2 µg ex-actuator, BID) in Japanese subjects with moderate to severe COPD.

This multi-center study will be conducted at approximately 25 sites, contributing approximately three subjects per site in Japan. Across these sites, it is planned that approximately 60 subjects with moderate to severe COPD will be randomized into the study to provide approximately 50 subjects to complete the study.

The entire study is scheduled to take a maximum of 19 weeks for each individual subject.

Prior to or at Screening (Visit 1a), all subjects are to sign an Informed Consent Form (ICF) prior to the conduct of any Screening assessments (see Table 8-1 for the study's Schedule of Events). The Investigator will obtain a medical history, physical examination, and any required documentation in order to determine eligibility for participation (inclusion/exclusion criteria; Section 5). Reversibility of FEV_1 within 30 to 60 minutes following four puffs of ipratropium bromide will be assessed at Screening to characterize the subject population but will not be used to determine eligibility to participate in the study. Subjects who are not using a prohibited medication and meet all other entry criteria will return to the clinic within 7 to 28 days after Visit 1a for Visit 2 (Randomization).

Starting at Screening (Visit 1a/b) and for the duration of the study, subjects will receive a Diary in which they will be asked to maintain a daily record of their study drug dosing, rescue medication use, and collection of COPD symptoms. Subjects who fail to demonstrate proper Diary compliance prior to Randomization (Visit 2) must be screen failed (see Section 7.1.2).

Subjects who meet all entry criteria but are using certain prohibited COPD medications (e.g., LAMAs, LABAs, LAMA/LABA combination medications, ICS combination medications) will discontinue these medications for the duration of the study and be switched to ipratropium bromide, administered as directed by the Investigator (at least one inhalation BID should be administered**,** *see footnote c* of Table 5-1) or in accordance with the local package insert, with or without ICS, for COPD maintenance during washout (see Section 5.4).

In order to allow for an adequate washout of previous maintenance medications, subjects will undergo a Washout Period of at least 7 days, but not greater than 28 days duration prior to returning to the clinic for Visit 2 (Randomization) (see Table 5-2 and Table 5-3).

At the Investigator's discretion, subjects who do not meet spirometry entry criteria at Screening (Visit 1a) can return to repeat spirometry at a second Screening Visit (Visit 1b).

Note: Visit 1b is to be used only for repeat spirometry entry criteria; all other repeat assessments, if needed, will be captured as an unscheduled visit.

At Visit 2 (Randomization Visit; Day 1 of Treatment Period 1), subjects will return to the clinic for study medication dosing before 10:00 am. Subjects who continue to meet entry inclusion/exclusion criteria and remain eligible for participation in the study will be randomized into one of the four pre-defined treatment sequences. All subjects will receive all four treatments (Placebo and GP MDI 28.8 µg BID, 14.4 µg BID, and 7.2 µg BID) if they complete the study.

The subject, clinical site personnel, and the Sponsor will be blinded to the treatment sequence assigned to a subject. Randomization will be centralized, through the use of an Interactive Web Response System (IWRS). Glycopyrronium MDI and its matching Placebo will be administered BID. Each of the four treatments will be administered for 7 days with a Washout Period of 5 to 21 days in between treatments.

During Visit 2 (Day 1 of Treatment Period 1), subjects will be dispensed study drug and will administer their first dose at the clinic under supervision. Before sites dispense the first dose at this visit, they must confirm the subject met all protocol-specified requirements and ensure adequate washout (6 hours or longer) of short-acting bronchodilators prior to any study procedures being performed. Subjects will be required to remain at the clinic until completion of all protocol-defined assessments to the 2-hour post-dose timepoint (see Table 8-2). Subjects will then be discharged from the clinic and will continue to administer study drug at home until Visit 3 (Day 8 of Treatment Period 1). Subjects will receive a Diary in which they will be asked to maintain a BID record of their study drug dosing, rescue medication use, and COPD symptoms during the Treatment Period.

At Visit 3 (Day 8 of Treatment Period 1) subjects will return to the clinic at approximately the same time as Visit 2 (±2 hours). Subjects will bring the Diary to the clinic for review. Site Personnel must review the Diary data prior to dosing study drug in the clinic and will return the Diary to the subject. Subjects will receive their last dose of Treatment Period 1 study drug that morning under supervision and will be required to remain at the clinic until completion of all protocol-defined assessments to the 2-hour post-dose timepoint (see Table 8-2). Following discharge, subjects will undergo a study drug Washout Period of 5 to 21 days prior to initiating the next treatment in their assigned treatment sequence.

Following the Washout Period, subjects will repeat a similar pattern of visits and assessments for the next three treatments in their assigned sequence, as follows:

Visits 4, 6, and 8 (Day 1 of Treatment Periods 2, 3, and 4, respectively): Subjects will be dispensed study drug and will administer their first dose of the Treatment Period's study drug in clinic under site personnel supervision, undergo all protocol-defined assessments up to and including 2-hour post-dose assessments (see Table 8-2), be discharged, and continue BID administration until the next scheduled visit.

Visits 5, 7, and 9 (Day 8 of Treatment Periods 2, 3, and 4, respectively): Subjects will administer their last dose of the Treatment Period's study drug from study drug supplies

dispensed at the Day 1 visit in clinic under site personnel supervision, undergo all protocol-defined assessments up to and including 2-hour post-dose assessments (see Table 8-2). At Visit 5 and 7 following discharge, subjects will undergo a study drug Washout Period of 5 to 21 days prior to initiating the next treatment in their assigned treatment sequence. After Visit 9, subjects will be returned to pre-study or appropriate inhaled COPD maintenance medication(s).

Visit 10 will serve as the Follow-up Visit. Subjects will complete all post-study assessments, including a final physical examination and recording of any AEs, and will then be discharged from the study (Table 8-1).

General Guidance for Treatment Visits 2 to 9 (in clinic)

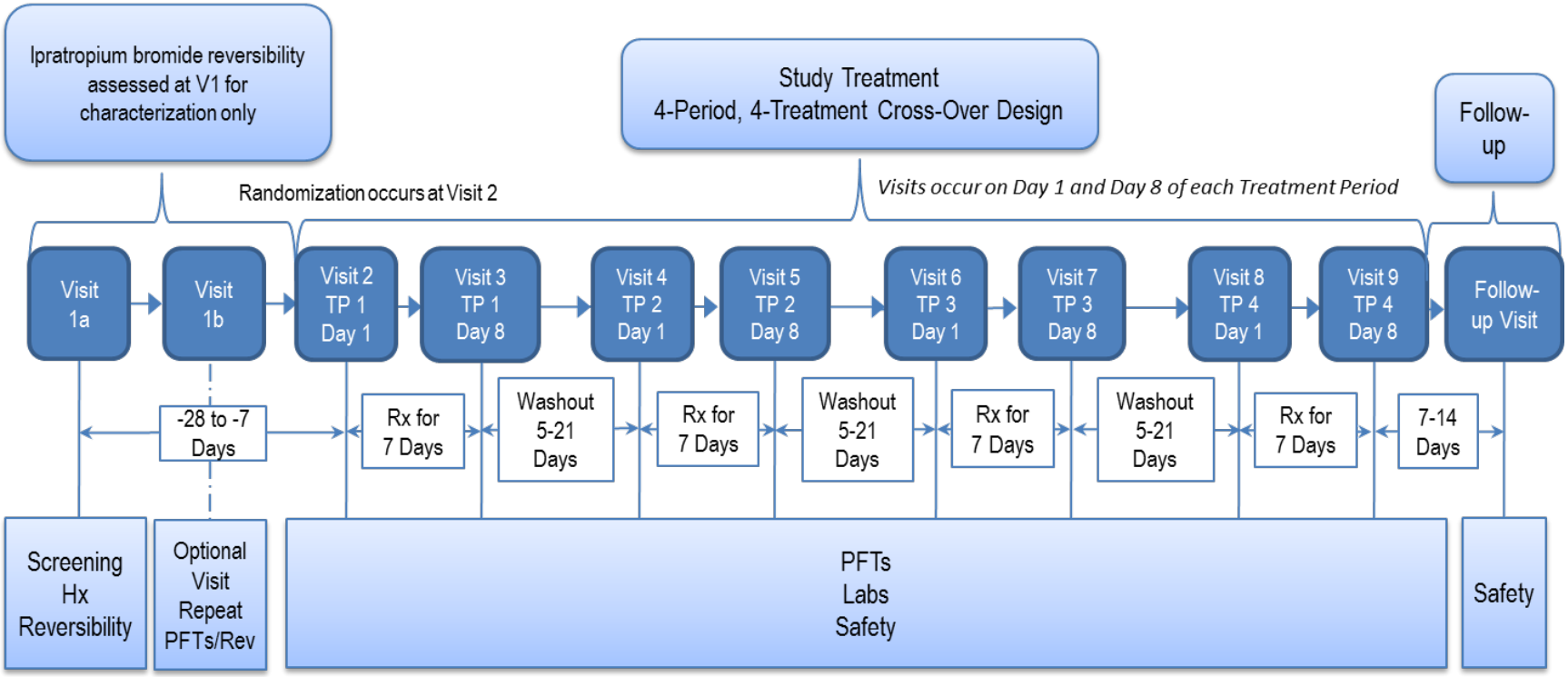
- At the start of each treatment visit, prior to any study procedures being performed, site personnel must confirm the subject withheld all COPD medications, including study drug and rescue medications (e.g., salbutamol sulfate) for at least 6 hours, by confirming the last time of dosing for all COPD medication(s).

  Note: Subjects who inadvertently took rescue medication(s) within 6 hours of the start of study procedures must be rescheduled as soon as is practical, but within the specified visit window. In addition, before the in-clinic dose is administered, the site must confirm the subject met all other protocol-specified requirements (e.g., FEV_1 baseline stability criteria; see Section 7.1.1.1). Subjects will remain in the clinic 2 hours post-dose for observation (safety).
- 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.
- Subjects are not allowed to consume grapefruits or grapefruit juice throughout the study.
- Subjects will be required to refrain from smoking (nicotine gums or patches are allowed) for at least 4 hours prior to each study visit and throughout the duration of each study visit.
- To ensure standardization of dosing times, it is recommended that sites encourage subjects to maintain a dosing schedule at home consistent with their in-clinic dosing time.
  - Subjects will be required to take their study drug BID in the morning between 06:00 and 10:00 am (breakfast time) and in the evening between 06:00 and 10:00 pm (dinner time).
- In order to minimize diurnal variance, sites should make every effort to assess subjects at the same time throughout the study and to discuss the importance of dosing in a timely manner every 12 hours.
  - Subjects will be required to return to the clinic at approximately the same time as Visit 2 for all treatment visits (±2 hours) but not past 10:00 am and will be required to remain at the clinic until completion of all protocol-defined visit assessments.
  - Sites should make every effort to ensure that the in-clinic dosing time is before 10:00 am and within 12±2 hours of the prior at-home evening dosing time.

- Sites are encouraged to call the subject on the day before a scheduled visit to remind the subject of the following:
    - To take their last dose the evening before (12±2 hours) the scheduled visit.
    - To bring their study drug with them to the clinic, to withhold all COPD medications (including ICS) for at least 6 hours prior to pulmonary function tests (PFTs).
    - Refrain from ingesting xanthine-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit.
    - Refrain from smoking for at least 4 hours prior to the study visit and throughout the duration of each study visit.
    - To bring their Diary and other study-related material to the clinic.
- The in-clinic dosing time will be recorded as the time of administration of the second puff of study drug.
- Site personnel will instruct subjects not to take any non-study COPD medications without site personnel permission during a visit, until all study procedures have been completed and the subject is discharged. Site personnel should take every precaution to prevent use of non-study COPD medications during the test day. Site personnel may request the subject to surrender all non-study COPD medications prior to start of the visit before performing any study procedures and return them to the subject at end of the visit when all study procedures are completed.
- If a subject is experiencing severe symptoms and requires salbutamol sulfate for relief of COPD symptoms at any time during a test day, site personnel must note the time and justification for use in the subject's chart and all subsequent spirometry assessments should be stopped during the current Treatment Visit. However, safety assessments should be continued at the discretion of the Investigator.
- Every effort must be made to ensure that subjects return to the clinic on Day 8 (1 week) following the initiation of each Treatment Period. To accommodate scheduling conflicts at Day 8 (Visits 3, 5, 7, and 9) a window of ±2 days from Day 8 is permitted (i.e., Day 8 procedures must be done between Day 6 and Day 10, inclusive).
- During the Treatment Periods (between Visits 2 and 3, Visits 4 and 5, Visits 6 and 7, and Visits 8 and 9), subjects will be permitted to use salbutamol sulfate as needed for relief of COPD symptoms. The dosage of salbutamol sulfate should be within the description of the local package insert.
- During the Washout Periods when subjects are not taking study drug (between Visits 3 and 4, Visits 5 and 6, and Visits 7 and 8), subjects will use the short-acting bronchodilator (ipratropium bromide) administered as directed by the Investigator (see footnote c of Table 5-1) or in accordance with the local package insert and may use rescue salbutamol sulfate as needed. The dosage of salbutamol sulfate should be within the description of the local package insert.
- Protocol-adjusted ICS therapy defined at Screening, if any, should be continued and remain stable for the duration of the study (see Section 5.4).

A Study Flow Diagram is displayed in Figure 4-1:

Figure 4-1: Study Design Diagram



Hx = Medical History; PFT = Pulmonary Function Test; TP = Treatment Period

Note: A Washout Period of 5 to 21 days will occur between each Treatment Period.

5 STUDY POPULATION SELECTION, AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Give their signed written informed consent to participate
2. Are between 40 to 80 years of age at Screening (Visit 1)
3. A female is eligible to enter and participate in the study if she is of:
   - Non-child bearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal); or
   - Child bearing potential, has a negative serum pregnancy test at Visit 1, and agrees to one of the following acceptable contraceptive methods used consistently and correctly as outlined below (i.e., in accordance with the approved product label and the instructions of the physician for the duration of the study – from Visit 1 (Screening) until 14 days after Follow-Up Visit (Visit 10):
     - Complete abstinence from intercourse or
     - Oral contraceptive (combined or progestogen only) administered for at least one monthly cycle prior to study drug administration; or
     - Double barrier method: condom or diaphragm containing spermicidal agent; or
     - An intrauterine device (IUD), inserted by a qualified physician, with published data showing that the highest expected failure rate is less than 1% per year
4. Tobacco Use: Current or former smokers with a history of at least 10 pack-years of cigarette smoking. [Number of pack-years = (number of cigarettes per day/20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years]. Former smokers are defined as those who have stopped smoking for at least 6 months prior to Screening (Visit 1).
5. COPD diagnosis: Subjects with an established clinical history and classification of moderate to severe COPD severity as defined by JRS Guidelines [JRS, 2013] characterized by $FEV_1/FVC < 70\%$ on spirometry after bronchodilator administration.
6. Stage of Disease: Subjects with an established clinical history of COPD and stage of disease defined as:
   - At Screening (Visit 1)
   - Pre- and post-bronchodilator FEV_1/FVC ratio of <70%
   - Post-bronchodilator FEV_1 must be ≥30% and <80% predicted normal value calculated using the JRS reference equations based on the stages of COPD as follows: **Stage 0** (at risk); **Stage I** (mild COPD) = $FEV_1 \geq 80\%$ of predicted value; **Stage II** (moderate COPD) = $50\% \leq FEV_1 < 80\%$ of predicted value; **Stage III** (severe COPD) = $30\% \leq FEV_1 < 50\%$ of predicted value; and **Stage IV** (very severe COPD) = $FEV_1 < 30\%$ of predicted value or $FEV_1 < 50\%$ of predicted value accompanied by chronic respiratory failure or right heart failure [JRS, 2013].

- At Baseline (Visit 2)
- Pre-bronchodilator FEV_1/FVC ratio of <70%
- Pre-bronchodilator FEV_1 must be <80% predicted normal value calculated using JRS reference equations [JRS, 2013].

7. Subject is willing and, in the opinion of the Investigator, able to change current COPD therapy as required by the protocol.
8. Screening clinical laboratory tests must be acceptable to the Investigator.
9. Screening ECG must be acceptable to the Investigator.
10. Chest x-ray or computed tomography (CT) scan within 6 months prior to Screening (Visit 1) must be acceptable to the Investigator. Subjects who have a chest x-ray (or CT scan) that reveals clinically significant abnormalities not believed to be due to the presence of COPD should not be enrolled. A chest x-ray must be conducted if the most recent chest x-ray or CT scan is more than 6 months old at the time of Screening (Visit 1).
11. Compliance: Subjects must be willing to remain at the study center as required per protocol to complete all visit assessments.

5.2 Exclusion Criteria

Subjects meeting any of the following criteria are to be excluded:

1. Pregnancy: Women who are pregnant or lactating or women of childbearing potential who are not using an acceptable method of contraception.
2. Respiratory related:
   a. Asthma: Subjects who have a primary diagnosis of asthma. **Note:** Subjects with a prior history of asthma are eligible if COPD is currently their primary diagnosis.
   b. Alpha-1 Antitrypsin Deficiency: Subjects who have a history of alpha-1 antitrypsin deficiency as the cause of COPD.
   c. Other Respiratory Disorders: Subjects who have other active pulmonary disease such as active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung disease, and uncontrolled sleep apnea (i.e., in the opinion of the Investigator, the severity of the disorder would impact the conduct of the study)
   d. Lung Volume Reduction: Subjects who have undergone lung volume reduction surgery, lobectomy, or bronchoscopic lung volume reduction (endobronchial blockers, airway bypass, endobronchial valves, thermal vapor ablation, biological sealants, and airway implants) within one year of Screening (Visit 1).
   e. Hospitalization: Subjects who have been hospitalized due to poorly controlled COPD within 3 months of Screening (Visit 1), or between Screening and Visit 2.
   f. Poorly Controlled COPD: Subjects who have poorly controlled COPD, defined as acute worsening of COPD that requires treatment with corticosteroids or antibiotics in the 6-week interval prior to Screening (Visit 1), or between Screening and Visit 2. **Note:** Subjects who are steroid dependent and maintained on an equivalent of 5 mg oral prednisone per day or 10 mg every other day for at least 3 months prior to Visit 1

are eligible for enrollment providing the dose of oral steroids remains stable during the Screening Period (Visit 1 up to Visit 2).

g. Lower Respiratory Tract Infection: Subjects who had lower respiratory tract infections that required antibiotics within 6 weeks prior to Screening (Visit 1), or between Screening and Visit 2.

h. Spirometry Performance

- Acceptability Criteria: Subjects who cannot perform acceptable spirometry, i.e., meet American Thoracic Society (ATS)/European Respiratory Society (ERS) acceptability criteria
- Repeatability Criteria: Subjects who cannot perform technically acceptable spirometry with at least three acceptable flow-volume curves with two or more meeting ATS repeatability criteria for FEV_1 at either the pre-bronchodilator or post-bronchodilator assessments at Screening (Visits 1a or 1b; as needed).

i. Oxygen: Subjects receiving long-term-oxygen therapy or nocturnal oxygen therapy required for >12 hours a day. **Note:** As-needed oxygen use is not exclusionary.

j. Subject use of any non-invasive positive pressure ventilation device. **Note:** Subjects using continuous positive airway pressure or bi-level positive airway pressure for sleep apnea syndrome are allowed in the study.

k. Pulmonary Rehabilitation: Subjects who have participated in the acute phase of a pulmonary rehabilitation program within 28 days prior to Screening (Visit 1); subjects who are in the maintenance phase of a pulmonary rehabilitation program are not to be excluded.

l. Change in smoking status (i.e., start or stop smoking,) or initiation of a smoking cessation program within 6 weeks of Visit 1 and throughout the Screening Period (Visit 1 up to Visit 2).

m. Medication Prior to Spirometry: Subjects who are medically unable to withhold their short-acting bronchodilators for the 6-hour period required prior to spirometry testing at each study visit will be excluded.

3. Cardiac related:

a. Subjects with documented myocardial infarction within 1 year of Screening are to be excluded. Subjects with a recent history of acute coronary syndrome, or who have undergone percutaneous coronary intervention or coronary artery bypass graft within 3 months of Screening are to be excluded.

b. Clinically significant abnormal ECG: Subjects who have a clinically significant abnormal 12-lead ECG. A clinically significant abnormal ECG is defined as (but not limited to) any of the following:

- Clinically significant conduction abnormalities (e.g., left bundle branch block, Wolff-Parkinson-White syndrome or evidence of second degree (Mobitz Type II) or third degree atrioventricular block)
- Clinically significant arrhythmias (e.g., atrial fibrillation with irregular ventricular response, atrial flutter, ventricular tachycardia) **Note:** atrial fibrillation that has been clinically stable for at least 6 months is appropriately treated with

anticoagulation and controlled with a rate control strategy (i.e., selective β-blocker, calcium channel blocker, digoxin or ablation therapy) for at least 6 months is allowed for inclusion. In such subjects, atrial fibrillation must be present at pre-randomization visits, with a resting ventricular rate <100/min. At Visit 1 (Screening), the atrial fibrillation must be confirmed by central reading.

- A mean corrected QT corrected using Fridericia's correction factor (QTcF) value at Screening >450 ms for males and females or an ECG that is not suitable for QT measurements (e.g., poorly defined termination of the T wave) at Screening (Visit 1), and that remains elevated on repeat testing up to Visit 2.
- Bradycardia with rate <45 beats per minute (bpm)
- Pathological Q waves of ≤1 year
- ST-T wave abnormalities deemed to be clinically significant by the Investigator. Subjects with non-specific ST-T wave abnormalities that are not deemed clinically significant (per Investigator) are allowed.

c. Clinically Uncontrolled Hypertension: Subjects who, in the opinion of the Investigator, have clinically significant uncontrolled hypertension.

4. Neurological
   a. Subjects with seizures requiring anticonvulsants within 12 months prior to Visit 1a (Screening). **Note:** Subjects treated with anticonvulsant medication for 12 months or more with no seizure events are eligible.
   b. Subjects taking selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors whose dose has not been stable for at least 4 weeks prior to Visit 1a or is altered at any point during the Screening Period (Visit 1a up to Visit 2), or exceeds the maximum recommended dose
5. Renal
   a. Subjects with symptomatic prostatic hypertrophy that is clinically significant in the opinion of the Investigator (if treated and asymptomatic, the subject is eligible for enrollment). Subjects with a trans-urethral resection of prostate or full resection of the prostate within 6 months prior to Visit 1a are excluded from the study.
   b. Subjects with bladder neck obstruction or urinary retention that is clinically significant in the opinion of the Investigator.
   c. Subjects with a calculated creatinine clearance ≤30 mL/minute using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [Levey, 2009] at Visit 1a and on repeat testing prior to Visit 2.

      Note: Subjects with overactive bladder syndrome treated with oral anticholinergics that have been on treatment for at least one month are allowed in the study.
6. Endocrine
   a. Subjects who in the opinion of the Investigator have uncontrolled hypo- or hyperthyroidism, hypokalemia, or hyperadrenergic state.
   b. Subjects who in the opinion of the Investigator have uncontrolled Type I or II diabetes.

7. Liver: Subject with abnormal liver function tests defined as aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, or total bilirubin ≥1.5 times upper limit of normal at Visit 1 and on repeat testing prior to Visit 2.
8. Cancer: Subjects who have cancer that has not been in complete remission for at least 5 years. **Note**: Subjects with squamous cell carcinoma and basal cell carcinoma of the skin that have been resected for cure are not considered exclusionary. Subjects with localized prostate cancer that in the opinion of the Investigator has been adequately worked up, is clinically controlled and the subject's participation in the study would not represent a safety concern, are eligible.
9. Glaucoma: Subjects with a diagnosis of angle closure glaucoma will be excluded, regardless of whether or not they have been treated. Subjects with a diagnosis of glaucoma (non-angle closure) that in the opinion of the Investigator, has not been adequately treated will also be excluded. Subjects with previously diagnosed glaucoma who have intraocular pressure controlled with medication(s) are eligible. All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective β-blockers such as betaxolol, carteolol, levobunolol, metipranolol, or timolol.
10. Drug Allergy: Subjects who have a history of hypersensitivity to any β_2-agonists, glycopyrrolate or other muscarinic anticholinergics, lactose/milk protein, or any component of the MDI.
11. Substance Abuse: Subjects who in the opinion of the Investigator significantly abuse alcohol or drugs.
12. Other Diseases: Subjects who have clinically significant medical conditions including, but not limited to, cardiovascular, neurological, psychiatric, hepatic, gastrointestinal, renal, immunological, glaucoma, symptomatic prostatic hypertrophy (if treated and asymptomatic, the subject is eligible for enrollment), endocrine (including uncontrolled diabetes or thyroid disease), hematological medical problems, and urinary retention problems (including bladder-neck obstruction [e.g., difficulty passing urine, painful urination]). Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the subject at risk through study participation or would affect the efficacy analysis if the disease/condition exacerbated during the study.
13. Prohibited COPD Medications: Subjects taking the following medications within the specified time intervals prior to Screening (Visit 1) are to be excluded:
    - 3 months: depot corticosteroids, intra-articular corticosteroids
    - 6 weeks: parenteral and oral corticosteroids administered for a COPD exacerbation **Note**: Subjects requiring chronic maintenance therapy with oral corticosteroids are excluded from participation in this study.
    - 6 weeks: antibiotics administered for a COPD exacerbation.
    - 4 weeks: use of ICS at a dose of >1000 µg /day of fluticasone propionate or equivalent within 30 days of Screening (Visit 1); initiation or discontinuation of ICS within 30 days of Screening (Visit 1)
14. Other Prohibited Medications:
    - Tricyclic antidepressants inhibitors for treatment of depression

- Monoamine oxidase inhibitors
- Anticonvulsants (i.e., barbiturates, hydantoins, and carbamazepine) for the treatment of seizure disorder
- Non-selective β-adrenergic antagonists
- Anti-tumor necrosis factor α antibodies (e.g., infliximab and any other members of this class of drugs)
- Antipsychotic drugs (phenothiazines)
- Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors, and cimetidine
- **Note**: Benzodiazepines are not exclusionary.

15. Non-compliance: Subjects unable to comply with study procedures, including an inability to abstain from smoking for 4 hours prior to each study visit and throughout the duration of each study visit as specified in the protocol. Subjects should meet the compliance requirement of ≥70% subject completion of Diary assessments in the last 7 days preceding the Randomization Visit (Visit 2) to be randomized in the study. Subjects who fail to demonstrate proper Diary compliance prior to randomization must be screen failed.
16. Consumption of grapefruits or grapefruit juice throughout the duration of the study.
17. Affiliations with Investigator site: Study principal Investigators, sub-Investigators, study coordinators, employees of a participating Investigator, or immediate family members of the aforementioned are excluded from participation in this study.
18. Questionable Validity of Consent: Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol), or other conditions that will limit the validity of informed consent to participate in the study.
19. Investigational Drugs or Devices: Treatment with investigational study drug or participation in another clinical study within the last 30 days or five half-lives prior to Screening (Visit 1), whichever is longer. **Note:** Subject participation in observational studies (i.e., studies that do not require change to medication or an additional intervention) is not exclusionary.
20. Hand-to-Breath Coordination: Subjects who requires the use of a spacer device to compensate for poor hand-to-breath coordination with a MDI. **Note:** Use of a nebulizer to deliver COPD medications is prohibited throughout the study.

5.3 Subject Identification

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

5.4 Prior, Concomitant, and Prohibited Medications

All prescription and over-the-counter (OTC) medications taken by the subject during 30 days before Screening (Visit 1) will be recorded on the Concomitant Medications Case Report Form (CRF) page. Any additions, deletions, or changes in the dose of these medications while in the study should be entered on the CRF. Any current ongoing medications, including OTC drugs and herbal supplements, will be allowed provided they are not prohibited by the protocol (see Section 5.4.2) and are approved by the Investigator. Subjects who develop an illness of any type are instructed to contact the Investigator.

All concomitant medications taken during the study will be recorded on the Concomitant Medications CRF page with indication, dose and administration, and dates of drug administration.

5.4.1 Allowed Concomitant Medications

The following medications used for the treatment of asthma and/or COPD are permitted during this study:

- During study treatment, salbutamol sulfate to be used as needed for relief of symptoms. The mode of administration is described in Table 5-1.
- During the Screening and Washout Periods: salbutamol sulfate and ipratropium bromide are acceptable but must be withheld for at least 6 hours before each study visit. The mode of administration is described in Table 5-1.

Table 5-1. Descriptions of Salbutamol and Ipratropium

Name and Dose	Strength	Dosage Form	Administration
Salbutamol Sulfate inhalation aerosol [a]	Each inhalation contains 120 µg Salbutamol Sulfate corresponding to 100 µg Salbutamol base.	MDI	Taken as needed within the dosage described in the local package insert.
Ipratropium Bromide inhalation aerosol [b]	Each inhalation contains 20 µg Ipratropium Bromide.	MDI	Taken as directed by the Investigator[c] or in accordance with the local package insert

Abbreviations: MDI=metered dose inhaler;

a. Rescue medication

b. Used for reversibility testing and COPD maintenance therapy during Screening and Washout Periods

c. At least one inhalation BID of ipratropium bromide should be administered. **Note:** 1 or 2 puffs of ipratropium bromide four times daily (QID) can be reduced to BID or three times daily (TID) if symptoms are under control and stabilized.

- Subjects receiving a maintenance dose of an ICS will be permitted to continue the ICS provided they have been maintained on a stable dose for at least 28 days prior to screening visit.

Ipratropium bromide and salbutamol sulfate will be dispensed and administered according to the following:

Ipratropium Bromide

Subjects taking COPD medications that require washout or treatment naïve subjects will be dispensed ipratropium bromide (or locally available comparable product with the same active pharmaceutical ingredients) to take as maintenance therapy during Screening (Visit 1 up to Visit 2) and during the Washout Periods between Visits 3 and 4, Visits 5 and 6, and Visits 7 and 8, as directed by the Investigator (***see footnote c*** of Table 5-1) or in accordance with the local package insert. The MDI should be stored at room temperature by the subject, avoiding temperature extremes and storage in direct sunlight. See manufacturer's instructions on the administration of ipratropium bromide. Dispense of ipratropium bromide MDI will be recorded according to the procedures provided in the separate document. Subjects will record the use of ipratropium bromide MDI on the subject Diary.

Salbutamol Sulfate

Subjects will be dispensed salbutamol sulfate MDI (or locally available comparable product with the same active pharmaceutical ingredients) to take as rescue medication, as needed, from Visits 1 to 9. The dosage of salbutamol sulfate should be within the description of the local package insert. Salbutamol sulfate should be stored at room temperature and primed per manufacturer's instructions prior to dispensing. Dispense of salbutamol sulfate MDI will be recorded according to the procedures provided in the separate document. Subjects will record the use of salbutamol sulfate MDI on the subject Diary.

5.4.2 Prohibited COPD Medications

The following medications used for the treatment of asthma and/or COPD are not permitted during this study:

  - Oral β_2-agonists
  - Any LABAs, LAMAs, and corticosteroid/LABA combination products
  - Cromoglycate or nedocromil inhalers
  - Leukotriene antagonists (e.g., zafirlukast, montelukast, zileuton)
  - Phosphodiesterase (PDE) inhibitors and PDE-4 inhibitors (PDE-5 inhibitors are allowed concomitant medications)
- Subjects taking the COPD medications requiring washout or treatment naïve subjects will be switched at Screening Visit to ipratropium bromide MDI administered as directed by the Investigator (see footnote c of Table 5-1) or in accordance with the local package insert, and salbutamol sulfate to be administered as needed for control of COPD

symptoms during the Screening Period. The dosage of salbutamol sulfate should be within the description of the local package insert.

- Subjects receiving a maintenance dose of an ICS as part of a fixed-dose combination therapy containing fluticasone and salmeterol, mometasone and formoterol, or formoterol and budesonide will be switched to the corresponding dose of fluticasone, mometasone, or budesonide administered as a single agent, with ipratropium bromide MDI administered as directed by the Investigator (**see footnote c** of Table 5-1) or in accordance with the local package insert, and salbutamol sulfate to be administered as needed for control of COPD symptoms during the Screening Period, provided they have been maintained on a stable dose for at least 28 days. The dosage of salbutamol sulfate should be within the description of the local package insert.
- All subjects treated with either a LABA (e.g., salmeterol or formoterol or indacaterol) or LAMA (e.g., tiotropium, glycopyrronium or umeclidinium) administered alone or as a loose combination will have these medications discontinued and replaced with ipratropium bromide MDI administered as directed by the Investigator (see footnote c of Table 5-1) or in accordance with the local package insert, and salbutamol sulfate to be administered as needed for control of COPD symptoms during the Screening Period. The dosage of salbutamol sulfate should be within the description of the local package insert.

The following medications used for the treatment of COPD are not permitted during this study. These medications must be discontinued at Screening (Visit 1) and are not permitted during the Screening Period. The minimum Washout Period between Visit 1 and Visit 2 is shown in Table 5-2.

Table 5-2. COPD Medications: Required Washout Period Prior to Visit 2

Class of Medication	Minimum Washout Period Prior to Visit 2
Long-acting anticholinergics	Tiotropium, 14 days; aclidinium[b], 2 days; glycopyrronium[b], 10 days; umeclidinium[b], 3 days
Short-acting anticholinergics	6 hours
LABA/LAMA	14 days
Fixed-combinations of LABA/ICS [a]	7 days (fluticasone furoate/vilanterol: 5 days [b]); at Screening (Visit 1) these medications must be switched to the nearest equivalent dose of ICS monotherapy
Fixed-combinations of SABAs and short-acting anticholinergics	6 hours
LABA [a]	48 hours; indacaterol, olodaterol[b], 15 days[c]
SABAs (including study rescue salbutamol sulfate)	6 hours
Phosphodiesterase-4 inhibitor[d]	6 days
Theophylline (total daily dose >400 mg/day) [e]	7 days

Abbreviations: COPD=chronic obstructive pulmonary disease;ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist; LAMA=long-acting muscarinic agonist; SABA=short-acting β_2-agonist

[a] Please note that the washout periods for the LABA/ICS fluticasone furoate and vilanterol inhalation powder and for the LABA indacaterol inhalation powder are 5 days and 15 days, respectively.

[b] Subject to their approval in the respective countries.

[c] Subjects treated with indacaterol or olodaterol at screening (visit 1a), will require an extension of the screening period by 1 day.

[d] Subjects taking roflumilast are allowed provided they have been on stable dose of therapy for at least 2 months prior to Randomization.

[e] Theophylline ($\leq$400 mg/day) is permitted provided the subject has been on a stable dose of therapy for at least 4 weeks prior to Randomization.

The following respiratory medications are not permitted during this study (Table 5-3).

Table 5-3. Other Respiratory/Nasal Medications: Required Washout Period Prior to Visit 2

Class of Medication	Minimum Washout Period Prior to Visit 2
Leukotriene antagonists (e.g., zafirlukast, montelukast, and zilueton)	3 days
Cromoglycate	7 days
Nedocromil	7 days
Ketotifen [a]	7 days

[a] Ketotifen eye drops are allowed.

5.4.3 Other Prohibited Medications

The following medications should be used under the stated conditions during this study (Table 5-4). Each concomitant drug must be individually assessed against all exclusion criteria. If in doubt, the Investigator should contact the representative of the Sponsor before randomizing a subject or allowing a new medication to be started.

Table 5-4. Non-COPD Medications Allowed Under Certain Condition

Medications Allowed Under Certain Conditions	Condition
Selective serotonin reuptake inhibitors	Treatment regimen has been stable for at least 4 weeks prior to Visit 1 (Screening) and not altered prior to Visit 2 and does not exceed the maximum recommended dose
Intranasal corticosteroids, intranasal antihistamines or combination thereof	Administered at constant dose and dosing regimen for at least 7 days prior to Visit 1 (Screening) and prior to Visit 2

Abbreviations: COPD=chronic obstructive pulmonary disease

Subjects who require the following medications are prohibited from this study (Table 5-5). Subjects who recently discontinued use of these medications may be considered for study enrollment providing they have met the minimum Washout Period prior to Screening (Visit 1). These medications are prohibited throughout the course of the study. If a subject requires use of any of the listed medications, they should be discontinued.

Table 5-5. Prohibited Medications

Prohibited Medications	Minimum cessation period prior to Screening (Visit 1)
Any drug with potential to significantly prolong the QT interval	14 days or 5 half-lives, whichever is longer
Other investigational drugs	30 days or 5 half-lives whichever is longer
Non-selective β-blocking agents	7 days
Cardiac antiarrhythmics Class Ia, III	7 days, amiodarone 3 months
Anticonvulsants for seizure disorder	Allowed if stable dose for 12 months and free of seizures for 1 year
Anticonvulsants for other indications	Allowed if stable dose for at least 3 months and the Investigator confirms there have been no seizures within the past 12 months
Tricyclic antidepressants	14 days
Monoamine oxidase inhibitors	14 days
Anti-tumor necrosis factor α antibodies (e.g., infliximab and any other members of this class of drugs)	30 days or 5 half-lives whichever is longer
Monoclonal antibodies	30 days or 5 half-lives whichever is longer
Antipsychotic drugs [a]	30 days
Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors, and cimetidine	30 days
Systemic anticholinergics [b]	7 days

Note: Benzodiazepines are not exclusionary.
[a] Antipsychotic agents used for other indications may be allowed after consultation with the representative of Sponsor.
[b] If systemic anticholinergics are used for treatment of overactive bladder and the treatment has been constant for at least 1 month, they are allowed.

5.5 Other Restrictions, Illicit Drugs, or Drugs of Abuse

Illicit drugs or drugs of abuse will not be allowed from the start of Screening (Visit 1) to the end of Visit 10 or 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.

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

After the screening visit (Visit 1a), 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.

After the screening visit (Visit 1a), subjects will be required to refrain from **smoking** for at least 4 hours prior to each study visit and throughout the duration of each study visit. Electronic cigarettes will be treated the same way as smoking is considered in the protocol. Study participants may utilize various nicotine replacement treatments such as chewing gum and patches as needed, in accordance with recommendations from the Investigator during the entire study visit.

5.6 Reasons and Procedures for Early Termination

Subjects may be withdrawn from the study at any time at their own request, upon request of the Investigator, or by the Sponsor at any time or for any reason.

If a subject is lost-to-follow-up (i.e., fails to return for study visits), reasonable efforts must be made to contact the subject and complete study termination procedures.

All subjects who discontinue the study because of AEs will be followed up at suitable intervals in order to evaluate the course of the AE and to ensure the reversibility or stabilization of the abnormality.

All subjects who prematurely discontinue the study after being randomized, regardless of the cause, should undergo only the assessments outlined in Section 8.6 on the date of discontinuation.

A subject will be discontinued if any of the following parameter changes are noted on two consecutive assessments conducted approximately 15 minutes apart or at the discretion of the Investigator:

- QTcF prolongation increase of >60 msec from test day baseline (QTcF obtained from test day baseline ECGs corrected using Fridericia's correction formula) and QTcF >500 msec at any time after taking study drug
- Heart rate (HR) increase of >40 bpm from test day baseline (before taking study drug) and >120 bpm at any time within the 12-hour interval after taking study drug
- Systolic blood pressure (SBP) increase of >40 mmHg from test day baseline (before taking study drug) and SBP >180 mmHg at any time within the 12-hour interval after taking study drug
- Paradoxical bronchospasm, defined as a reduction in FEV_1 of >20% from the mean FEV_1 values obtained 60 and 30 minutes prior to study drug administration on that day, with associated COPD symptoms of wheezing, shortness of breath, or cough to be assessed by the Investigator

If a subject experiences a significant decline in pre-dose FEV_1 at any visit (i.e., pre-dose FEV_1 declines ≥ 30% from the pre-dose value obtained at Randomization [Visit 2]), the Investigator or designee will need to determine whether the subject is having a COPD exacerbation and will also make a determination as to the suitability of continuing the subject in the specific Treatment Period.

Subjects who suffer a moderate or severe COPD exacerbation will be discontinued from the study.

A COPD exacerbation will be defined as a change in the subject's baseline dyspnea, cough, and/or sputum (increase in volume or change in color towards purulence) that lasts ≥3 days, is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication. The severity of COPD exacerbations will be classified as follows:

- Mild: Exacerbations that do not require systemic steroids or antibiotics and do not result in hospitalization or death
- Moderate: Exacerbations that require treatment with systemic steroids and/or antibiotics, and do not result in hospitalization or death
- Severe: Exacerbations that result in hospitalization or death

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.

Study personnel will have access to an IWRS to allocate subjects, to assign drug to subjects, and to manage the distribution of clinical supplies. Clinical supplies will be packaged according to a component schedule provided by the Sponsor. Each person accessing the IWRS system must be assigned an individual unique personal identification number (PIN). They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

6.2 Product Descriptions

Study drugs will be provided by Sponsor as summarized in Table 6-1. Treatments will be blinded in terms of dose administered; the Placebo was created by Sponsor in the image of the active test product.

Table 6-1. Descriptions of Study Drugs

Name and Dosage of Study Drug	Strength of Study Drug	Dosage Form	Fill Count	Administration
GP MDI 28.8 µg ex-actuator	GP MDI 14.4 µg per actuation	MDI	1 MDI 120 actuations	Taken as 2 inhalations, BID
GP MDI 14.4 µg ex-actuator	GP MDI 7.2 µg per actuation	MDI	1 MDI 120 actuations	Taken as 2 inhalations, BID
GP MDI 7.2 µg ex-actuator	GP MDI 3.6 µg per actuation	MDI	1 MDI 120 actuations	Taken as 2 inhalations, BID
Placebo	Formulation does not contain active ingredient	MDI	1 MDI 120 actuations	Taken as 2 inhalations, BID

BID=twice daily; GP MDI=glycopyrronium metered dose inhaler; MDI=metered dose inhaler; µg=micrograms

Note: All study drugs will be administered by oral inhalation.

6.3 Primary Packaging and Labeling Information

Study drugs will be packaged by Pearl as summarized in Table 6-1.

GP MDI will be supplied as blinded study drug.

Blinded Supplies: Each GP MDI and Placebo will be labeled with a single label. The foil pouch will be labeled with a single label.

Labels will be printed with black ink and may include the following text:

• Lot # (Packaging Lot Trace ID) • Space for Entry of Screening # • Component ID # • Space for Entry of Randomization # • Fill Count & Dosage Form	• Visit # (Space for Entry of Interval ID) • Storage Conditions • Protocol # • Country Regulatory Requirements • Sponsor Address

6.4 Secondary Packaging and Labeling Information

Blinded investigational drug and placebo may be provided in boxes containing one MDI, however, box configuration is subject to change as a result of packaging constraints.

Each box will be labeled with a single panel label printed with black ink and may include the following text:

• Lot # (Packaging Lot Trace ID) • Space for Entry of Screening # • Component ID # • Space for Entry of Randomization # • Kit Contents (One MDI)	• Visit # (Space for Entry of Interval ID) • Storage Conditions • Protocol # • Country Regulatory Requirements • Sponsor Address

6.5 Unblinding Procedures

The IWRS should be used in order to unblind subjects and to unmask drug identity. The Sponsor or representative will not provide a disclosure envelope with the clinical supplies. 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 Sponsor or representative or appropriate study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the Investigator must notify the Sponsor or representative 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

Store all blinded study supplies as indicated on the package label.

The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this

protocol or in the product label. Documentation of temperature monitoring should be maintained.

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

GP MDIs and Placebo

Individual GP MDIs and Placebo will be packaged in a foil pouch and contained in an individual visit treatment box/carton. Both the visit treatment box and the foil overwrap will have a label with a component ID number. Confirm that the identifier given by IWRS and the component ID number written on the label are the same. The box/carton is labeled with a single label. Write the subject number and treatment visit number on each of the two-part labels. The tear-off part of the label is to be placed onto the IWRS confirmation report.

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

The MDI must be primed in a separate room from the subject treatment area. Since the MDI is primed in a separate room before dosing, there is a possibility that there may be a delay between priming and dosing, and therefore to ensure consistency in the administration for all subjects, the MDIs are to be gently shaken (5 to 10 seconds) immediately before each actuation (puff).

To prime the inhaler, gently shake the inhaler for 5-10 seconds and then spray once into the air away from yourself and others. Wait approximately 30 seconds and repeat the process three more times.

Each dose will consist of two puffs from the MDI. Subjects will be dispensed the MDI and instructed to continue taking study drug BID, two puffs in the morning and two puffs in the evening approximately 12 hours apart, for 7 days at home. The MDI should be stored at room temperature by the subject, avoiding temperature extremes and storage in direct sunlight. See Appendix 3 for instructions on the administration of GP MDI and Placebo.

If subjects complain of a failure of the actuator, the study site must report it to Pearl, regardless of the kind of actuator failure. Pearl will examine the details of the failure. During the period of examination, all study drugs must be retained under the condition described on the label.

6.8 Drug Accountability/Return of Clinical Supplies

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

The head of the study site is responsible for ensuring accountability for study drug, including reconciliation of drugs and maintenance of drug records. The head of the study site can delegate the control of and accountability for study drug to the study drug storage manager and the manager's designee.

Study drugs must be received by the head of the trial site or the study drug storage manager or the manager's designee at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated assistants have access. Storage conditions for the clinical supplies should be observed, monitored, and documented. Study drugs are to be dispensed only in accordance with the protocol. The head of the trial site or the study drug storage manager or the manager's designee is responsible for keeping accurate records of the study drugs received from Pearl, the amount dispensed to and returned by the subjects/patients, and the amount remaining at the conclusion of the study. Study drugs should be handled in accordance with the pharmacy manual of the study drugs. The Clinical Monitor should be contacted with any questions concerning study drugs where special or protective handling is indicated. At the end of the study, all study drugs including partial and empty containers must be returned as directed by the Sponsor.

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

The head of the trial site or the study drug storage manager or designated assistant should not open individual clinical supply containers until all pre-dose assessments have been completed and the subject is eligible to be randomized/continue with the study. Deviations from this process must be escalated to Pearl or designee for evaluation.

Used subject supplies will be kept at room temperature in a secure and locked cabinet until returned to Pearl or designee. **Note:** Used study drug will be stored separately from unused study drug.

7 STUDY PROCEDURES

A time and events schedule is provided in Table 8-1. Detailed schedules for pre- and post-dose procedures to be performed on Day 1 (Visits 2, 4, 6, and 8) and Day 8 (Visits 3, 5, 7, and 9) of each Treatment Period are provided in Table 8-2.

All assessments during Visits 2 to 9 are recommended to be conducted in the following order: vital signs, ECGs, clinical laboratory assessments, and spirometry.

7.1 Efficacy Assessments

7.1.1 Pulmonary Function Tests

Forced expiratory spirometry for derivation of FEV_1, FVC, and PEFR will be assessed using a spirometer that meets or exceeds minimum performance recommendations of the ATS (see Appendix 1).

A spirometry assessment will be conducted pre- and post-bronchodilator at Visit 1a. **Note:** Subjects who do not meet spirometry criteria at Visit 1a may, at the discretion of the investigator or designee, repeat evaluation of spirometry criteria at Visit 1b.

At Visits 2, 4, 6, and 8 (Day 1 of each Treatment Period), spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration. The average of these two assessments will be used to establish test day baseline FEV_1, FVC, and PEFR. Following study drug administration, spirometry will be obtained at 15 and 30 minutes, and at 1 and 2 hours post-dosing of study drug.

At Visits 4, 6, and 8 (Day 1 of each Treatment Period), subjects must meet the FEV_1 Baseline Stability Criteria (see Section 7.1.1.1) prior to dosing.

At Visits 3, 5, 7, and 9 (Day 8 of each Treatment Period), spirometry will be conducted 60 minutes and 30 minutes prior to study drug administration. The average of these two assessments will be used to calculate morning pre-dose trough FEV_1, FVC, and PEFR. Following study drug administration, spirometry will be obtained at 15 and 30 minutes, and at 1 and 2 hours post-dosing of study drug.

7.1.1.1 FEV_1 Baseline Stability Criteria

It is important to ensure that the baseline FEV_1 is stable and reflective of the subject's COPD severity prior to being randomized into the study. As such, the baseline FEV_1 at Visits 4, 6, and 8 must be within ±20% or 200 mL of the pre-dose FEV_1 obtained at the Randomization Visit (Visit 2). At Visits 4, 6, and 8, if the pre-dose FEV_1 average is outside of the ±20% or 200 mL range, but the 30-minute pre-dose assessment is within ±22% or 220 mL, then another assessment may be conducted 30 minutes later. If the last two assessments meet the baseline stability requirements (i.e., within ±20% or 200 mL), the initial 60-minute pre-dose assessment will not be used and the last two assessments will be used to establish the eligibility criteria. If the test day baseline FEV_1 is not within ±20% or 200 mL, the visit may

be rescheduled (for a maximum of three attempts) at the Investigator's discretion (e.g., within 1 week), or the subject may be discontinued.

7.1.1.2 Characterization of Reversibility Criteria

Reversibility is defined as ≥12% and ≥200 mL in baseline FEV_1 following administration of four puffs of ipratropium bromide. Reversibility to ipratropium bromide will be evaluated at Screening (Visit 1a/1b) to characterize the subject population but will not be used as inclusion criteria. The procedure will be as follows:

- Perform pre-bronchodilator PFTs prior to administration of ipratropium bromide
- Administer four puffs of ipratropium bromide
- Perform post-bronchodilator PFTs within 30 to 60 minutes after the administration of ipratropium bromide

Reversibility will be a comparison of the average best FEV_1 effort obtained pre-bronchodilator to the best FEV_1 effort obtained within 30 to 60 minutes post-bronchodilator.

7.1.1.3 Standardization of Spirometry Collections

All PFTs include FEV_1, FVC, and PEFR as defined in ATS/ERS guidelines and will be performed in accordance with ATS criteria [Miller, 2005].

To standardize spirometry, all sites will be provided with identical spirometry systems [redacted] with customized, study-specific software. All study staff responsible for performing PFTs will receive standardized training at the Investigator meetings or other training. All technicians are required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable PFTs (ATS criteria) [Miller, 2005] prior to performing testing on study subjects. After each test is performed, the spirometry software will provide immediate feedback to the technician indicating whether the effort meets ATS acceptability and reproducibility standards. All efforts will be stored electronically. After completion of testing, the study staff will electronically transmit the spirometric measurements for centralized quality assurance review [redacted]. Feedback on the quality of the measurements will be provided to the investigational site and to Pearl or designee for central data management.

The volume accuracy of the spirometer is to be checked on each test day, using a 3-L syringe across three flow ranges (i.e., at <2 L/sec, 4 to 6 L/sec and >8 L/sec) with temperature and barometric pressure correction. The calibration syringe must meet ATS specifications and must not be used beyond the expiry date. Required accuracy is ±3%; i.e., 3.09 L to 2.91 L (ATS/ERS). The results will be printed and maintained in a calibration log, which will be monitored for compliance during the monitoring visits (see Appendix 2, Spirometry Assessment Criteria).

Refer to Section 7.1.1.1 for specific FEV_1 criteria that prompt subjects to be discontinued from the study.

7.1.2 Subject Diary Data Collection

Subjects will be provided with a Diary to be completed BID to record their study drug dosing, and rescue medication use.

Starting at Screening (Visit 1a/b) and for the duration of the study, subjects will be issued and trained on diary collection. They will be asked to maintain a daily record of their study drug dosing, and rescue medication use.

Site personnel will review the Diary entries during the Screening Period to assess the subject's compliance and understanding of how to use the Diary to maintain a daily record of their study drug dosing, and rescue medication use.

At the Randomization Visit (Visit 2), subjects should meet the compliance requirement of ≥70% subject completion of Diary assessments in the last 7 days preceding the Randomization Visit to be randomized in the study. Subjects who fail to demonstrate proper Diary compliance prior to Randomization must be screen failed.

Note: In-clinic dosing times will be documented in the source by the site staff and will not be entered by subjects into their Diary.

At all treatment visits (Visits 2 to 9) site personnel must review the Diary prior to dosing study drug in the clinic Table 8-1).

The patient is to return the completed diary at each scheduled visit. The study coordinator will be responsible for reviewing the diary for completeness and accuracy with the patient. All fields should be completed by the patient. The patient will sign (initial) and date each page of the diary on the day it was completed and the study coordinator will initial and date each diary page at the site visit when the diary is returned to validate the authenticity of the entries. If discrepancies or omissions of data are observed at this review, the patient, not the study coordinator, should make the corrections. The patient should draw a single line through the error and initial and date all corrections. The patient should make all entries in the diary in blue or black ink.

Furthermore, in conjunction with review of the diary, the patient will be prompted by the study coordinator about missed doses of study medication and additional COPD medication. The patient should be instructed to record this information in the diary. Missing data from >24 hours prior to the site visit should be left blank. Subjects should be instructed to record the time and doses of study medication and rescue medication in hours and minutes a.m. or p.m., not in 24-hour clock time. Study sites will enter the Diary information into the eCRF.

7.1.3 Rescue Salbutamol Sulfate Use

The subject will record the total number of puffs of rescue salbutamol sulfate used in the Diary on a PRN basis. The number of puffs of rescue salbutamol sulfate to be recorded is the number of actuations of the canister. For example, when rescue salbutamol sulfate is

required and two actuations are inhaled, this should be recorded as two puffs. In the event the subject requires four actuations, this should be recorded as four puffs. Subjects requiring more than eight puffs per day on three or more consecutive days with worsening symptoms should contact the site.

7.1.4 Medication Compliance

Time of dosing with study drug will be recorded in the subject's Diary for each day of treatment, except in-clinic dosing time. Study drug compliance will be checked at all visits and any issues identified will be noted in the appropriate study files.

7.2 Safety Assessments

The safety assessments include AEs and SAEs, vital sign measurements (BP, HR, respiratory rate, and temperature), clinical laboratory values (hematology and clinical chemistry), and ECGs.

7.2.1 Medical/Surgical History and Physical Examination

Medical history will be taken at Screening (Visit 1), including COPD exacerbations within 12 months of Screening Period.

A complete physical examination will be performed at Screening (Visit 1a) and the Follow-up Visit (Visit 10), and include the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. Weight, assessed in ordinary indoor clothing with shoes off, will be recorded at Screening (Visit 1) and Visit 10, and height will be recorded at Screening (Visit 1) only.

7.2.2 Vital Sign Measurements

Heart rate, systolic and diastolic blood pressure (SBP/DBP), respiratory rate and temperature will be assessed at each visit; assessments will be obtained in either the supine or seated position. Vital signs to be assessed as follows:

- A single set of vitals will be obtained at Screening (Visit 1a), Follow-up Visit (Visit 10), and at the Premature Discontinuation Visit (if applicable)
- At Visits 2 through 9 of each treatment period, all pre-dose vitals will be conducted at 60 and 30 minutes prior to study drug administration; post-vitals will be conducted at 15 and 30 minutes, and 1 and 2 hours after study drug administration,
- Temperature will be obtained at Screening (Visit 1a), and at pre-dose at all visits and will not be repeated post-dose at subsequent timepoints unless clinically indicated.

Refer to Section 5.6 for specific criteria for HR and SBP/DBP readings that could result in subjects to be discontinued from the study.

7.2.3 12-Lead ECG

An ECG will be obtained at Screening (Visit 1a), Follow-up Visit (Visit 10), and at Premature Discontinuation Visit (if applicable).

At Visits 2, 4, 6 and 8 (Day 1 of each Treatment Period), ECGs will be obtained pre-dose within 60 minutes prior to study drug administration, and post-dose at 30 minutes and 2 hours after study drug administration.

At Visits 3, 5, 7 and 9 (Day 8 of each Treatment Period), ECGs will be obtained pre-dose within 60 minutes prior to study drug administration, and post-dose at 30 minutes and 2 hours after study drug administration.

Additional ECGs will be obtained if the subject's HR is <60 bpm and is >20 bpm below test day baseline or is >100 bpm and is >20 bpm above the test day baseline value (where baseline is defined as the mean of the HR assessments obtained 60 and 30 minutes prior to study drug administration on the same test day).

7.2.4 Clinical Laboratory Tests

Clinical safety laboratory tests will be analyzed by a local or central laboratory according to standardized, validated assays. The laboratory will supply detailed instructions and all containers for blood investigations. Blood sample volumes will meet the laboratory's specification. All clinical laboratory tests will be obtained at Screening and Follow-up.

On Day 1 and Day 8 of each Treatment Period (Visits 2 to 9), hematology (complete blood count) and chemistry (comprehensive metabolic panel [CMP]) samples will be obtained within 60 minutes prior to dosing. A basic metabolic panel (BMP) with focus on potassium and glucose parameters will be obtained at 2 hours post-dose for all subjects (see Table 8-2).

In all women of childbearing potential, a serum pregnancy testing will be performed at Screening and at the Follow-up Visit (Visit 10), with urine human chorionic gonadotropin (HCG) testing occurring prior to the start of each Treatment Period (Visits 2, 4, 6, and 8).

The clinical laboratory parameters in Table 7-1 will be assessed.

Table 7-1. Clinical Laboratory Parameters

Hematology	
Hemoglobin	Mean Corpuscular Hemoglobin
Hematocrit	Mean Corpuscular Hemoglobin Concentration
White Blood Cell Count with Differential	Mean Corpuscular Volume
Red Blood Cell Count	
Platelet Count	
Clinical Blood Chemistry	
Liver Enzyme and Other Function Tests	**Other Clinical Blood Chemistry**
Alanine Aminotransferase	Albumin
Aspartate Aminotransferase	BUN[a]
Alkaline Phosphatase	Calcium[a]
Bilirubin, Total	Chloride[a]
Gamma-glutamyl Transferase	Cholesterol
	Bicarbonate
	Creatinine[a]
	Glucose[a]
	Magnesium
	Potassium[a]
	Phosphate
	Protein, Total
	Sodium[a]
	Triglycerides
Other Tests: Females of childbearing potential only: Serum pregnancy test at Screening and Follow-Up Visit only; urine HCG at Visits 2, 4, 6, and 8. Creatinine clearance will be estimated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.	

Abbreviations: BMP=basic metabolic panel; BUN=blood urea nitrogen; HCG=human chorionic gonadotropin

[a] Parameters included in the BMP

7.2.4.1 Blood Sample Collection for Metabolite Assay

Blood plasma will be collected from all subjects at a pre-specified, single timepoint, randomized manner at 15 minutes, 30 minutes, 1 hour or 2 hours post-dose on Day 8 of each Treatment Period (see Table 8-2). Samples will be stored by the central laboratory as plasma at -70^{o} C and retained until after in vitro characterization is completed. Contingent upon the results of the in vitro characterization, the plasma samples may be analyzed to characterize any potential metabolites of glycopyrronium or will be destroyed.

7.2.5 Adverse Events Assessments

7.2.5.1 Performing Adverse Event Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's CRF and on the AE Reporting Form. If the AE is considered alarming, the Investigator must report the AE immediately to the Sponsor or representative. In addition, certain AEs (as described in Section 7.2.5.7) are classified as serious and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as an SAE.

In the case of SAEs, after discussing the details of the AE, the Investigator and the Sponsor or representative may discontinue the subject prematurely.

Adverse events will be collected from the time that the ICF is signed to the time of study termination or study exit. For ongoing AEs at the time of the Follow-up Visit, study termination, or study exit, additional data, such as AE resolution date, will be collected and reported to Sponsor or representative. If these data are collected after the study database is locked, it will be reported to Sponsor or representative, but will not be included in the study database.

7.2.5.2 Adverse Event Definitions

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Adverse events include but are not limited to:

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

An AE does not include:

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

7.2.5.3 Pre-Randomization Adverse Events

Adverse events that occur between the time the subject signs the ICF for the study and the time when that subject is randomized will be summarized as medical history and not as a study AE unless the event meets the definition of an SAE as defined below in Section 7.2.5.7.

7.2.5.4 Severity

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

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

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

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

7.2.5.5 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.

7.2.5.6 Clinical Laboratory Adverse Events

Many laboratory abnormalities observed during the course of a study will be included under a reported AE describing a clinical syndrome (e.g., 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 (e.g., elevated creatinine in a setting of renal failure) does not need to be recorded as an AE. However, isolated laboratory abnormalities should be reported as AEs if they are considered to be clinically significant by the Investigator.

Criteria for a clinically significant laboratory abnormality are:

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

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

7.2.5.7 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 serious when, based upon appropriate judgment, they may jeopardize the subject or patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in 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 Sponsor. All SAEs must be reported to the Sponsor 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. After the initial report, as necessary, the Investigator must provide any additional information on an SAE to the Sponsor or representative within two working days after he/she receives that information. This follow-up information will be a detailed written report that may include copies of hospital records, case reports, autopsy reports, and other pertinent documents.

Post-study SAEs following the last dose of study drug must be reported to the Sponsor or representative as described in Section 7.2.5.8.

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

7.2.5.8 Supplemental Investigations of Serious Adverse Events

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

7.2.5.9 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 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 CRF or reported to the Sponsor or representative if the CRFs 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.

7.2.5.10 Notification of Post-Study Serious Adverse Events

Investigators must actively follow subjects up to the completion of the study (7-14 days after the last dose: the Follow-up visit). However, if the Investigator becomes aware of a post-study SAEs which are considered related to the study drug and occurring after the Follow-up visit, the event must be reported to the Sponsor or representative. All SAEs must be reported to the Sponsor or representative no later than 24 hours after the Investigator recognizes/classifies the event as an SAE.

7.2.5.11 Institutional Review Board Notification of Serious Adverse Events

The principal Investigator is responsible for promptly notifying the head of her/his site and the sponsor of all SAEs, including any follow-up information, occurring at her/his site. The head of the study site is responsible for reporting that SAE information to the IRB of the site. The Sponsor will report any SAE regulatory report, including any follow-up reports to the principal Investigators, the head of the study sites, and the IRB. Documentation of the submission to the IRB must be retained for each safety report. If the IRB decides that revision of ICF is required base on the SAE information, the IRB will notify that to the head of the study site and the head of the study site will notify that to the principal Investigator and the Sponsor, and the principal Investigator will revise the ICF.

7.2.5.12 Health Authority Safety Reports

Pearl or its representatives will submit a safety report to the PMDA, FDA, and/or any other appropriate regulatory agencies, for any suspected adverse reaction that is both serious and unexpected within the appropriate time frame. In addition, expected adverse reactions of which seriousness is death or life threatening must be reported to the PMDA.

Pearl or its representatives will send copies of each safety report submitted to the PMDA, FDA, and/or other regulatory agencies to all Investigators who are actively participating in

Pearl-sponsored clinical studies, the heads of their sites, and the IRBs of their sites. Documentation of the submission to the IRB must be retained for each safety report.

7.2.6 Adverse Events of Special Interest

7.2.6.1 Paradoxical bronchospasm

Paradoxical bronchospasm may occur following inhalation from an MDI. Monitoring for paradoxical bronchospasm will occur at Visits 2 to 9 at 15 and 30 minutes post-dose. In this study, paradoxical bronchospasm is defined as a reduction in FEV_1 of >20% from test day mean FEV_1 values obtained 60 and 30 minutes prior to study drug administration, occurring within 30 minutes post-dosing, with associated symptoms of COPD (wheezing, shortness of breath, or cough). All AEs and SAEs will be recorded as appropriate.

7.2.6.2 Dry mouth

Subjects will be specifically asked about the presence of dry mouth at specified intervals (pre-dose and at 1 and 2 hours post-dose on Day 1 and Day 8). On Day 8, if dry mouth persists at 2 hours, additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day (see Table 8-2). If present, the severity (mild, moderate, and severe) of dry mouth symptoms will be assessed. If dry mouth is not noted at 2 hours post study drug administration, further dry mouth assessments do not need to be collected. All reports of dry mouth will be recorded as AEs.

Instructions for Recording Dry Mouth AE:

1) The Investigator should assess subjects for history of dry mouth at Screening (Visit 1) and prior to dosing at Randomization (Visit 2). If yes, record dry mouth in the subject medical history.

2) If subject reports an event of dry mouth post-randomization capture as an AE.

3) The Investigator should follow all AEs of dry mouth to resolution.

4) Duration is captured from onset (when first reported by subject) to resolution (when subject reports event has resolved).

7.2.7 Overdose

An overdose is defined as a dose greater than the highest dose level evaluated in this study as described in Section 6.2 (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 Sponsor or representative. 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 being used in this study. Such documents may include are not limited to the IB and approved product labeling for GP MDI, salbutamol sulfate, and ipratropium bromide.

7.2.8 Pregnancy

Any pregnancy of a female subject or a female partner of a male subject that occurs from Screening until study completion must be reported to the Sponsor or representative. To ensure subject safety, each pregnancy must be reported to Pearl within 24 hours of learning of its occurrence. The pregnancy of a female subject must be followed up to determine outcome (including premature termination) and status of mother and child. If a female partner of a male subject become pregnant, the same follow up should be performed after consent is obtained from the female partner.

7.2.9 Malfunction of Devices

Any malfunction of devices including ECG and spirometer must be reported to Pearl or their designee. The detailed procedures will be provided in the separate document.

7.3 Termination of Study

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

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

The study will be placed on hold in the event of:

- 2 or more deaths deemed to be cardiac or respiratory in origin; or
- 3 or more deaths from any cause during the study.

Stopping criteria based on deaths were based on estimates of rates of mortality taken from the integrated data from umeclidinium and vilanterol program PADAC, 2013. These criteria imply an approximately 0.2% chance of placing the study on hold if there is no true increase in mortality.

8 STUDY ACTIVITIES

A time and events schedule is provided in Table 8-1. Detailed schedules for pre- and post-dose procedures to be performed on Day 1 (Visits 2, 4, 6, and 8) and Day 8 (Visits 3, 5, 7, and 9) of each Treatment Period are provided in Table 8-2.

Table 8-1. Schedule of Events

Procedures	Screening		Treatment Period 1		Treatment Period 2		Treatment Period 3		Treatment Period 4		Follow-up
	Visit 1a	Visit 1b (optional)	Visit 2 (Rand) Day 1	Visit 3 Day 8	Visit 4 Day 1	Visit 5 Day 8	Visit 6 Day 1	Visit 7 Day 8	Visit 8 Day 1	Visit 9 Day 8	Visit 10 Follow-up Visit
Study Day [a]	**-28 to -7**		**0**	**7±2**	**14**	**21±2**	**28**	**35±2**	**42**	**49±2**	**63**
Informed Consent	X										
Eligibility Criteria	X	X	X								
Verify Continued Eligibility by spirometry					X		X		X		
Reversibility testing to Ipratropium Bromide [b]	X	X									
Demographics & Medical/Surgical History	X										
Concomitant Medications [c]	X		X	X	X	X	X	X	X	X	X
Spirometry [d]	X	X	X	X	X	X	X	X	X	X	
Physical Examination [e]	X										X
Vital Signs	X		X	X	X	X	X	X	X	X	X
Chest imaging test [f]	X										
12-Lead ECG [g]	X		X	X	X	X	X	X	X	X	X
Pregnancy Test [h]	X		X		X		X		X		X
Clinical Laboratory Testing [i] (Volume of blood collected (mL))	X 10mL		X 15mL	X 15mL	X 15mL	X 15mL	X 15mL	X 15mL	X 15mL	X 15mL	X 10mL
Adjust COPD Medications Per Protocol [j]	X									X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Inhalation Device Training	X		X	X	X	X	X	X	X	X	
Study Drug Administration [k]			X	X	X	X	X	X	X	X	
Review Subject Diary [l]			X	X	X	X	X	X	X	X	
Study Drug Dispensing			X		X		X		X		
Study Drug Collection				X		X		X		X	
Ipratropiun Bromide Dispensing	X[m]			X[n]		X[n]		X[n]			
Ipratropium Bromide Collection			X[o]		X[n]		X[n]		X[n]		
Salbutamol Sulfate Dispensing [p]	X		(X)	(X)	(X)	(X)	(X)	(X)	(X)		
Salbutamol Sulfate Collection										X	
Paradoxical Bronchospasm [q]			X	X	X	X	X	X	X	X	
Metabolite Blood Sample [r] (Volume of blood collected (mL))				X 10mL		X 10mL		X 10mL		X 10mL	
Assessment of Dry Mouth [s]	X		X	X	X	X	X	X	X	X	

Abbreviations: BMP=basic metabolic panel; BP=blood pressure; COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; HCG=human chorionic gonadotropin; HR=heart rate; MDI=metered dose inhaler; PEFR=peak expiratory flow rate; Rand=randomization

Note: Premature Discontinuation Visits will be captured as unscheduled visits.

[a] Scheduling Visits: The maximum Screening Period is 28 days. The indicated Study Days are estimates based on a 7-Day Treatment Period and a Washout Period of 7 days. Each subject will receive 7 days of study treatment with each of their assigned treatments for a total of four separate Treatment Periods. A Washout Period of 5 to 21 days will occur between each Treatment Period. Sites should make every effort to maintain subjects within the scheduled visit window. Subjects who fall outside the visit window will be placed in the appropriate visit window at the next scheduled visit.

[b] Subjects will be tested for reversibility to ipratropium bromide at Visits 1a, Visit 1b (if applicable), within 30 to 60 minutes following four puffs of ipratropium bromide.

[c] At all visits beyond Screening, note time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, visit should be rescheduled).

[d] Spirometry (FEV_1, FVC, and PEFR) will be assessed at Screening and at Visit 2 through Visit 9. See Table 8-2 for spirometry assessments and specific timepoints.

[e] Includes evaluation of weight at Screening (Visit 1) and Follow-up (Visit 10) and height at Screening (Visit 1) only.

[f] Obtain a new chest x-ray if the chest x-ray or computed tomography scan performed within the 6 months prior to Screening (Visit 1) is not available.

[g] Electrocardiograms are to be performed at Screening (Visit 1) and at Visits 2 through 10. See Table 8-2 for ECG assessments and specific timepoints.

[h] Females of childbearing potential: Serum at Screening (Visit 1) and Follow-Up (Visit 10); urine HCG screening at Visits 2, 4, 6, 8. Blood for Pregnancy test is taken from the Chemistry tube so no extra sampling is required.

[i] Clinical laboratory tests will be obtained at Screening (Visit 1) and at Day 1 and Day 8 of each Treatment Period (Visits 2 to 9) within 60 minutes prior to dosing and 2 hours post dose. Clinical laboratory testing will also be performed at the Follow-up Visit (Visit 10). At Visits 2, 4, 6, and 8 (Day 1), BMP with focus on potassium and glucose parameters will be obtained at 2 hours post-dose on all subjects (see Table 8-2). The total volume of collected blood for clinical laboratory testing may be up to 140 mL. Also note that, if including the Metabolite Blood Sample, the total volume of collected blood may be up to 180 mL (see footnote r)

[j] At Screening (Visit 1), stop prohibited COPD medications and change COPD medications as specified in Section 5.4 (i.e., ipratropium bromide with or without ICS). At the end of Visit 9, return subject to pre-study or other appropriate inhaled maintenance COPD medications.

[k] At the start of each treatment visit, subject must withhold all COPD medications, including study drug, rescue medication, and ICS for at least 6 hours prior to start of test day procedures. In-clinic dosing time is recorded as time of the second puff/inhalation. The in-clinic dosing time should be timed to be within 12±2 hours of the prior evening dosing time.

[l] Issue and train subjects on Diary use only after a subject is determined to qualify to proceed to Visit 2. Subjects will be asked to maintain a daily record of their study drug dosing, and rescue medication use.

[m] Ipratropium bromide is dispensed for use during the screening period.

[n] Ipratropium bromide is dispensed for use during Washout Periods and collected at the start of the next Treatment Period.

[o] Ipratropium bromide from Screening is collected at Randomization (Visit 2).

[p] Subjects will be dispensed salbutamol sulfate MDI at Screening to take as rescue medication throughout the treatment periods from Visits 2 to 9.

[q] Please refer to Section 7.2.6.1for definition of paradoxical bronchospasm.

[r] In addition to standard clinical lab tests, a single blood draw of 10 mL will be conducted in all subjects in a pre-specified, single timepoint, randomized manner at 15 minutes, 30 minutes, 1 hour or 2 hours post-dose on Day 8 of each treatment period for metabolite assay. The total volume of collected blood may be up to 40 mL. Refer to Section 7.2.4.1.

[s] Please refer to Section 7.2.6.2 for definition of dry mouth.

Table 8-2. Visit Procedures on Day 1 and Day 8 of Each Treatment Period (Visits 2 through 9)

Clinical Variable	Pre-dose		Post-dose			
	-1 hour	-30 minutes	15 minutes	30 minutes	1 hour	2 hours
Paradoxical Bronchospasm Assessment [a]			X	X		
Dry Mouth Assessment [b, c]		X			X	X
Vital Signs [c, d]	X	X	X	X	X	X
12-Lead ECG [c, e]	X			X		X
Clinical Laboratory Testing [c, f]	X					X
Spirometry (FEV_1, FVC, and PEFR) [g]	X	X	X	X	X	X
Metabolite Blood Sample [h]			X	X	X	X
Review Subject Diary	X					
Dispense/Collect Drug Supplies [i]		X				

Abbreviations: BMP=basic metabolic panel; ECG=electrocardiogram; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; PEFR=peak expiratory flow rate
Note: The timepoint at which dosing is to occur is regarded as "0 minutes".
Note: Where data collection timepoints are concurrent, variables are recommended be collected in the following order: vital signs, ECGs, clinical laboratory assessments, and spirometry. If the time window does not allow for this order, spirometry measurements should be prioritized.

[a] Please refer to Section 7.2.6.1 for definition of paradoxical bronchospasm.

[b] Please refer to Section 7.2.6.2 for definition of dry mouth.

[c] Safety assessments (vital signs, dry mouth assessments clinical laboratory assessments, ECG) should be started approximately 5 to 10 minutes ahead of the specified timepoint to ensure that spirometry for FEV_1, FVC, and PEFR determination will be conducted as close to the specified timepoints as possible (i.e., FEV_1, FVC, and PEFR assessments need to be conducted within ±15 minutes of specified time prior to study drug administration; ±5 minutes of specified time for the first 60 minutes after study drug administration; ±15 minutes of specified timepoint for assessments obtained thereafter).

[d] Temperature will be obtained pre-dose at all visits and will not be repeated post-dose at subsequent timepoints unless clinically indicated.

[e] Please refer to Section 7.2.3 for ECG parameters

[f] All clinical laboratory parameters will be obtained within 60 minutes prior to study drug administration; BMP with focus on potassium and glucose parameters will be obtained at 2 hours post-dose for all subjects.

[g] The baseline FEV_1 at Visit 4, 6 and 8 must be within ±20% or 200mL of the baseline FEV_1 obtained at the Randomization Visit (Visit 2). If the test day FEV_1 is not within ±20%, the visit may be rescheduled at the Investigator's discretion (e.g., within 7 days), or the subject may be discontinued. The 30 minute post-dose PEFR on Day 1 should be obtained after spirometry assessments allowing enough time for the subject to recover from the pulmonary function test maneuvers.

h. A single blood draw of up to 10 mL will be conducted in all subjects in a pre-specified, single timepoint, randomized manner at 15 minutes, 30 minutes, 1 hour or 2 hours post-dose on Day 8 of each treatment period for metabolite assay. Refer to Section 7.2.4.1.

[i] Ipratropium bromide is dispensed for use during Washout Periods and collected at the start of the next Treatment Period.

8.1 Screening Visit (Visits 1a and 1b)

- Obtain informed consent
- Register subject in IWRS to obtain subject Screening number
- Obtain demographic data, including age, race, smoking history, medical/surgical history including dry mouth, glaucoma, and age at onset of COPD
- Obtain history of COPD exacerbations within 12 months of the Screening Visit
- Verify subject meets inclusion/exclusion criteria
- Obtain medication history, including COPD medications
- Conduct a serum pregnancy test for all female subjects unless it is documented in the medical history that the subject has been irreversibly surgically sterilized (hysterectomy, oophorectomy, or bilateral tubal ligation) or they are at least 2 years post-menopausal
- Conduct a complete physical examination (general appearance, skin, head, eyes, ears, nose, throat, neck [including thyroid], lymph nodes, chest, heart, abdomen, extremities, and nervous system)
- Obtain height, weight, and vital signs
- Obtain a 12-lead ECG
- Conduct baseline spirometry assessments (FEV_1, FVC, and PEFR)
- Conduct inhalation device training
- Dispense ipratropium bromide for use during the Screening Period
- Dispense salbutamol sulfate as a rescue medication throughout screening to treatment period (Visit 1 to Visit 9)
- Conduct reversibility testing to four puffs ipratropium bromide (see also Section 7.1.1.2)
- Obtain laboratory samples (hematology and chemistry)
- Obtain a new chest x-ray, if chest x-ray or CT scan within six months of Visit 1a (Screening) is not available
- Stop prohibited COPD medications and change concurrent COPD medications as specified in protocol (see Section 5.4)
- Dispense subject Diary and provide instruction to record needed information on Diary completion
- Adverse events must be recorded during the Screening Period; i.e., from the time of consent to the start of study treatment. Adverse events that occur between the time the subject signs the ICF for the study and the time when that subject is randomized will be summarized as medical history and not as a study AE unless the event meets the definition of an SAE (see Section 7.2.5.7)
- Arrange date of Visit 1b (optional) or Visit 2 as appropriate. Schedule Visit 2 within 7 to 28 days after Visit 1a
- **Note**: Visit 1b is to be used only for repeat spirometry entry criteria only, all other repeat assessments, if needed, will be captured as an unscheduled visit

8.2 Randomization Visit (Visit 2; Day 1 of Treatment Period 1)

- Review subject Diary (if Diary is not completed, re-instruct subject and Visit 2 must be rescheduled)
- Determine the last dosing of short-acting bronchodilator and other COPD medications (if <6 hours, Visit 2 must be rescheduled)
- Review subject's eligibility to continue
- Review concomitant medications to ensure adherence to COPD regimen
- Record AEs (if any)
- Collection of ipratropium bromide
- Perform all pre-dose assessments, including vital signs, ECGs, clinical laboratory testing, urine pregnancy testing (if appropriate), and spirometry (refer to Table 8-2)
- Obtain subject treatment assignment information from IWRS
    - At 15-30 minutes prior to dosing, it is recommended that the seal around the study day treatment box is opened and the instructions for administration of study drug followed. Refer to Section 6.7 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits.
- The subject is to be considered randomized after receiving a randomization number from the IWRS
- Subject will administer first dose of newly assigned study drug at the clinic
- Perform all post-dose assessments (refer to Table 8-2)
- Confirm subject's ability to use MDI correctly (provide training as appropriate)
- Ensure subject has adequate supply of rescue medication (salbutamol sulfate)
- Schedule Visit 3

8.3 Visit 3 (Day 8 of Treatment Period 1)

- Review subject Diary; provide instructions for Diary completion, if needed
- Determine the last dosing of short-acting bronchodilator and other COPD medications (if <6 hours, visit must be rescheduled)
- Review concomitant medications and ensure adherence to COPD regimen
- Confirm eligibility to continue
- Record AEs (if any)
- Collect blinded study drug dispensed during the prior visit
- Complete all pre-dose assessments, including vital signs, clinical laboratory testing, urine pregnancy testing (if appropriate), and spirometry (refer to Table 8-2)
- Perform all post-dose assessments (see Table 8-2)

- Schedule next visit (following a Washout Period of 5 to 21 days) and ensure subject has adequate supply of rescue medication salbutamol sulfate
- Dispense washout medication ipratropium bromide

8.4 Visits 4, 6, and 8 (Day 1 of Treatment Periods 2, 3, and 4)

- Review subject Diary; provide instructions for Diary completion, if needed
- Determine the last dosing of short-acting bronchodilator and other COPD medications (if <6 hours, visit must be rescheduled)
- Confirm subject's eligibility to continue
- Review concomitant medications to ensure adherence to COPD regimen
- Record AEs (if any)
- Collect ipratropium bromide
- Complete all pre-dose assessments, including vital signs, ECGs, clinical laboratory testing, urine pregnancy testing (if appropriate), and spirometry (see Table 8-2)
- Obtain subject treatment assignment information from IWRS
  - At 15-30 minutes prior to dosing, it is recommended that the seal around the study day treatment box is to be opened and the instructions for administration of study drug followed. Refer to Section 6.7 for detailed instructions for preparation of treatment for administration, including priming the MDI prior to subject use.
- Subject will administer a dose of the newly dispensed study drug at the clinic under site supervision
- Perform all post-dose assessments (refer to Table 8-2)
- Schedule next visit (Visit 8) and ensure subject has adequate supply of rescue medication salbutamol sulfate

8.5 Visits 5, 7, and 9 (Day 8 of Treatment Periods 2, 3, and 4)

- Review subject Diary; provide instructions on Diary completion, if appropriate
- Determine the last dosing of short-acting bronchodilator and other COPD medications (if <6 hours, visit must be rescheduled)
- Review concomitant medications and ensure adherence to COPD regimen
- Collect blinded study drug dispensed during the prior visit
- Complete all pre-dose assessments, including vital signs, clinical laboratory testing, urine pregnancy testing (if appropriate), and spirometry (see Table 8-2)
- Perform all post-dose assessments (refer to Table 8-2)
- **At Visits 5 and 7 only**: Schedule next visit (following a Washout Period of 5 to 21 days) and ensure subject has adequate supply of and rescue medication salbutamol sulfate. Dispense washout medication ipratropium bromide.

- **At Visit 9 only**: Collect salbutamol sulfate. Schedule the Follow-up Visit at least 7 days but no longer than 14 days from Visit 9. At completion of all Visit 9 assessments, return subject to pre-study or appropriate inhaled maintenance COPD medications.

8.6 Visit 10 (Follow-up Visit/Premature Discontinuation)

- Review concomitant medications
- Record AEs (if any)
- Conduct a physical examination and record vital signs
- Obtain a 12-lead ECG
- Obtain laboratory samples (hematology and chemistry)
- Conduct a serum HCG pregnancy test for women of childbearing potential
- Inform subject about reporting all SAEs up to 14 days following the last dose of study drug
- If not adjusted following Visit 9, return subject to pre-study or appropriate inhaled maintenance COPD medications
- Complete study completion page of CRF

Note: Premature Discontinuation Visits will be captured as unscheduled visits. In addition to the above assessments, the reason for subject discontinuation should be noted. If the Discontinuation Visit is performed >14 days post last study drug dosing, a follow-up visit will not be required.

8.7 Unscheduled Visits

- Visit 1b is to be used only for repeat spirometry entry criteria only, all other repeat assessments, if needed, will be captured as an unscheduled visit.

8.8 Completion of the Study

The Investigator will document the completion or the reason for early withdrawal by a randomized subject in the CRF. The following categories should be used to describe these events in the CRF:

- Subject discretion (document reason)
- Investigator or designee considers it to be in the best interest of the subject
- AEs
- Administrative reasons (e.g., early termination of the study)
- Subject lost-to-follow-up
- Lack of efficacy
- Major protocol deviation
- Death

- Completion of the study
- Protocol-specific discontinuation criteria (see Section 5.6)

9 PLANNED STATISTICAL METHODS

9.1 Introduction

This study will be conducted as a four-period, four-treatment, cross-over design evaluating the following treatments in approximately 60 subjects:

- GP MDI 28.8 µg ex-actuator
- GP MDI 14.4 µg ex-actuator
- GP MDI 7.2 µg ex-actuator
- Placebo

The primary objective of this study is to assess the efficacy as measured by lung function of GP MDI relative to Placebo in Japanese subjects with moderate to severe COPD across the range of doses evaluated in this protocol. To this end, each dose of GP MDI will be compared with Placebo with respect to the primary efficacy endpoint, change from baseline in morning pre-dose trough FEV_1 on Day 8. The secondary objective of the study is to characterize the dose-response curve for GP MDI.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

Since pre-dose values are known to be variable and an isolated timepoint may not accurately reflect the true baseline, the following baseline will be used for analyses of efficacy unless otherwise specified: the mean of available pre-dose values on the first day of each Treatment Period, i.e., the mean of pre-dose values at Visits 2, 4, 6, and 8, where the mean of the -60 and -30 minute value for each visit day is obtained and then all visit means are averaged. Note that all spirometry and Diary-based endpoints will utilize changes from baseline and that area under the curve (AUC) assessments will be normalized by dividing the AUC by the length of follow up post-dosing (typically 2 hours).

9.2.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is:

- Change from baseline in morning pre-dose trough FEV_1 on Day 8

9.2.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are as follows:

- FEV_1 AUC_{0-2} on Day 1 and Day 8
- Peak change from baseline in FEV_1 on Day 1 and Day 8
- FVC AUC_{0-2} on Day 8

9.2.1.3 Other Efficacy Endpoints

The other efficacy endpoints of this study are as follows:

- Change from baseline in FEV_1 at each post-dose timepoint on Day 1 and Day 8
- Change from baseline in morning pre-dose trough FVC on Day 8
- FVC AUC_{0-2} on Day 1
- Peak change from baseline in FVC on Day 1 and Day 8
- Change from baseline in FVC at each post-dose timepoint on Day 1 and Day 8
- Change from baseline in morning pre-dose trough PEFR on Day 8
- PEFR AUC_{0-2} on Day 1 and Day 8
- Peak change from baseline in PEFR on Day 1 and Day 8
- Change from baseline in PEFR at each post-dose timepoint on Day 1 and Day 8
- Change from baseline in average daily use of rescue salbutamol sulfate over the Treatment Period

9.2.2 Safety Endpoints

The safety assessments include ECGs, vital sign measurements, clinical laboratory tests, physical examination findings, AEs, and SAEs.

9.3 Study Populations

The following analysis populations are defined in this study:

- The **Intent-To-Treat (ITT) Population** is defined as all subjects who are randomized to treatment and receive at least one dose of the study treatment. Subjects will be analyzed in each period according to the treatment they were assigned to per randomization scheme. (Note that a subject who used a study treatment but took less than one full dose of treatment will qualify for this population).
- A **Modified ITT (mITT) Population** is a subset of the ITT Population including subjects who received treatment and have post-treatment efficacy data from at least two Treatment Periods. Data judged to be impacted by major protocol deviations will be determined prior to unblinding and excluded. Statistical tabulations and analyses will be

by randomized treatment, but data obtained after subjects receive an incorrect treatment will be excluded from the affected periods.

- The **Safety Population** is defined as all subjects who are randomized to treatment and receive at least one dose of the study treatment. Subjects will be analyzed according to treatment received rather than per randomization scheme. Statistical analyses and tabulations will be by the treatment actually received.
- The **Not Randomized Population** is defined as subjects who did not receive a randomization number and therefore did not receive a dose of study treatment (e.g., subjects who were screen failures or stopped participation prior to having been randomized).

Analyses will be performed as follows:

Demographics will be summarized for the ITT, mITT, Safety, and Not Randomized Populations. Extent of exposure will be summarized for the Safety Population. The Safety Population will be used to summarize safety.

Efficacy analyses will be performed for the mITT and ITT Populations, with the mITT Population being considered the primary population for these analyses.

9.4 Analyses

9.4.1 Primary Efficacy Analysis

The primary efficacy analysis involves the comparison of the primary efficacy endpoint (change from baseline in morning pre-dose trough FEV_1 at Day 8) for each GP MDI dose with Placebo. In addition, comparisons among the GP MDI doses will be conducted as supportive analyses. Efficacy analyses will be conducted using mixed models repeated measures with baseline FEV_1, the response to ipratropium bromide at Screening (Visit 1), and treatment as covariates. Within-subject correlation will be modeled by including subject as a random effect. The model will not include treatment sequence or period unless those terms are determined to be important ($p<0.10$).

For the primary efficacy objective, the family-wise Type I error will not be controlled for multiplicity. As the aim of the study is to describe the dose-ranging profile of GP MDI, all doses of GP MDI will be tested relative to Placebo. The totality of the data will be used to select an appropriate dose.

9.4.2 Secondary Efficacy Analysis

9.4.2.1 FEV_1 AUC_{0-2} on Day 1 and Day 8

FEV_1 AUC_{0-2} will be evaluated using mixed model repeated measures. The model will include baseline FEV_1, the response to ipratropium bromide at Screening (Visit 1), Day (1 or 8), treatment, and the treatment by day interaction as covariates. The model will also include

subject as a random effect to model correlation within subject across the entire study, and the covariance structure for subject within period will be compound symmetric. The model will not include treatment sequence or period unless those terms are determined to be important ($p<0.10$). Thus the same model will be used to produce estimated treatment differences on Day 1 and on Day 8.

9.4.2.2 Peak Change from Baseline in FEV_1 on Days 1 and Day 8

Peak change from baseline in FEV_1 will be evaluated using mixed model repeated measures. The model will include baseline FEV_1, the response to ipratropium bromide at Screening (Visit 1), Day (1 or 8), treatment, and the treatment by Day interaction as covariates. The model will also include subject as a random effect to model correlation within subject across the entire study, and the covariance structure for subject within period will be compound symmetric. The model will not include treatment sequence or period unless those terms are determined to be important ($p<0.10$). Thus the same model will be used to produce estimated treatment differences on Day 1 and on Day 8.

9.4.2.3 FVC AUC_{0-2} on Day 8

FVC AUC_{0-2} will be evaluated using mixed model repeated measures. The model will include baseline FVC, the response to ipratropium bromide at Screening (Visit 1), Day (1 or 8), treatment, and the treatment by Day interaction as covariates. The model will also include subject as a random effect to model correlation within subject across the entire study, and the covariance structure for subject within period will be compound symmetric. The model will not include treatment sequence or period unless those terms are determined to be important ($p<0.10$). Thus the same model will be used to produce estimated treatment differences on Day 1 (an other endpoint) and on Day 8 (a secondary endpoint).

9.4.3 Other Efficacy Analysis

Measures of trough values on Day 8 will use a similar model as the primary analysis with baseline of the respective measures used as a covariate instead of baseline FEV_1. Measures of peak and AUC_{0-2} values will use a similar model to the one specified for the secondary endpoints. Analyses of Diary-based measures will use weekly averages of non-missing values and a similar model as the primary analysis. Baseline for Diary-based measures will be calculated as the average of the non-missing values from the 7 days immediately prior to Visit 2.

9.4.4 Safety Analysis

9.4.4.1 AEs

Adverse events during each treatment regime will be summarized by the number of subjects experiencing an event. They will be tabulated at the level of the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and the MedDRA system organ class. The version of MedDRA current at the time of database lock will be used for final analysis of the data. Tabulations will be broken down by seriousness, severity, and by relationship to study

drug. No hypothesis tests will be performed. Tables will show the overall incidence of AEs, and the incidence for each treatment.

9.4.4.2 Paradoxical Bronchospasm

Paradoxical bronchospasm will be considered an AE of special interest and will be tabulated separately. Bronchospasm will be summarized by the number of subjects experiencing the event during a particular Treatment Period. We note that tabulations for bronchospasms differ from those for general AEs, since the tabulation involves tabulating the incidence of paradoxical bronchospasm with onset during a Treatment Period. Bronchospasm with onset outside a Treatment Period will be listed separately. No hypothesis tests will be performed, but an appropriate confidence interval (CI) may be provided.

9.4.4.3 Dry Mouth

Dry mouth will be considered an AE of special interest and will be tabulated separately. The incidence of dry mouth will be summarized by the number of subjects experiencing the event during a particular Treatment Period. We note that tabulations for dry mouth differ from those for general AEs, since the tabulation involves tabulating the incidence of dry mouth with onset during a Treatment Period. Dry mouth with onset outside a Treatment Period will be listed separately. No hypothesis tests will be performed, but an appropriate CI may be provided.

9.4.4.4 Clinical Laboratory Measurements

Summary statistics (mean, median, standard deviation [SD], and range) for raw and change from baseline values will be tabulated for each treatment and each assessment time. For clinical laboratory measurements, baseline values will be defined by the last available value prior to Randomization. Potentially clinically significant values will be identified and summarized.

9.4.4.5 Vital Signs

Summary statistics (mean, median, SD, and range) for raw values and change from baseline values will be tabulated for each treatment and assessment time. For vital signs, baseline values will be defined by the last available value prior to Randomization. Potentially clinically significant values will be identified and summarized.

9.4.4.6 ECGs

Summary statistics (mean, median, SD, and range) for raw values and change from baseline values will be tabulated for each treatment and assessment time. For ECG parameters, baseline values will be defined by the last available value prior to Randomization. Potentially clinically significant values will be identified and summarized.

9.5 Randomization

Subjects will be randomly assigned to one of the following four treatment sequences in a 1:1:1:1 ratio using an IWRS where each letter represents one of the four treatments included in the study by random assignment. There will be no stratification factors.

ABCD
BDAC
CADB
DCBA

If all subjects complete, then each sequence will be used 15 times, and the design will be balanced for period and first-order carry-over effects. Subjects will not be replaced unless they did not receive any treatment after randomization.

9.6 Sample Size Consideration

Power calculations were based on the properties of the primary endpoint, the change from baseline in morning pre-dose trough FEV_1 on Day 8. Estimates of within-subject SD were obtained from previous studies. A within-subject SD of 130 mL is assumed. Under the further assumption of 15% dropout and 60 randomized subjects, the study is approximately 80% powered to demonstrate a difference between any two treatments of 75 mL using a two-sided alpha level of 0.05.

9.7 Data Validation and Transformation

In general, the distribution of spirometry measures is well approximated by a normal distribution. Under some circumstances, however, (e.g., during a COPD exacerbation, unrelated to treatment) extreme and atypical values can arise. Such values have high influence on estimation of variance parameters and on standard errors of fixed effect estimates. The distribution of residuals and influence statistics will be examined to identify such cases. In the event that a single, or small number of such outlying values, are found to exist and to be highly influential, the effects may be ameliorated either by transformation or removal of the outlier. Transformations to be considered may include the logarithmic transformation or normal rank transformations. Where outliers are removed, sensitivity analyses including those values will be reported.

Changes in spirometry measures from baseline and from timepoint to timepoint will be examined graphically before database lock and before unblinding, as part of data quality management. This will include production of normal probability plots, kernel density estimates, and normal order outlier statistics.

9.8 Analysis Plan

All analyses will be specified in a detailed Statistical Analysis Plan (SAP) that will include table and data listing shells with mock graphical representations. The SAP will be approved by signature before database lock.

9.9 Handling of Missing Data

Pre-dose spirometry values will use the average of the non-missing -60 minute and -30 minute values.

For the mITT analyses, FEV_1 AUC_{0-2} and peak FEV_1 will be calculated if there are at least two non-missing data points during the first 2 hours post-dose. The FEV_1 AUC_{0-2} and peak FEV_1 will be included in the ITT analyses as long as there is one non-missing post-dose value.

Weekly averages for Diary-based parameters will use all non-missing values.

9.10 Interim Analysis

No interim analysis is planned for this study.

9.11 Statistical Software

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

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Notification

The sponsor's representative will notify the PMDA to conduct the study in accordance with applicable regulatory requirements prior to a site initiating the study.

10.2 Ethical Conduct of the Study and IRB 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 [ICH 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].
- Standards stipulated in Article 14, Paragraph 3, and Article 80-2 of the Japan Pharmaceutical Affairs Law
- Japan Ministerial Ordinance on Standards for the Implementation of Clinical Studies on Pharmaceutical Product (GCP)
- Any additional regulatory requirements.

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

The Sponsor will provide the head of the study sites with relevant document(s)/data that are needed for IRB review and approval of the study. If the protocol, the ICF, or any other information that the IRB has approved for presentation to potential subjects is amended during the study, the head of the study sites is responsible for ensuring the IRB 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 approval of the amended form before new subjects consent to take part in the study using this version of the form. The IRB approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the Sponsor promptly.

10.3 Subject Information and Consent

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

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

10.4 Confidentiality

10.4.1 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, 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.

10.4.2 Confidentiality of Subject/Patient Records

By signing this protocol, the Investigator agrees that Pearl (or representative), IRB, or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/CRF 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/CRF 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 data used and disclosed in connection with this study in accordance with all applicable privacy laws (i.e., Health Insurance Portability and Accountability Act), rules, and regulations.

10.5 Quality Control and Assurance

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

10.6 Data Management

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

10.7 Study Monitoring

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

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

The Investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

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

- Return of all study data to Pearl.
- 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 10.8. The Investigator will also permit inspection of the study files by the Sponsor's quality assurance auditors and authorized representatives of the FDA or other applicable regulatory agencies.

10.8 Retention of Data

Documents that individually and collectively permit evaluation of the conduct of the study and the quality of the data produced must be maintained for review by the Sponsor's quality assurance auditors and by all applicable regulatory authorities. The following period of time these documents must be maintained is governed by applicable regulations:

Study Center

(1) Materials to be retained

The head of study center shall retain records, including documents and data, which related to study in accordance with GCP.

(2) Retention Period

The head of study center shall retain records for the required period in accordance with GCP. However, if the sponsor requests to that these materials are retained for a longer period of time, the head of the study center shall discuss the retention period and method with the sponsor.

Investigator

The investigator shall retain records, including documents and data, which relate to the study in accordance with instruction from the head of the study center.

Institutional Review Board

(1) Materials to be retained

The person who establishes the IRB shall retain the records pertaining to the IRB, including documents and data, in accordance with GCP.

(2) Retention Period

The person who establishes the IRB shall retain records for required period in accordance with GCP. However, if the sponsor requests that these records be retained longer than described, the person who established the IRB will discuss the retention period and method with the sponsor.

Sponsor

(1) Materials to be retained

The sponsor shall retain records, including documents and data, which related to the study in accordance with GCP.

(2) Retention Period

The sponsor shall retain records for required period in accordance with GCP.

10.9 Financial Disclosure

The principal Investigator or sub-Investigators 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.

10.10 Investigator's Final Report

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

10.11 Liability and Insurance

Liability and insurance provisions for this study are provided in the contract.

10.12 Publication Policy

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

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

1. **Responsibility:** Each principal Investigator is responsible for the accuracy and completeness of all data from their site. Pearl Therapeutics (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.
2. **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted at least 30 days prior to submission for publication or presentation to Pearl Therapeutics for review, approval, and to ensure consistency with the policy in this protocol. Pearl Therapeutics will have the right to request appropriate modification to correct facts and to represent its opinions, or the opinions of the publication committee, if these differ with the proposed publication.

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

11 REFERENCE LIST

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Appendix 1 Spirometry Performance Recommendations

Spirometry data of the highest quality must be obtained for proper interpretation of the results of this protocol. To these ends, a standard spirometer will be used (provided by Pearl), central training provided, qualification will be required, and specific operating instruction will also be provided (according to standardization published by Miller, 2005).

FEV_1 AND FVC MANEUVERS

Equipment Requirements

The spirometer must be capable of accumulating volume for ≥15 seconds (longer times are recommended) and measuring volumes of ≥8 L (body temperature; i.e., 37°C), ambient pressure, saturated with water vapor, body temperature and pressure saturated (BTPS) with an accuracy of at least ±3% of reading or ±0.050 L, whichever is greater, with flows between 0 and 14 $L\text{-}s^{-1}$. The total resistance to airflow at 14.0 $L\text{-}s^{-1}$ must be <1.5 $cmH_2O\ L^{-1}s^{-1}$ (0.15 kPa $L^{-1}s^{-1}$). The total resistance must be measured with any tubing, valves, pre-filter, etc., included that may be inserted between the subject and the spirometer. Some devices may exhibit changes in resistance due to water vapor condensation, and accuracy requirements must be met under BTPS conditions for up to eight successive FVC maneuvers performed in a 10-minute period without inspiration from the instrument.

Display

For optimal quality control, both flow–volume and volume–time displays are useful, and test operators should visually inspect the performance of each maneuver for quality assurance before proceeding with another maneuver. This inspection requires tracings to meet the minimum size and resolution requirements set forth in this standard. Displays of flow versus volume provide more detail for the initial portion (first 1 second) of the FVC maneuver. Since this portion of the maneuver, particularly the PEFR, is correlated with the pleural pressure during the maneuver, the flow–volume display is useful to assess the magnitude of effort during the initial portions of the maneuver. The ability to overlay a series of flow-volume curves registered at the point of maximal inhalation may be helpful in evaluating repeatability and detecting sub-maximal efforts. However, if the point of maximal inhalation varies between blows, then the interpretation of these results is difficult because the flows at identical measured volumes are being achieved at different absolute lung volumes. In contrast, display of the FVC maneuver as a volume–time graph provides more detail for the latter part of the maneuver. A volume–time tracing of sufficient size also allows independent measurement and calculation of parameters from the FVC maneuvers. In a display of multiple studies, the sequencing of the blows should be apparent to the user. For the start of test display, the volume–time display should include ≥0.25 seconds, and preferably 1 second, before exhalation starts (zero volume). This time period before there is any change in volume is needed to calculate the back extrapolated volume (EV) and to evaluate effort during the initial portion of the maneuver. Time zero, as defined by EV, must be presented as the zero point on the graphical output. The last 2 seconds of the maneuver should be displayed to indicate a satisfactory end of test.

When a volume–time curve is plotted as hardcopy, the volume scale must be ≥10 mm L^{-1} (BTPS). For a screen display, 5 mm L^{-1} is satisfactory (Table A-1).

Table A-1. Recommended Minimal Scale Factors for Time, Volume, and Flow on Graphical Output

Parameter	Instrument Display		Hardcopy Graphical Output
	Resolution Required	Scale Factor	Resolution Required
Volume [a]	0.050 L	5 mm-L^{-1}	0.050 L
Flow [a]	0.200 L-s^{-1}	2.5 mm L^{-1} s^{-1}	0.200 L-s^{-1}
Time	0.2 s	10 mm-s^{-1}	0.2 s

[a] The correct aspect ratio for flow versus volume display is two units of flow per one unit of volume.

The time scale should be ≥20 mm-s^{-1}, and larger time scales are preferred (≥30 mm-s^{-1}) when manual measurements are made. When the volume–time plot is used in conjunction with a flow–volume curve (i.e., both display methods are provided for interpretations and no hand measurements are performed), the time scale requirement is reduced to 10 mm-s^{-1} from the usually required minimum of 20 mm-s^{-1} (Table A-1). The rationale for this exception is that the flow–volume curve can provide the means for quality assessment during the initial portion of the FVC maneuver. The volume–time curve can be used to evaluate the latter part of the FVC maneuver, making the time scale less critical.

Validation

It is strongly recommended that spirometry systems should be evaluated using a computer-driven mechanical syringe or its equivalent, in order to test the range of exhalations that are likely to be encountered in the test population. Testing the performance of equipment is not part of the usual laboratory procedures.

Quality Control

Attention to equipment quality control and calibration is an important part of GLP. At a minimum, the requirements are as follows: 1) a log of calibration results is maintained; 2) the documentation of repairs or other alterations which return the equipment to acceptable operation; 3) the dates of computer software and hardware updates or changes; and 4) if equipment is changed or relocated (e.g., industrial surveys), calibration checks and quality-control procedures must be repeated before further testing begins.

Key aspects of equipment quality control are summarized in Table A-2.

Table A-2. Summary of Equipment Quality Control

Test	Minimal Interval	Action
Volume	Daily	Calibration check with a 3-L syringe
Leak	Daily	3 cmH_2O (0.3 kPa) constant pressure for 1 minute
Volume Linearity	Quarterly	1-L increments with a calibrating syringe measured over the entire volume range
Flow Linearity	Weekly	Test at least three different flow ranges
Time	Quarterly	Mechanical recorder check with stop watch
Software	New versions	Log installation date and perform test using known subject

Calibration is the procedure for establishing the relationship between sensor-determined values of flow or volume and the actual flow or volume. A calibration check is different from calibration and is the procedure used to validate that the device is within calibration limits, e.g., ±3% of true. If a device fails its calibration check, then a new calibration procedure or equipment maintenance is required. Calibration checks must be undertaken daily, or more frequently, if specified by the manufacturer. The syringe used to check the volume calibration of spirometers must have an accuracy of ±15 mL or ±0.5% of the full scale (15 mL for a 3-L syringe), and the manufacturer must provide recommendations concerning appropriate intervals between syringe calibration checks. Users should be aware that a syringe with an adjustable or variable stop may be out of calibration if the stop is reset or accidentally moved. Calibration syringes should be periodically (e.g., monthly) leak tested at more than one volume up to their maximum; this can be done by attempting to empty them with the outlet corked. A dropped or damaged syringe should be considered out of calibration until it is checked.

With regard to time, assessing mechanical recorder time scale accuracy with a stopwatch must be performed at least quarterly. An accuracy of within 2% must be achieved.

Quality Control for Volume-Measuring Devices

The volume accuracy of the spirometer must be checked at least daily, with a single discharge of a 3-L calibrated syringe. Daily calibration checking is highly recommended so that the onset of a problem can be determined within 1 day, and also to help define day-to-day laboratory variability. More frequent checks may be required in special circumstances, such as: 1) during industrial surveys or other studies in which a large number of subject maneuvers are carried out, the equipment's calibration should be checked more frequently than daily; and 2) when the ambient temperature is changing (e.g., field studies),

volume accuracy must be checked more frequently than daily and the BTPS correction factor appropriately updated.

The accuracy of the syringe volume must be considered in determining whether the measured volume is within acceptable limits. For example, if the syringe has an accuracy of 0.5%, a reading of ±3.5% is appropriate.

The calibration syringe should be stored and used in such a way as to maintain the same temperature and humidity of the testing site. This is best accomplished by keeping the syringe in close proximity to the spirometer, but out of direct sunlight and away from heat sources.

Volume-type spirometer systems must be evaluated for leaks every day. The importance of undertaking this daily test cannot be overstressed. Leaks can be detected by applying a constant positive pressure of ≥3.0 cmH_2O (0.3 kPa) with the spirometer outlet occluded (preferably at or including the mouthpiece). Any observed volume loss of 0.30 mL after 1 minute indicates a leak and needs to be corrected.

At least quarterly, volume spirometers must have their calibration checked over their entire volume range using a calibrated syringe or an equivalent volume standard. The measured volume should be within ±3.5% of the reading or 65 mL, whichever is greater. This limit includes the 0.5% accuracy limit for a 3-L syringe. The linearity check procedure provided by the manufacturer can be used if it is equivalent to one of the following procedures: 1) consecutive injections of 1-L volume increments while comparing observed volume with the corresponding cumulative measured volume, e.g., 0 to 1, 1 to 2, 2 to 3,…6 to 7 and 7 to 8 L, for an 8-L spirometer; and 2) injection of a 3-L volume starting at a minimal spirometer volume, then repeating this with a 1-L increment in the start position, e.g., 0 to 3, 1 to 4, 2 to 5, 3 to 6, 4 to 7 and 5 to 8 L, for an 8-L spirometer. The linearity check is considered acceptable if the spirometer meets the volume accuracy requirements for all volumes tested.

Quality Control for Flow-Measuring Devices

With regards to volume accuracy, calibration checks must be undertaken at least daily, using a 3-L syringe discharged at least three times to give a range of flows varying between 0.5 and 12 $L\text{-}s^{-1}$ (with 3-L injection times of 6 seconds and 0.5 seconds). The volume at each flow should meet the accuracy requirement of ±3.5%. For devices using disposable flow sensors, a new sensor from the supply used for subject tests should be tested each day.

For linearity, a volume calibration check should be performed weekly with a 3-L syringe to deliver three relatively constant flows at a low flow, then three at a mid-range flow and finally three at a high flow. The volumes achieved at each of these flows should each meet the accuracy requirement of ±3.5%.

VITAL CAPACITY MANEUVERS

Equipment

For measurements of vital capacity (VC), the spirometer or flow meter must comply with the requirements for FVC (as described previously) and be capable of accumulating volume for ≥30 s. Expiratory maneuvers should be included in the display of VC maneuver. Regardless of whether the expiratory maneuver is used for deriving measurements, a display of the entire recorded VC maneuver must be provided. The maximal expiratory volume must be assessed to determine whether the subject has obtained a plateau in the expiratory effort. For display of the slow VC, the time scale may be reduced to 5 mm-s^{-1}.

TECHNICAL CONSIDERATIONS

Minimal Recommendations for Spirometry Systems

Accurate results require accurate equipment. Spirometer equipment recommendations apply to all spirometers and are minimal requirements. In some circumstances, it may be appropriate to exceed these requirements (i.e., in some research/surveillance applications). Instrumentation recommendations should be followed to provide accurate spirometric data and information that is comparable from laboratory to laboratory and from one time period to another. The accuracy of a spirometry system depends on characteristics of the entire system, from the volume or flow transducer and the use of an in-line filter, to the recorder, display or processor. Changes in any aspect of the equipment or errors at any step in the process can affect the accuracy of the results. For example, if the BTPS correction factor is wrong, an accurately measured FVC will be incorrectly reported. Spirometers are not required to measure all of the indices in Table A-3, but must meet the recommendations for those that are measured. Accuracy and repeatability recommendations (Table A-3) apply over the entire volume range of the instrument.

Table A-3. Range and Accuracy Recommendations Specified for Forced Expiratory Maneuvers

Test	Range/Accuracy (BTPS)	Flow Range ($L\text{-}s^{-1}$)	Time (s)	Resistance and Back Pressure	Test Signal
VC	0.5-8 L, ±3% of reading or ±0.050 L, whichever is greater	0-14	30		3-L calibration syringe
FVC	0.5-8 L, ±3% of reading or ±0.050 L, whichever is greater	0-14	15	<1.5 $cmH_2O\ L^{-1}\ s^{-1}$ (0.15 $kPa\ L^{-1}s^{-1}$)	24 ATS waveforms, 3-L calibration Syringe
FEV_1	0.5-8 L, ±3% of reading or ±0.050 L, whichever is greater	0-14	1	<1.5 $cmH_2O\ L^{-1}\ s^{-1}$ (0.15 $kPa\ L^{-1}s^{-1}$)	24 ATS waveforms
Time Zero	The timepoint from which all FEV_t measurements are taken.			Back extrapolation	

Abbreviations: ATS=American Thoracic Society; BTPS=Body Temperature and Pressure Saturated; FEV_1=forced expiratory volume in 1 second; FEV_t: forced expiratory volume in t seconds; FVC=forced vital capacity; VC=vital capacity

BTPS Correction

All spirometry values should be reported at BTPS by any method (measuring temperature and barometric pressure) proven effective by the manufacturer. For volume-type spirometers, the temperature inside the spirometer should be measured for each breathing maneuver. Regardless of the BTPS correction technique used, the ambient temperature must always be recorded with an accuracy of ±1°C. In situations where the ambient air temperature is changing rapidly (>3°C in <30 minutes), continuous temperature corrections may be necessary. Spirometer users should be aware of potential problems with testing performed at lower ambient temperatures: 17°C is the lower limit for ambient temperature, unless a manufacturer states that their spirometer will operate accurately at lower ambient temperatures. If barometric pressure is not used in calculating the BTPS correction factor, the range of barometric pressures over which the BTPS correction factor is valid must be published.

Appendix 2 Spirometry Assessment Criteria

Acceptable Versus Usable Tests

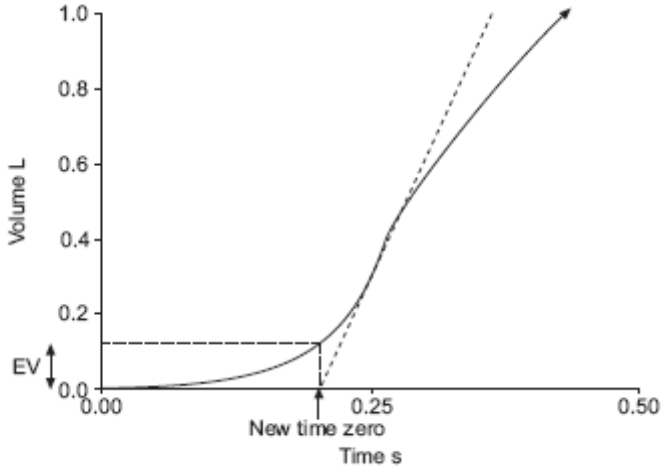
***Acceptable* tests must meet the following seven criteria:**

1. Acceptable start of exhalation with brisk upstroke, no hesitation or false start, and EV <5% of FVC or 0.150 L, whichever is the greater. (See example in Figure A-1 below.)
2. No cough during the first second.
3. No Valsalva maneuver.
4. No leak.
5. No obstruction of mouthpiece.
6. No extra breaths.
7. Plateau achieved, i.e., the volume-time curve shows no change in volume (<0.025 L) for ≥1 s, and the subject has tried to exhale for at least 6 seconds.

An acceptable test meets all seven criteria listed. This is to be considered the gold standard.

Usable spirometry tracings are those that only meet criteria 1 and 2. When this occurs, repeat testing up to eight attempts in an effort to obtain three acceptable spirograms. If only usable tests are obtained, report results based on the three best usable trials with observed limitations.

Figure A-1. Example of a Usable Spirogram



Abbreviations: EV=back extrapolation volume

The expanded version of the early part of a subject's volume-time spirogram, illustrating back extrapolation through the steepest part of the curve, where flow is PEF, to determine the new time zero. Forced vital capacity-4.291 L; EV – 0.123 L (2.9% FVC): back extrapolation line through PEF.

Between-Maneuver Reproducibility Criteria

After three acceptable spirograms have been obtained, apply the following tests

- The two largest values of FVC must be within 0.150 L of each other
- The two largest values of FEV_1 must be within 0.150 L of each other

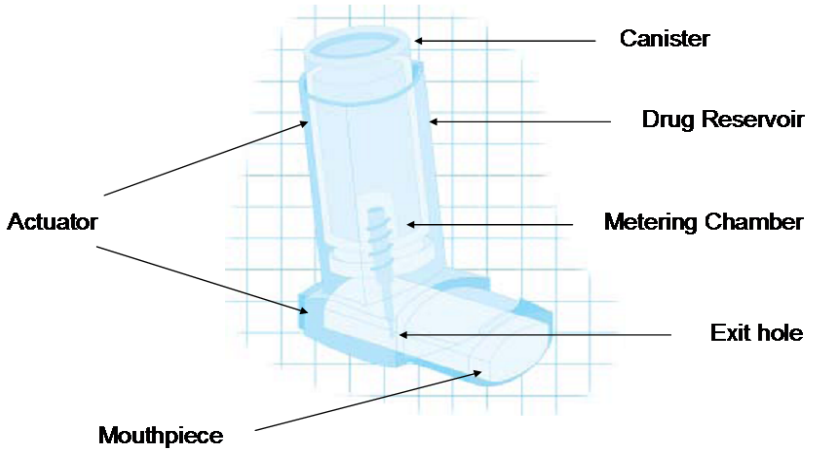
If these criteria are met, the spirometry testing for that timepoint may conclude. The highest FEV_1 and the highest FVC obtained at each testing timepoint (even if from different reproducible tracings), will be collected.

If acceptability criteria are not met, continue testing until they are met or the subject cannot/should not continue (maximum of eight attempts).

Appendix 3 Subject Instructions for Use of GP MDI and Placebo Devices

1. The inhaler should be stored at room temperature.
2. Take the cap off the mouthpiece of the actuator.
3. Inspect the front of the inhaler and make sure there is nothing inside the mouthpiece of the inhaler. Make sure the canister is fully and firmly inserted into the actuator.
4. All MDIs must be primed before the first use. Priming involves releasing a certain number of sprays (four) into the air before the first use of the inhaler. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that it's ready to use. To prime the inhaler, gently shake the inhaler for 5 to 10 seconds and then spray once into the air away from yourself and others. Wait approximately 30 seconds and repeat the process three more times.
5. Gently shake the inhaler for 5 to 10 seconds before each spray.
6. Breathe out fully through your mouth, expelling as much air from your lungs as possible. Tilt your head back slightly, place the mouthpiece into your mouth, holding the inhaler with the mouthpiece down, and closing your lips around it. To allow the medication to enter your lungs, keep your tongue flat on the floor of your mouth.
7. While breathing in deeply and slowly through your mouth, fully depress the top of the metal canister with your index finger. Immediately after the spray is delivered, release your finger from the canister. When you have breathed in fully, remove the inhaler from your mouth and close your mouth.
8. Hold your breath as long as possible, up to 10 seconds, and then breathe normally.
9. If you are taking more than one puff, repeat steps 5 to 7, with gentle shaking for 5 to 10 seconds prior to each spray.
10. Put the cap back on the mouthpiece after every time the inhaler is used.

METERED DOSE INHALER SCHEMA



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APPENDIX 4. SPONSOR SIGNATORY

Study Title: A Randomized, Double-Blind, Chronic Dosing (7-Day), Four-Period, Four-Treatment, Placebo-Controlled, Cross-Over, Multi-Center Study to Assess the Efficacy and Safety of Three Doses of PT001 in Japanese Subjects With Moderate to Severe COPD

Study Number: PT001004-01

Version 1.0 Final Date: [redacted]

Version 2.0 Final Date: [redacted]

Signature: [redacted] Date: [redacted]

Name: [redacted]

Title: [redacted]

Pearl Therapeutics, Inc.

Appendix 5 Investigator's Agreement and Signature Page

Study Title: A Randomized, Double-Blind, Chronic Dosing (7-Day), Four-Period, Four-Treatment, Placebo-Controlled, Cross-Over, Multi-Center Study to Assess the Efficacy and Safety of Three Doses of PT001 in Japanese Subjects With Moderate to Severe COPD

Study Number: PT001004-01

Version 1.0 Final Date: [redacted]

Version 2.0 Final Date: [redacted]

I agree:

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

Signature:_____ Date:_____

Name: _____

Affiliation: _____

_____