Clinical Trial Protocol: PT0031002

Study Title:	A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (7 Days), Four-Period, Eight-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Two Doses of PT003, Two Doses of PT005 and One Dose of PT001 in Patients With Moderate to Very Severe COPD, Compared With Foradil® Aerolizer® (12 µg, Open-Label) and Spiriva® Handihaler® (18 µg, Open-Label) as Active Controls
Study Number:	PT0031002
Study Phase:	IIb
Product Name:	Glycopyrrolate/Formoterol Fumarate Inhalation Aerosol; PT003 Formoterol Fumarate Inhalation Aerosol; PT005 Glycopyrrolate Inhalation Aerosol; PT001
IND Number:	107739
Indication:	COPD
Investigators:	Multicenter
Sponsor:	[redacted]
Sponsor Contact:	[redacted]

	Version Number	Date
Original Protocol:	Version 1.0	[redacted]
Amemndment 1	Version 2.0	[redacted]
Amemndment 2	Version 3.0	[redacted]
Amemndment 3	Version 4.0	[redacted]

SUMMARY OF CHANGES TO PROTOCOL AMENDMENT 2 VERSION 3.0, [redacted]

The protocol is amended to expand recruitment of this study to include the United States.

This change is reflected in the Synopsis: Study Design (paragraph 2, pg 7) and Section 4.1 (paragraph 2, pg 34) as follows: "This multi-center study will be conducted at approximately **12-16** sites, contributing approximately **5** to 12 patients per site, in Australia, New Zealand and the **United States**."

The US IND number **107739** has been added to pg 1 to indicate the IND under which this study will be conducted in the United States.

SPONSOR SIGNATURE PAGE

Study Title: A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (7 Days), Four-Period, Eight-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Two Doses of PT003, Two Doses of PT005 and One Dose of PT001 in Patients With Moderate to Very Severe COPD, Compared With Foradil® Aerolizer® (12 µg, Open-Label) and Spiriva® Handihaler® (18 µg, Open-Label) as Active Controls

Study Number: PT0031002

Final Date: Version 4.0, [redacted]

Amendment 2 Date: [redacted]

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed [redacted] Date: [redacted]

Signed [redacted] Date: [redacted]

Signed [redacted] Date: [redacted]

Signed [redacted] Date: [redacted]

SYNOPSIS

Sponsor:
Pearl Therapeutics

Names of Finished Products:
Glycopyrrolate/Formoterol Fumarate Inhalation Aerosol; PT003
Formoterol Fumarate Inhalation Aerosol; PT005
Glycopyrrolate Inhalation Aerosol; PT001

Name of Active Ingredients:
Glycopyrrolate/Formoterol Fumarate
Formoterol Fumarate
Glycopyrrolate

Study Title:
A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (7 Days), Four-Period, Eight-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Two Doses of PT003, Two Doses of PT005 and One Dose of PT001 in Patients With Moderate to Very Severe COPD, Compared With Foradil® Aerolizer® (12 µg, Open-Label) and Spiriva® Handihaler® (18 µg, Open-Label) as Active Controls

Study Number: PT0031002

Study Phase: IIb

Study Objective(s):

For combination drug development, a study is required to demonstrate superiority of the combination (Glycopyrrolate/Formoterol Fumarate MDI) to its components (Glycopyrrolate and Formoterol Fumarate MDI), and to assess the relative contribution of the components compared with placebo. This study will be conducted in two parts, Part A and Part B. Each part has separately defined primary and secondary objectives.

Part A is a comparison of the improvement in lung function (FEV_1 AUC_{0-12}) following administration of the combination versus the single agents.

Part B is a comparison of the improvement in lung function (FEV_1 AUC_{0-12}) following administration of Formoterol Fumarate MDI to Placebo.

Separate statistical analysis plans will be written for Part A and Part B of this study. Within each part of this study, secondary assessments will be conducted to refine the appropriate doses to carry forward in future studies.

Objective(s) for Part A (Combination versus components):

Primary objective for Part A:
The primary objective for Part A is to assess the improvement in FEV_1 AUC_{0-12} of Glycopyrrolate/Formoterol Fumarate MDI (72/9.6 µg ex-actuator) administered in a fixed combination compared with administration of its components Formoterol Fumarate MDI (9.6 µg ex-actuator) and Glycopyrrolate MDI (36 µg ex-actuator) as single agents. Superiority to both components must be demonstrated in order to satisfy the primary objective of this study.

Secondary Objectives for Part A:
The secondary objective for Part A of the study is to provide additional information to characterize dose-response and to help identify candidate doses for further development. The primary and secondary endpoints identified in Section 3.1 will be assessed across the following comparisons (excluding comparisons already described for the primary objective above):

Glycopyrrolate/Formoterol Fumarate MDI (72/9.6 µg ex-actuator) versus:

- Formoterol Fumarate MDI (9.6 µg ex-actuator)
- Formoterol Fumarate MDI (7.2 µg ex-actuator)
- Glycopyrrolate MDI (36 µg ex-actuator)
- Spiriva® (18 µg per capsule)
- Foradil® Aerolizer® (12 µg per capsule)

Glycopyrrolate/Formoterol Fumarate MDI (36/9.6 µg ex-actuator) versus:

- Same comparators as for Glycopyrrolate/Formoterol Fumarate MDI (72/9.6 µg ex-actuator) above

Glycopyrrolate/Formoterol Fumarate MDI (72/9.6 µg ex-actuator) versus Glycopyrrolate/Formoterol Fumarate MDI (36/9.6 µg ex-actuator)

Glycopyrrolate MDI (36 µg ex-actuator) vs. Spiriva® (18 µg per capsule)

Safety Objective for Part A:
The safety objective of Part A is to evaluate the safety of Glycopyrrolate/Formoterol Fumarate MDI delivered as a fixed combination (36/9.6 µg or 72/9.6 µg ex-actuator) in patients with moderate to very severe COPD, compared with placebo MDI, Formoterol Fumarate MDI (7.2 and 9.6 µg ex-actuator), Glycopyrrolate MDI (36 µg ex-actuator), Foradil® Aerolizer® (formoterol fumarate, 12 µg) and Spiriva® Handihaler® (tiotropium bromide, 18 µg).

Objective(s) for Part B (Formoterol Fumarate MDI versus placebo and active control):

Primary Objective for Part B:
The primary objective for Part B is to compare the improvement in FEV_1 AUC_{0-12} of Formoterol Fumarate MDI (9.6 µg ex-actuator) to placebo MDI.

Secondary Objectives for Part B:
The secondary objective of the study is to provide additional information to characterize dose-response and to help identify the optimum doses for further development. The primary and secondary endpoints identified in Section 3.1 will be assessed across the following comparisons (excluding comparisons already described for the primary objective above):

Formoterol Fumarate MDI (9.6 µg ex-actuator) versus:

- Placebo
- Foradil® Aerolizer® (formoterol fumarate, 12 µg) (Non-Inferiority)

Formoterol Fumarate MDI (7.2 µg ex-actuator) versus:

- Placebo
- Foradil® Aerolizer® (formoterol fumarate, 12 µg) (Non-Inferiority)

Formoterol Fumarate MDI (9.6 µg ex-actuator) versus Formoterol Fumarate MDI (7.2 µg ex-actuator).

Safety Objective for Part B:
The safety objective of Part B is to evaluate the safety of Formoterol Fumarate MDI (7.2 and 9.6 µg ex-actuator) as single agents in patients with moderate to very severe COPD compared with placebo MDI and Foradil® Aerolizer® (12 µg).

Pharmacokinetic Objective(s):
A combination study is required to demonstrate superiority of the combination to its components, and to assess the relative contribution of the components compared with placebo. From a PK perspective, it is important to assess whether a pharmaceutical effect is demonstrated when the components are administered in a fixed combination compared with administration of the components as single agents.

To this end, the PK objective for Part A is to assess the PK profile of both Glycopyrrolate and Formoterol Fumarate when administered from the combination compared with administration of the components as single agents.

Part B will be used to assess the PK profile of two doses of Formoterol Fumarate and will compare the findings to the PK profile of Formoterol Fumarate administered as Foradil® Aerolizer®.

The PK assessments obtained in part A will contribute to the analysis of Part B and vice versa where appropriate.

Study Design:
This is a randomized, double-blind (test products and placebo), chronic dosing (7 days), four-period, eight-treatment, placebo-controlled, incomplete block, cross-over, multi-center study to assess efficacy and safety of two doses of Glycopyrrolate/Formoterol Fumarate MDI (36/9.6 µg and 72/9.6 µg ex-actuator), two doses of Formoterol Fumarate MDI (7.2 and 9.6 µg ex-actuator) and one dose of Glycopyrrolate MDI (36 µg ex-actuator) in patients with moderate to very severe COPD, compared with Foradil® Aerolizer® (formoterol fumarate inhalation powder 12 µg, open-label) and Spiriva® Handihaler® (tiotropium bromide inhalation powder 18 µg, open-label) as active controls.

This multi-center study will be conducted at approximately 12-16 sites, contributing approximately 5 to 12 patients per site, in Australia, New Zealand and the United States. Across these sites, it is planned that approximately 84 patients (approximately 48 and 36 patients in Parts A and B, respectively) with moderate to very severe COPD will be randomized into the study to provide the target of between 32 and 52 (inclusive) evaluations per study treatment.

This study will be recruited in two parts, Part A and Part B. Subjects recruited to Part A will not be eligible for Part B. All patients will undergo the same study procedures regardless of the study part for which they are recruited. The entire study period is scheduled to take approximately 10-14 weeks for each individual patient; however, no patient should be in the study for longer than 20 weeks. The study is anticipated to run for approximately 9 months and should not exceed 18 months.

To provide additional assurance of safety, 4 sentinel patients will be evaluated prior to initiating enrollment of this study. These subjects will be randomized to treatment using a separate randomization scheme.

All patients will sign an informed consent form prior to the conduct of any screening assessments (Visit 1a). The Investigator will obtain a medical history, physical examination, and any required documentation in order to determine eligibility for participation (inclusion/exclusion criteria). Reversibility of FEV_1 30 minutes following 4 puffs of albuterol (salbutamol) MDI will be assessed at Screening to characterize the patient population but will not be used to determine eligibility to participate in the study. Patients who are not using a prohibited medication and meet all other entry criteria will return to the clinic at least 1 week (≥2 weeks if taking tiotropium) after screening for Visit 2 (Randomization).

Patients who meet all entry criteria, but are using certain prohibited COPD medications will discontinue these medications for the duration of the trial and be switched to short-acting bronchodilators at the Investigator's discretion (see Section 5.4).

For some COPD maintenance medications, a washout period of at least 1 week (≥2 weeks if taking tiotropium), but not greater than 4 weeks will be required prior to returning to the clinic for Visit 2 (Randomization).

Patients who do not meet the entry criteria at Visit 1a can return for re-evaluation at a second Screening visit (Visit 1b) at the Investigator's discretion.

At Visit 2 (Randomization Visit; Rx 1, Day 1), patients will return to the clinic before

10:00 a.m. Patients who continue to meet entry inclusion/exclusion criteria and remain eligible for participation in the study will be randomized into one of the treatment sequences. Each sequence in Part A will include exactly 4 of the 8 treatment groups included in this study [placebo, active controls (Spiriva® Handihaler® 18 µg or Foradil® Aerolizer® 12 µg), or study drug at one of the following doses: Glycopyrrolate/Formoterol Fumarate 36/9.6 and 72/9.6 µg, Formoterol Fumarate 7.2 and 9.6 µg, or Glycopyrrolate 36 µg]. Each sequence in Part B will include exactly 4 of the 8 treatment groups included in this study [placebo, active control (Foradil® Aerolizer® 12 µg), or study drug at one of the following doses: Formoterol Fumarate 7.2 and 9.6 µg]. Note: No patient will receive more than 2 weeks of treatment with either Formoterol Fumarate MDI or Glycopyrrolate MDI regardless of whether administered alone or in combination.

The 48 treatment sequences to which patients will be randomized during Part A are generated as a set of Williams square designs based on each of the treatment selections shown in Table 7. In Part B, there are 24 possible treatment sequences, and each treatment sequence will be assigned to at least one patient. Twelve of the possible treatment sequences in Part B will be assigned to two patients. The treatment sequences assigned to two patients during Part B will be generated as a set of three Williams square designs.

Randomization will be performed centrally, using an IWRS.

Glycopyrrolate/Formoterol Fumarate, Formoterol Fumarate, Glycopyrrolate, Placebo and Foradil® Aerolizer® will be administered twice daily while Spiriva® (18 µg) will be administered once daily. Each of the 4 treatments will be administered for 1 week with a washout period of at least 1 week (up to 3 weeks) in between treatments. During Visit 2, patients will be dispensed study medication and will administer their first dose at the clinic under supervision. Patients will be required to remain at the clinic until completion of all protocol-defined assessments to the 2-hour post-dose time point (see Table 5). Patients will then be discharged from the clinic and will continue to administer study medication daily for 1 week at home.

Patients will return to the clinic following 1 week of treatment for Visit 3 (Rx 1, Day 7) at approximately the same time as Visit 2 (± 2 hours). Patients will receive their last dose of study medication, for the current treatment period, that morning under supervision and will be required to remain at the clinic until completion of all protocol-defined assessments to the 12-hour post-dose time point (see Table 6). Following discharge, patients will undergo a study medication washout period of at least 1 week but no more than 3 weeks duration prior to initiating the next treatment in their assigned treatment sequence.

Following the washout period, patients will repeat a similar pattern of visits and assessments for the next three treatments in their assigned sequence.

Every effort will be made to ensure that patients return to the clinic on Day 7 (1 week) following initiation of each treatment. To accommodate scheduling conflicts a window of 7 ±2 days is permitted (i.e., Treatment Day 7 procedures must be done within a minimum of 5 days and a maximum of 9 days from Treatment Day 1). If any patient exceeds 9 days of treatment for any treatment except Spiriva® Handihaler® and Foradil® Aerolizer®, the Sponsor should be notified and the patient may be withdrawn from the study.

Starting at the Screening Visit, patients will receive a diary in which they will be asked to maintain a daily record of their study medication dosing, rescue medication use, and daily peak flow rates using a sponsor-provided portable peak flow meter.

Patients will be scheduled to return for the Final Visit (Visit 10, Follow-up Visit) approximately one week after Visit 9 to undergo final study assessments, including a final physical examination and recording of any AEs, and will then be discharged from the study.

Study Population:
Approximately 84 patients with moderate to very severe COPD will be enrolled to provide at least 32 evaluations per study treatment.

Test Product, Dose, and Mode of Administration:
Investigational materials will be provided by the Sponsor as summarized in the table below.

Product Descriptions

Product Name & Potency	Dosage Form	Comments
Glycopyrrolate/Formoterol Fumarate 72/9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 36/4.8 µg per actuation strength MDI
Glycopyrrolate/Formoterol Fumarate 36/9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 18/4.8 µg per actuation strength MDI
Formoterol Fumarate 9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 4.8 µg per actuation strength MDI
Formoterol Fumarate 7.2 µg ex-actuator	MDI	Taken as 2 inhalations of the 3.6 µg per actuation strength MDI
Glycopyrrolate 36 µg ex-actuator	MDI	Taken as 2 inhalations of the 18 µg per actuation strength MDI
Placebo	MDI	Taken as 2 inhalations. Formulation does not contain active ingredient
Tiotropium inhalation powder† 18 µg	Dry Powder Inhaler (DPI)	US source: (Spiriva® delivered via the Handihaler®) *Supplies are open-label.*
Formoterol Fumarate inhalation powder† 12 µg	DPI	US source: (Foradil® Aerolizer®) Each capsule contains 12 µg corresponding to 10 µg formoterol fumarate dihydrate delivered from the mouthpiece *Supplies are open-label.*
Albuterol Sulfate inhalation aerosol§ 90 µg	MDI	US source: (Ventolin® HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece *Supplies are open-label.*

† Active controls

§ Rescue medication

Note:
-All study drugs will be administered by oral inhalation.
-No patient will receive more than 2 weeks of either Formoterol Fumarate MDI or Glycopyrrolate MDI regardless of whether administered alone or in combination.

All placebos are created by Pearl Therapeutic in the image of the active test product.

The 7.2 and 9.6 µg ex-actuator doses of formoterol fumarate are equivalent to 7.5 and 10 µg of formoterol fumarate *dihydrate*, respectively. The corresponding ex-valve doses for formoterol fumarate are 9 and 12 µg, respectively. The 36 and 72 µg ex-actuator doses of Glycopyrrolate are equivalent to 44 and 88 µg ex-valve of Glycopyrrolate, respectively.

Duration of Treatment:
Each patient (except sentinel patients) will receive 1 week of study treatment with each of their assigned treatments, one treatment in each of the 4 separate treatment periods with a washout period of at least 1 week (up to 3 weeks) between treatments. The entire study period is scheduled to take approximately 10-14 weeks for each individual patient; however, no patient should be in the study for longer than 20 weeks (see Figure 1).

Efficacy Assessments:
All efficacy assessments are relative to baseline, and will be compared with individual agents and/or placebo where appropriate. Baseline is defined as the average of pre-dose values obtained prior to dosing with study medication at randomization (Visit 2).

Primary Efficacy Endpoint Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing):

- Forced expiratory volume in 1 second area under the curve (FEV_1 AUC_{0-12}) relative to baseline following chronic dosing (1 week).

Secondary Efficacy Endpoints:
Secondary Endpoints Evaluated on Treatment Day 1 (Visits 2, 4, 6 and 8):

- Peak FEV_1 (defined as peak improvement in FEV_1)
- Time to onset of action (≥10% improvement in mean FEV_1)
- Proportion of patients achieving ≥ 12% improvement in FEV_1.
- Peak improvement in Inspiratory Capacity (IC) (mean of 1 and 2 hour post-dose)

Secondary Endpoints Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing):

- Improvement in morning pre-dose FEV_1
- Peak FEV_1 (defined as peak improvement in FEV_1)
- Peak improvement in IC (mean of 1 and 2 hours post-dose)
- Trough FEV_1 (trough FEV_1 is defined as the mean of the FEV_1 assessments taken at 11.5 and 12 hours post-dose)
- Mean daily peak flow readings taken by patients and recorded in patient diaries, during

each treatment sequence

Exploratory Endpoints Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing):

- Peak expiratory flow rate (PEFR),
- Forced vital capacity (FVC),
- Trough IC (mean of 11.5 and 12 hours post-dose).
- Mean number of puffs of rescue medication recorded in patient diaries, during each treatment sequence

Safety Assessments:
The safety assessments include ECGs, vital signs, clinical laboratory tests, monitoring for paradoxical bronchospasm, assessment of symptoms of tremor and dry mouth in addition to recording AEs and SAEs (including physical examination abnormalities).

Pharmacokinetic Assessments:
Pharmacokinetics will be evaluated in approximately one-half of patients enrolled (i.e., approximately 42 patients), with the following blood sampling scheme at the end of each treatment period: pre-dose, 2, 6, 20 minutes and 1, 2, 4, 8, 10, and 12 hours post-dose.

Statistical Methods:
Sample Size Determination: Sample size was based on the properties of the primary endpoint: FEV_1 AUC_{0-12} on the last day of each dosing period following administration of the study drug. Power was calculated for a generalized least squares analysis, with the covariance structure induced by the incomplete block structure of the experiment. The minimal clinically significant difference was assumed to be 0.1L, and power was calculated assuming two-sided tests at the 0.05 significance level. Between subject variance component and within subject variance component were assumed to be 0.13L (giving a total standard deviation of 0.18L). Note that variance components here are expressed as the standard deviation of the relevant random effect (not the variance).

Power for several of the secondary objectives (e.g., Glycopyrrolate vs. Spiriva®) will be acceptable at the end of Part A, but power for the primary objectives will be low (approximately <20%). Power for all Part A objectives will be acceptable with use of data from Part B.

Efficacy Analyses: Efficacy analysis will be based on a linear mixed model in which Treatment will be a fixed effect, subject will be a random effect, and within subject errors are correlated, but between subject errors are independent. Unstructured, compound symmetry and first order autoregressive error models will be considered, and the appropriate model selected using Akaike's information criterion (Akaike, 1974). Fixed and random effects will be estimated using the REML algorithm (Patterson and Thompson, 1971), which allows for the recovery of inter-block (subject) information. The analysis of primary efficacy objectives for Part A and Part B will include testing for unequal carryover effects.

A subset of the efficacy objectives will be analyzed on completion of Part A. These objectives have essentially all the relevant information available at that time (as measured by the ratio of the Fisher's information for the comparison on completion of Part A to the information on completion of Part B). No comparison that is analyzed on completion of Part A will be re analyzed on completion of Part B. No comparison that is analyzed on completion of Part B will have been analyzed on completion of Part A.

Secondary efficacy objectives will be analyzed using the same mixed model (but without testing for carryover effects).

Non-inferiority comparisons using the difference between treatments will be performed with a margin of 0.1L.

Pharmacokinetic Analyses: Non-compartmental parameter estimates will be analyzed using a linear mixed model in which Treatment will be a fixed effect and within subject errors are correlated, but between subject errors are independent. Unstructured, compound symmetry and first order autoregressive error models will be considered, and the appropriate model selected using Akaike's information criterion (Akaike, 1974). AUC and C_{max} will be log-transformed before analysis.

Relative bioavailability will be calculated for each dose relative to the control, using the mixed model results. A 90% confidence interval for each relative bioavailability (a ratio) will be calculated.

Safety analyses: Safety analyses will be based on descriptive statistics for ECG, vital sign and laboratory measurements as appropriate, and also on frequencies of adverse events and the number of patients with adverse events.

Statistical Analysis Plans(for Part A and Part B): All statistical analyses will be documented in a statistical analysis plan, which will define study populations, endpoints, statistical models, table and listing formats and graphical presentations. All statistical analyses will be performed using SAS (Version 8.2 or higher). The pharmacokinetic data will be analyzed using WinNonLin (Version 5.1 or higher).

Date of Original Approved Protocol: [redacted]

Date of Most Recent Protocol Amendment (if applicable): [redacted]

Prepared in: Microsoft Word 2007

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the curve
AV	Atrioventricular block
Bid	bis in die, twice daily
BMI	Body mass index
BMP	Basic Metabolic Panel
BP	Blood Pressure
BPM	Beats per minute
BTPS	Body Temperature and Pressure Saturated
BUN	Blood urea nitrogen
$CaCl_2$	Calcium chloride
CFR	Code of Federal Regulations
CO_2	Carbon dioxide
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
CRO	Contract Research Organization
CT	Computerized Tomography
DBP	Diastolic blood pressure
DPI	Dry Powder Inhaler
DSPC	Distearoylphophatidylcholine
e.g.	Exempli gratia, for example
EC	Ethics Committee
ECG	Electrocardiogram
ERS	European Respiratory Society

EV	Back extrapolation volume
ex-actuator	dose delivered from the actuator (i.e., mouthpiece) of the MDI
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
HCG	Human chorionic gonadotropin
HR	Heart Rate
HFA	Hydrofluroalkane
i.e.	*Id est,* that is
IC	Inspiratory Capacity
ICF	Informed consent form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive Web Response System
L	Liter
LABA	Long-acting beta agonist
LAMA	Long-acting antimuscarinic agents
LOCF	Last observation carried forward
LTOT	Long Term Oxygen Therapy
MAO	Monoamine oxidase inhibitor
MDI	Metered Dose Inhaler
mITT	Modified ITT

mL	Milliliter
Msec (ms)	Millisecond
NHANES III	Third National Health and Nutrition Examination Survey
OTC	Over-the-counter
PEFR	Peak expiratory flow rate
PK	Pharmacokinetics
PRN	pro re nata
Rx	Treatment
QTcB	QT corrected using Bazett's formula ($QT/(RR^{1/2})$)
QTcF	QT corrected using Fridericia's formula ($QT/(RR^{1/3})$)
SABA	Short-acting beta agonist
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SOP	Standard operating procedure
SVC	Slow Vital Capacity
TLC	Total Lung Capacity
US	United States

TRADEMARK INFORMATION

Trademarks Not Owned By Pearl Therapeutics

Aerolizer

Foradil

Handihaler

PulmoSphere

Spiriva

Ventolin

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 (Calverly, 2003a; 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 9-10% (Halbert 2003 and 2006). 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.

COPD 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 the first second of exhalation (FEV_1). 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.

Traditionally, bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are both short-acting and long-acting β_2-agonists (SABA and LABA, respectively), both short and long-acting anticholinergics, and methylxanthines used as monotherapy or in combination. Regular treatment with LABAs is more effective in the management of COPD than SABAs (GOLD, 2008).

Formoterol is a potent and selective β2-agonist approved in many countries worldwide for use in asthma and COPD. In patients with COPD, formoterol is typically administered at an orally inhaled dose of 12 μg twice daily with doses up to 24 μg twice daily approved in some countries. Formoterol is classified as a LABA, although it has a rapid onset of action similar to SABAs. It is marketed in Australia and New Zealand as Foradile® and as Foradil® in the United States.

Glycopyrrolate (Robinul® and Robinul Forte®) is an anticholinergic drug that is marketed in Australia, New Zealand and the United States as a parenteral formulation. Glycopyrrolate is a quaternary ammonium derivative that when inhaled results in minimal mucosal absorption and systemic side effects. Glycopyrrolate is not approved for respiratory inhalation. However, another anticholinergic drug, tiotropium bromide (Spiriva®), is licensed in the United States (US), Europe (Hansel, 2002) and Australia (eMIMS 2008) as a powder for inhalation. It has been shown to reduce the rate of COPD exacerbations and to improve the effectiveness of pulmonary rehabilitation (Niewoehner, 2005; Casaburi, 2005).

A large body of published data has evaluated the use of inhaled glycopyrrolate in healthy volunteers, patients with asthma, and patients with COPD (see Glycopyrrolate [PT001]

Investigator's Brochure). These data support the further evaluation of glycopyrrolate in the management of patients with COPD.

Pearl Therapeutics, Inc. has licensed and developed a particle engineering technology that utilizes porous particles for pulmonary drug delivery via metered dose inhalers. This technology is based on spray-dried porous particles comprised of DSPC and $CaCl_2$ that are cosuspended with crystalline active drug substances and formulated into suspension-based hydrofluoroalkane (HFA) metered dose inhalers (MDIs). In-vitro and in-vivo testing suggests that the Pearl formulations will provide highly efficient, reproducible administration of therapeutics from metered dose inhalers (MDIs) in a wide dosing range (Hirst, 2002; Dellamary, 2000). Pearl Therapeutics is developing a broad range of MDI-based inhalation products using its porous particle technology platform.

Combining bronchodilators may improve efficacy and decrease the risk of side effects compared with increasing the dose of a single bronchodilator (GOLD, 2008). Anticholinergics and β_2-agonists reduce bronchoconstriction through different mechanisms and there is a long history of combination therapy for COPD with short-acting agents in these classes (See Investigator's Brochure).

Pearl Therapeutics is developing a combination MDI product comprising the LABA formoterol fumarate and the anticholinergic glycopyrrolate in the porous particle platform for the maintenance treatment of bronchoconstriction associated with COPD (Glycopyrrolate and Formoterol Fumarate Inhalation Aerosol; hereafter referred to as Glycopyrrolate/Formoterol Fumarate MDI). Pearl Therapeutics has recently completed first-in-human clinical studies with its formulation of the combination product as well as Phase IIa dose ranging studies in patients with COPD with each of the individual component products.

Study PT0030901 was a single center, randomized, double-blind, 4-period cross over study evaluating 4 single-dose inhaled treatments (glycopyrrolate MDI 72 µg ex-actuator, Formoterol Fumarate MDI 9.6 µg ex-actuator, and Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg ex-actuator delivered individually and glycopyrrolate MDI 72 µg ex-actuator and Formoterol Fumarate MDI 9.6 µg ex-actuator delivered together in separate inhalers) in healthy subjects. The objectives of this study were to evaluate safety and pharmacokinetics following each treatment. A total of 16 subjects were enrolled (5 males, 11 females; mean age: 27 years), 13 of whom completed the study. All 4 treatments were safe and well-tolerated in this study. No serious adverse events (SAEs) or adverse events (AEs) leading to withdrawal occurred following any treatment and no clinically significant changes were noted in QTc values or serum potassium values. The average bioavailability of glycopyrrolate administered in fixed combination with formoterol fumarate was reduced by 21% compared with the loose combination and by one half compared with glycopyrrolate administered alone. On the other hand, the average bioavailability of formoterol was increased by approximately 20% when administered in combination with glycopyrrolate, whether in fixed or loose combination, compared with formoterol fumarate administered alone. These safety findings support further evaluation of Glycopyrrolate/Formoterol Fumarate MDI in patients with COPD.

Study PT0010801, conducted under an active IND with the US FDA, the first-in-human study of the Glycopyrrolate MDI, was a randomized, double-blind, single ascending dose, four-period, six-treatment, balanced, incomplete block, cross-over, placebo and active-controlled, multi-center study that was conducted in patients with mild to moderate COPD deemed clinically stable by their physician. This study was conducted in the US. The primary objective was to evaluate the efficacy and safety of four doses of Glycopyrrolate MDI (18, 36, 72, and 144 µg) compared to placebo MDI and Spiriva® Handihaler® 18 µg. Spirometry measures were performed at baseline, 15 and 30 minutes and 1, 2, 4, 6, 8, 10, 12, 16, 22, 23 and 24 hours post-dose. A total of 33 patients were enrolled (19 males, 14 females; mean age: 59 years), 30 of whom completed the study per protocol. Two patients were withdrawn from the study prior to completing all 4 treatments due to rescue medication use in either of the first two study periods. One additional patient completed the study but was also excluded from the efficacy analyses due to rescue medication use on all test days. All 4 doses of Glycopyrrolate MDI (18, 36, 72 and 144 µg) demonstrated superior efficacy compared to placebo in terms of Peak FEV_1 ($p<0.001$), the primary endpoint of the study, with a clear dose-response relationship. The Glycopyrrolate MDI 72 and 144 µg doses demonstrated statistically non-inferior bronchodilator efficacy relative to Spiriva for several FEV_1 parameters including peak FEV_1, FEV_1 AUC_{0-12}, and FEV_1 AUC_{0-24}, and also for 12-hour trough FEV_1 and FEV_1 AUC_{12-24} for the 144 µg dose. Dry mouth was the most frequently reported adverse event (AE) with Glycopyrrolate MDI treatment, although a clear dose relationship was not observed (1 [4.8%] patient following 18 µg, no patients following 36 µg, 3 [14.3%] patients following 72 µg, 1 [4.8%] patient following 144 µg, 2 [9.1%] patients following Spiriva, and 2 [9.5%] patients following placebo). Oropharyngeal pain was reported in 2 patients following Glycopyrrolate MDI treatment (18 µg and 144 µg). No substantial differences were noted between the Glycopyrrolate MDI treatment groups and placebo or Spiriva on any other safety parameter. No death, serious adverse events (SAEs) or AEs leading to withdrawal occurred during the study. One death due to complications of COPD occurred outside of the protocol specified reporting period (>30 days from last dose) and was deemed not related to study drug by the investigator. These findings support further development of Glycopyrrolate MDI for the management of patients with COPD.

Pearl Therapeutics has conducted a Phase I/IIa clinical study with Formoterol Fumarate MDI. Study PT0050801 was a randomized, double-blind, five-period, placebo and active-controlled, ascending dose, cross-over, multi-center study that was conducted in patients with moderate to severe COPD deemed clinically stable by their physician. This study was conducted in Australia and New Zealand. The primary objective was to evaluate the safety and tolerability of Formoterol Fumarate MDI at doses of 2.4, 4.8, and 9.6 µg ex-actuator compared to placebo MDI and Foradil® Aerolizer® 12 µg (corresponding to 10 µg delivered from the mouthpiece). Spirometry measures were performed at baseline, 15 and 30 minutes, and 1, 2, 4, 6, 8, 10, 11.5, and 12 hours post-dose. A total of 34 patients were enrolled (18 males, 16 females; mean age: 65 years), 29 of whom received all 5 treatments. All 3 doses of Formoterol Fumarate MDI demonstrated superior efficacy compared to placebo in terms of FEV_1 AUC_{0-12}, the primary endpoint of the study ($p<0.001$). Furthermore, the Formoterol Fumarate MDI 9.6 µg ex-actuator dose demonstrated non-inferior bronchodilator efficacy relative to Foradil® Aerolizer® 12 µg over the 12-hour period ($p<0.001$) and at every

individual time point assessed ($p<0.05$). Formoterol Fumarate MDI at a dose of 9.6 µg ex-actuator also demonstrated a comparable pharmacokinetic profile to Foradil Aerolizer 12 µg, with similar concentration-time plots and similar AUC_{0-12} and C_{max}. No substantial differences were noted between the Formoterol Fumarate MDI treatment groups and placebo or Foradil® Aerolizer® in terms of safety and there were no trends in QTc changes or changes in serum potassium values across the doses. Two serious adverse events (SAEs) were reported, one following placebo (small intestinal obstruction) and one following Formoterol Fumarate MDI 4.8 µg ex-actuator (exacerbation of COPD); neither were deemed related to study drug by the Investigator.

Note: Unless otherwise indicated, throughout this document all references to doses of Glycopyrrolate/Formoterol Fumarate MDI will be to the ex-actuator or "delivered" doses (36/9.6 and 72/9.6 µg), all references to doses of Formoterol Fumarate MDI will be to the ex-actuator or "delivered" doses (7.2 and 9.6 µg), all references to doses of Glycopyrrolate MDI will be to the ex-actuator or "delivered" doses (36 µg), all references to the Foradil® Aerolizer® dose will be to the capsule content of 12 µg (corresponds to approximately 10 µg delivered dose), all references to Spiriva® (tiotropium bromide, 18 µg) will be to the capsule content of 18 µg (delivered via the Handihaler®) and all references to Ventolin® HFA (albuterol sulfate inhalation aerosol) will be 108 µg corresponding to 90 µg albuterol base from the mouthpiece. Since Ventolin HFA will be sourced from the US, the generic term albuterol will be used instead of salbutamol throughout this protocol.

1.1 Study Rationale

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and published literature support the rationale for developing a combination product containing a long-acting β_2-agonist and an anticholinergic in a single device.

Formoterol is a well-established and extensively tested LABA that is clinically indicated for the management of COPD. Glycopyrrolate (Robinul® and Robinul Forte®) is an anticholinergic drug that is marketed in Australia, New Zealand and the United States as a parenteral formulation. A large body of published data has evaluated the use of inhaled glycopyrrolate in healthy volunteers, patients with asthma, and patients with COPD (See Investigator's Brochure). These data support the further evaluation of glycopyrrolate in the management of patients with COPD.

Novel technology based on spray-dried porous particles comprised of DSPC and $CaCl_2$ that are cosuspended with crystalline active drug substances and formulated into suspension-based hydrofluoroalkane (HFA) metered dose inhalers (MDIs) has enabled the development of Glycopyrrolate/Formoterol Fumarate either alone or as fixed combination MDI products, and could have the potential to improve the delivery of drug to the lower respiratory tract, improve the physical stability of the drug, and improve dose uniformity. Pearl Therapeutics is evaluating Glycopyrrolate/Formoterol Fumarate either alone or as fixed combination MDI products in this porous particle platform for the long-term, twice daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

A combination study is required to demonstrate superiority of the combination to its components, and to assess the relative contribution of the components compared with placebo. This study will be conducted in two parts, Part A and Part B. Patients enrolled for Part A will not be eligible for Part B. Each part has separately defined primary and secondary objectives. By combining Part A and Part B into one protocol this study ensures that the number of patients exposed to the test products, during development, is no more than ethically necessary. This combined approach increases the statistical power and therefore reduces the number of patients needed to achieve the study objectives by approximately half compared with conducting these studies separately.

Part A is designed to evaluate the efficacy and safety of two doses of Glycopyrrolate/Formoterol Fumarate MDI (36/9.6 and 72/9.6 µg ex-actuator) administered in a fixed combination compared with administration of Formoterol Fumarate MDI (9.6 µg and 7.2 µg ex-actuator) and Glycopyrrolate MDI (36 µg ex-actuator) as single agents.

Part B is designed to evaluate the efficacy and safety of two doses of Formoterol Fumarate MDI (9.6 µg and 7.2 µg ex-actuator) compared with placebo MDI.

Foradil® Aerolizer® (12 µg) and Spiriva (18 µg) are active controls in this study.

Data from Part B will be used to augment the assessment of Part A objectives, and *vice versa*.

The doses selected for evaluation in this study are based on the findings from prior clinical studies (PT0010801, PT0030901 and PT0050801). In Study PT0010801, the 18, 36, 72 and 144 µg doses of Glycopyrrolate MDI demonstrated superior efficacy compared with placebo MDI in terms of Peak FEV_1, the primary endpoint of the study and FEV_1 $AUC_{0\text{-}24hr}$ ($p \leq 0.003$). The 72 and 144 µg doses were non-inferior to Spiriva® (18 µg) for the primary endpoint. These doses will be carried forward in combination with Formoterol Fumarate as 36 and 72 µg BID in the current study.

In Study PT0050801, Formoterol Fumarate MDI 9.6 µg showed similar efficacy and PK when compared with Foradil® Aerolizer® 12 µg, while the two lower doses studied (2.4 and 4.8 µg) were inferior to Foradil® Aerolizer® in terms of efficacy. These findings support the evaluation of formoterol fumarate at 9.6 µg and a lower dose (i.e., 7.2 µg) in the current study. Since the 9.6 µg has been shown to be non-inferior to Foradil, and the efficacy of 7.2 µg has not been established, only the 9.6 µg dose will be carried forward in combination with glycopyrrolate in this study.

In Study PT0030901, Glycopyrrolate/Formoterol Fumarate MDI at a dose of 72/9.6 µg demonstrated Glycopyrrolate/Formoterol Fumarate given as a single dose fixed combination was safe and well tolerated compared with the individual components given either alone or together from separate inhalers. Formoterol was found to have slightly increased (geometric mean ratio of $AUC_{0\text{-}12}$ for Formoterol between treatments was 119%) bioavailability in combination with the glycopyrrolate than when administered as monotherapy. In contrast, the average bioavailability of glycopyrrolate administered in combination with formoterol

was reduced by approximately half (geometric mean ratio of AUC_{0-12} for glycopyrrolate between treatments was 51%) compared with glycopyrrolate administered as monotherapy. The geometric mean ratio of C_{max} between glycopyrrolate administered in combination and the monotherapy was 90% after removing one statistical outlier compared with of 76% when the outlier was included. These safety and pharmacokinetic findings support further evaluation of Glycopyrrolate/Formoterol Fumarate MDI in patients with COPD.

A treatment duration of 1 week should be adequate to characterize the safety and efficacy of Glycopyrrolate/Formoterol Fumarate MDI and select a dose(s) for further development. In clinical trials in patients with COPD, Foradil® Aerolizer® has demonstrated similar bronchodilatory effects (FEV_1 >120 mL at every time point over 12-hours compared with placebo MDI) after the first dose and following 12-weeks of treatment (Dahl, 2001). Given the reported half-life of 10 hours (Foradil® Aerolizer® U.S. Prescribing Information, 2006), it is expected that formoterol will have reached steady state plasma levels following 1 week of dosing. Similarly, in clinical trials in patients with COPD, tiotropium bromide (Spiriva®) has demonstrated that lung function will have reached steady state within 1 week of dosing (Casaburi, 2000).

The duration of exposure to Glycopyrrolate/Formoterol Fumarate MDI in this study is supported by 14-day toxicology studies in rats and dogs conducted in compliance with Good Laboratory Practices regulations that include a full range of safety assessments including recovery groups, toxicokinetics and abbreviated safety pharmacology. In addition, weekly exposure to PulmoSpheres® in rats and dogs for up to 6 months has demonstrated the safety of the porous particle platform (summarized in the Investigator's Brochure).

To provide additional assurance of safety, 4 sentinel patients will be evaluated prior to initiating enrollment of this study.

2 STUDY OBJECTIVES

For combination drug development, a study is required to demonstrate superiority of the combination (Glycopyrrolate/Formoterol Fumarate MDI) to its components (Glycopyrrolate and Formoterol Fumarate MDI), and to assess the relative contribution of the components compared with placebo. This study will be conducted in two parts, Part A and Part B. Each part has separately defined primary and secondary objectives.

Part A is a comparison of the improvement in lung function (FEV_1 AUC_{0-12}) following administration of the combination versus the single agents.

Part B compares the improvement in lung function (FEV_1 AUC_{0-12}) following administration of Formoterol Fumarate MDI to Placebo.

It is acknowledged that there is no dose ranging for Glycopyrrolate in either Part A or Part B. Additional dose ranging assessments of glycopyrrolate will be performed separate to this study.

Separate statistical analysis plans will be written for Part A and Part B of this study. Within each part of this study, secondary assessments will be conducted to refine the appropriate doses to carry forward in future studies.

2.1 Objective(s) for Part A (Combination versus components as single agents)

2.1.1 Primary Objective for Part A

The primary objective for Part A is to assess the improvement in FEV_1 AUC_{0-12} of Glycopyrrolate/Formoterol Fumarate MDI (72/9.6 µg ex-actuator) administered in a fixed combination compared with administration of its components Formoterol Fumarate MDI (9.6 µg ex-actuator) and Glycopyrrolate MDI (36 µg ex-actuator) as single agents. Superiority to both components must be demonstrated in order to satisfy the primary objective of this study.

2.1.2 Secondary Objectives for Part A

The secondary objective of the study is to provide additional information to characterize dose-response and to help identify candidate doses for further development. The primary and secondary endpoints identified in Section 3.1 will be assessed across the following comparisons (excluding comparisons already described for the primary objective above):

Glycopyrrolate/Formoterol Fumarate MDI (72/9.6 µg ex-actuator) versus:

- Formoterol Fumarate MDI (9.6 µg ex-actuator)
- Formoterol Fumarate MDI (7.2 µg ex-actuator)
- Glycopyrrolate MDI (36 µg ex-actuator)

- Spiriva® (18 µg)
- Foradil® Aerolizer® (12 µg)

Glycopyrrolate/Formoterol Fumarate MDI (36/9.6 µg ex-actuator) versus:

- Same treatments as for Glycopyrrolate/Formoterol Fumarate MDI (72/9.6 µg ex-actuator) above

Glycopyrrolate/Formoterol Fumarate MDI (72/9.6 µg ex-actuator) versus Glycopyrrolate/Formoterol Fumarate MDI (36/9.6 µg ex-actuator)

Glycopyrrolate vs. Spiriva® (18 µg)

2.1.3 Other/Exploratory Objectives

Similar comparisons for PEFR and FVC will be performed as defined for the secondary endpoints above. Additional exploratory analyses will be defined in the SAP.

- Trough IC (mean of 11.5 and 12 hour post-dose assessments)
- Change in estimated creatinine clearance following administration of study drug

2.1.4 Safety Objective for Part A

The safety objective of Part A is to evaluate the safety of Glycopyrrolate/Formoterol Fumarate MDI delivered as fixed combinations (36/9.6 µg or 72/9.6 µg ex-actuator) in patients with moderate to very severe COPD, compared with placebo MDI, Formoterol Fumarate MDI (7.2 and 9.6 µg ex-actuator), Glycopyrrolate MDI (36 µg ex-actuator), Foradil® Aerolizer® (12 µg) and Spiriva® (18 µg).

2.2 Objective(s) for Part B (Formoterol MDI versus placebo and active control)

2.2.1 Primary Objective for Part B

The primary objective for Part B is to assess the improvement in FEV_1 AUC_{0-12} of Formoterol Fumarate MDI (9.6 µg ex-actuator) compared with placebo.

2.2.2 Secondary Objectives for Part B

The secondary objective of the study is to provide additional information to characterize dose-response and to help identify the optimum doses for further development. The primary and secondary endpoints identified in Section 3.1 will be assessed across the following comparisons (excluding comparisons already described for the primary objective above):

Formoterol Fumarate MDI (9.6 µg ex-actuator) versus:

- Placebo
- Foradil® Aerolizer® (Non-Inferiority)

Formoterol Fumarate MDI (7.2 µg ex-actuator) versus:

- Placebo
- Foradil® Aerolizer® (Non-Inferiority)

Formoterol Fumarate MDI (9.6 µg ex-actuator) versus Formoterol Fumarate MDI (7.2 µg ex-actuator).

2.2.3 Other/Exploratory Objectives

Similar comparisons for PEFR and FVC will be performed as defined for the secondary endpoints above. Additional exploratory analyses will be defined in the SAP.

- Trough IC (mean of 11.5 and 12 hour post-dose assessments)
- Change in estimated creatinine clearance following administration of study drug

2.2.4 Safety Objective for Part B

The safety objective of Part B is to evaluate the safety of Formoterol Fumarate MDI (7.2 and 9.6 µg ex-actuator) as single agents in patients with moderate to very severe COPD compared with placebo MDI and Foradil® Aerolizer® (12 µg).

2.3 Pharmacokinetic Objective

For combination drug development, a combination study is required to demonstrate superiority of the combination to its components, and to assess the relative contribution of the components compared with placebo. From a PK perspective, it is important to assess whether a pharmaceutical effect is demonstrated when the components are administered in a fixed combination compared with administration of the components as single agents.

To this end, the objective for Part A is to assess the PK profile of both Glycopyrrolate and Formoterol Fumarate when administered from the combination compared with administration of the components as single agents.

Part B data will be used to assess the PK profile of two doses of Formoterol Fumarate MDI and will be used to compare the findings to the PK profile of formoterol administered as Foradil® Aerolizer®.

The PK assessments obtained in Part A will contribute to the analysis of Part B and vice versa where appropriate.

3 STUDY ENDPOINTS

While the study has two parts, the endpoints will be obtained in a consistent manner and are defined for both Part A and Part B below.

3.1 Efficacy Endpoints

All efficacy assessments are relative to baseline, and will be compared with individual agents and/or placebo where appropriate. Baseline is defined as the average of pre-dose values obtained prior to dosing with study medication at randomization (Visit 2).

3.1.1 Primary Efficacy Endpoint

Primary Efficacy Endpoint Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing)

- Forced expiratory volume in 1 second FEV_1 AUC_{0-12} relative to baseline following chronic dosing (1 week).

3.1.2 Secondary Efficacy Endpoints

Secondary Endpoints Evaluated on Treatment Day 1 (Visits 2, 4, 6 and 8):

- Peak FEV_1 (defined as peak improvement in FEV_1)
- Time to onset of action (≥10% improvement in mean FEV_1)
- Proportion of patients achieving ≥ 12% improvement in FEV_1
- Peak improvement in Inspiratory Capacity (IC) (mean of 1 and 2 hour post-dose)

Secondary Endpoints Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing):

- Improvement in morning pre-dose FEV_1
- Peak FEV_1 (defined as peak improvement in FEV_1)
- Peak improvement in IC (mean of 1 and 2 hour post-dose)
- Trough FEV_1 (trough FEV_1 is defined as the mean of the FEV_1 assessments taken at 11.5 and 12 hours post-dose)
- Mean daily peak flow readings taken by patients and recorded in patient diaries, during each treatment sequence

3.1.3 Other/Exploratory Endpoints

Exploratory Endpoints Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing):

- Peak expiratory flow rate (PEFR)
- Forced vital capacity (FVC)
- Trough IC (mean of 11.5 and 12 hours post-dose)
- Mean number of puffs of rescue medication recorded in patient diaries, during each treatment sequence
- Change in estimated creatinine clearance following administration of study drug

3.2 Safety Endpoints

The safety assessments include ECGs, vital sign measurements, clinical laboratory tests, monitoring for paradoxical bronchospasm, assessment of symptoms of tremor and dry mouth assessments, in addition to recording AEs and SAEs (including physical examination findings).

3.3 Pharmacokinetic Endpoints

Pharmacokinetics will be evaluated in approximately one-half of patients enrolled (i.e., approximately 42 patients across Parts A and B), with the following blood sampling scheme: pre-dose on Day 1 of each treatment period and pre-dose and 2, 6, 20 minutes, and 1, 2, 4, 8, 10, and 12 hours post-dose at the end of each treatment period (Day 7).

The pharmacokinetic endpoints for this study are obtained following chronic dosing (Day 7) and include the following:

- $AUC_{0\text{-}12}$: Area under the plasma concentration versus time curve from time 0 to 12 hours post-dose, where time 0 is defined as the pre-dose measurement
- $AUC_{0\text{-}tlast}$: Area under the plasma concentration versus time curve from time 0 to time of last quantifiable concentration, where time 0 is defined as the pre-dose measurement
- $AUC_{0\text{-}inf}$: Area under the plasma concentration versus time curve from time 0 to infinity, where time 0 is defined as the pre-dose measurement
- C_{max}: Maximum plasma concentration
- T_{max}: Time to C_{max}
- $t_{1/2}$: Apparent terminal elimination half-life
- CL/F: Apparent systemic clearance after oral inhalation administration

- Vz/F: Apparent volume of distribution during the terminal phase after oral inhalation administration.

The terminal elimination rate constant (k_e), the apparent terminal elimination half-life ($t_{1/2}$) and the area under the plasma concentration versus time curve from time 0 to infinity (AUC_{0-inf}) will be calculated if the data permit.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind (test products and placebo), chronic dosing (7 days), four-period, eight-treatment, placebo-controlled, incomplete block, cross-over, multi-center study to assess efficacy and safety of two doses of Glycopyrrolate/Formoterol Fumarate inhalation aerosol (36/9.6 µg and 72/9.6 µg ex-actuator), two doses of formoterol fumarate (7.2 and 9.6 µg ex-actuator) and one dose of glycopyrrolate (36 µg ex-actuator) in patients with moderate to very severe COPD, compared with Foradil® Aerolizer®, (formoterol fumarate inhalation powder 12 µg, open-label) and Spiriva® Handihaler® (tiotropium 18 µg, open-label) as active controls.

This multi-center study will be conducted at approximately 12-16 sites, contributing approximately 5 to 12 patients per site, in Australia, New Zealand and the United States. Across these sites, it is planned that approximately 84 patients (approximately 48 and 36 patients in Part A and B respectively) with moderate to very severe COPD will be randomized into the study to provide the target of between 32 and 52 (inclusive) evaluations per study treatment.

This study will be recruited in two parts, Part A and Part B, as outlined below with no patients recruited to both parts. Throughout all parts of the study, each treatment will be administered for 1 week with a washout period of at least 1 week between treatments. All patients will undergo the same study procedures regardless of the study part they are recruited to.

Part A: 4-period, 8-treatment, incomplete block cross-over study evaluating the following 8 treatments in approximately 48 patients:

- Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg ex-actuator twice daily
- Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg ex-actuator twice daily
- Glycopyrrolate MDI 36 µg ex-actuator twice daily
- Formoterol Fumarate MDI 9.6 µg ex-actuator twice daily
- Formoterol Fumarate MDI 7.2 µg ex-actuator twice daily
- Placebo MDI twice daily
- Foradil® Aerolizer® 12 µg twice daily
- Spiriva® Handihaler® 18 µg once daily

Part B: 4-period, 4-treatment, full cross-over, evaluating the following 4 treatments in approximately 36 patients:

- Formoterol Fumarate MDI 9.6 µg ex-actuator twice daily
- Formoterol Fumarate MDI 7.2 µg ex-actuator twice daily
- Placebo MDI twice daily

- Foradil® Aerolizer® 12 µg twice daily

The entire study period is scheduled to take approximately 10-14 weeks for each individual patient; however, no patient should be in the study for longer than 20 weeks. The study is anticipated to run for approximately 9 months and should not exceed 18 months.

All patients are to sign an informed consent form prior to the conduct of any screening assessments (Visit 1a). The Investigator will obtain a medical history, physical examination, and any required documentation in order to determine eligibility for participation (inclusion/exclusion criteria). Reversibility of FEV_1 30 minutes following 4 puffs of albuterol (salbutamol) MDI will be assessed at Screening to characterize the patient population but will not be used to determine eligibility to participate in the study. Patients who are not using a prohibited medication and meet all other entry criteria will return to the clinic at least 1 week (≥2 weeks if taking tiotropium) after screening for Visit 2 (Randomization).

Patients who meet all entry criteria but are using certain prohibited COPD medications (e.g., oral β_2 agonists, LABAs, corticosteroid/LABA combination products, theophylline, cromoglycate or nedocromil inhalers, leukotriene antagonists [e.g., zafirlukast, montelukast, zileuton], or tiotropium) will discontinue these medications for the duration of the trial and be switched to short-acting bronchodilators (albuterol MDI, ipratropium MDI or albuterol/ipratropium combination MDI) per the Investigator's discretion (see Section 5.4).

In order to allow for an adequate washout of previous maintenance medications, patients will undergo a washout period of at least 1 week (at least 2 weeks if taking tiotropium), but not greater than 4 weeks duration prior to returning to the clinic for Visit 2 (Randomization).

Patients who do not meet the entry criteria at Visit 1a can return for re-evaluation at a second Screening visit (Visit 1b) at the Investigator's discretion.

At Visit 2 (Randomization Visit; Treatment [Rx] 1, Day 1), patients will return to the clinic before 10:00 am. Patients who continue to meet entry inclusion/exclusion criteria and remain eligible for participation in the study will be randomized into one of the pre-defined treatment sequences. During Part A, patients will be randomized into one of the 48 treatment sequences generated as a set of Williams square designs based on each of the treatment selections shown in Table 7. During Part B patients will be randomized into one of the 24 possible treatment sequences for the four Part B treatments. During Part B, every one of the 24 possible treatment sequences will be allocated to at least one patient, and the treatment sequences assigned to two patients during Part B will be generated as a set of three Williams' square designs.

Randomization will be centralized, through the use of an IWRS (Interactive Web Response System).

Each sequence will include exactly 4 of the 8 treatment groups included in this study [placebo, active controls (Spiriva® 18 µg or Foradil® Aerolizer® 12 µg), or study drug at one

of the following doses: Glycopyrrolate/Formoterol Fumarate 36/9.6 and 72/9.6 µg, Formoterol Fumarate 7.2 and 9.6 µg, and Glycopyrrolate 36 µg].

No sequence will have a Glycopyrrolate component in more than 2 treatment periods regardless of whether given as fixed combination or as a single agent (e.g., a sequence can have no more than 2 of the following glycopyrrolate treatment possibilities Glycopyrrolate/Formoterol Fumarate 36/9.6 µg, Glycopyrrolate/Formoterol Fumarate 72/9.6 µg and Glycopyrrolate 36 µg). In addition, no sequence will have a Formoterol Fumarate component in more than 2 treatment periods regardless of whether given as fixed combination or as a single agent (e.g., a sequence can have no more than 2 of the following Formoterol Fumarate treatment possibilities: Glycopyrrolate/Formoterol Fumarate 36/9.6 µg, Glycopyrrolate/Formoterol Fumarate 72/9.6 µg, Formoterol Fumarate 7.2 µg and Formoterol Fumarate 9.6 µg).

Glycopyrrolate/Formoterol Fumarate, Formoterol Fumarate, Glycopyrrolate, Placebo and Foradil® Aerolizer® (12 µg) will be administered twice daily while Spiriva® (18 µg) will be administered once daily. Each of the 4 treatments will be administered for 1 week with a washout period of at least 1 week (up to 3 weeks) in between treatments. During Visit 2 (Rx 1, Day 1), patients will be dispensed study medication and will administer their first dose at the clinic under supervision. Patients will be required to remain at the clinic until completion of all protocol-defined assessments to the 2-hour post-dose time point (see Table 5). Patients will then be discharged from the clinic and will continue to administer study medication for 1 week at home.

Patients will return to the clinic following 1 week of treatment for Visit 3 (Rx 1, Day 7) at approximately the same time as Visit 2 (± 2 hours). Patients will receive their last dose of Rx 1 study medication that morning under supervision and will be required to remain at the clinic until completion of all protocol-defined assessments to the 12-hour post-dose time point (see Table 6). Following discharge, patients will undergo a study medication washout period of at least 1 week but no more than 3 weeks duration prior to initiating the next treatment in their assigned treatment sequence.

Following the washout period, patients will repeat a similar pattern of visits and assessments for the next three treatments in their assigned sequence, as follows:

Visit 4 (Rx 2, Day 1): Administer Rx 2 study medication, undergo 2-hour post-dose assessments, discharge and continue daily administration for 1 week.

Visit 5 (Rx 2, Day 7): Administer last dose of Rx 2 study medication, undergo 12-hour post-dose assessments, discharge and undergo washout for at least 1 week (up to 3 weeks).

Visit 6 (Rx 3, Day 1): Administer Rx 3 study medication, undergo 2-hour post-dose assessments, discharge and continue daily administration for 1 week.

Visit 7 (Rx 3, Day 7): Administer last dose of Rx 3 study medication, undergo 12-hour post-dose assessments, discharge and undergo washout for at least 1 week (up to 3 weeks).

Visit 8 (Rx 4, Day 1): Administer Rx 4 study medication, undergo 2-hour post-dose assessments, discharge and continue daily administration for 1 week.

Visit 9 (Rx 4, Day 7): Administer last dose of Rx 4 study medication and undergo 12-hour post-dose assessments.

Visit 10: Visit 10 will serve as the final/follow-up visit. Patients will complete all post-study assessments, including a final physical examination and recording of any AEs, and will then be discharged from the study.

Every effort must be made to ensure that patients return to the clinic on Day 7 (1 week) following initiation of each treatment arm. To accommodate scheduling conflicts a window of 7 ± 2 days is permitted (i.e., Treatment Day 7 procedures must be done within a minimum of 5 days and a maximum of 9 days from Treatment Day 1). If any patient exceeds 9 days of treatment for any treatment except Spiriva® and Foradil®, the Sponsor should be notified and the patient may be withdrawn from the study.

Starting at the Screening Visit, patients will receive a diary in which they will be asked to maintain a daily record of their study medication dosing, rescue medication use, and daily peak flow rates using a sponsor provided portable peak flow meter.

During the treatment periods (between Visits 2 and 3, Visits 4 and 5, Visit 6 and 7 and Visits 8 and 9), patients will be permitted to use sponsor provided Ventolin® HFA on an as needed basis for relief of COPD symptoms.

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), patients will be permitted to use short-acting bronchodilators (albuterol MDI, ipratropium MDI or albuterol/ipratropium combination MDI) per the Investigator's discretion.

Protocol-adjusted inhaled corticosteroid (ICS) therapy defined at Screening, if any, should be continued and remain stable for the duration of the trial (see Section 5.4).

All COPD medications, including ICS, must be withheld for at least 6 hours prior to each visit, or the visit will need to be rescheduled as soon as it is practical but within the specified visit windows.

4.2 Sentinel Patients

Four sentinel patients will be studied in advance of the remaining patients (84 patients) to be randomized. The sentinel patients and one reserve sentinel patient will be identified at pre-selected site(s). The first four sentinel patients will be informed that they have been recruited to participate in the sentinel only portion of the study. The fifth patient will be informed that he/she is a reserve patient and may not be required to participate in the study and that this will be established at check-in at the start of Rx 1. If any of the first four recruited sentinel patients has ceased to be eligible (e.g., as a result of a protocol violation or pregnancy) or

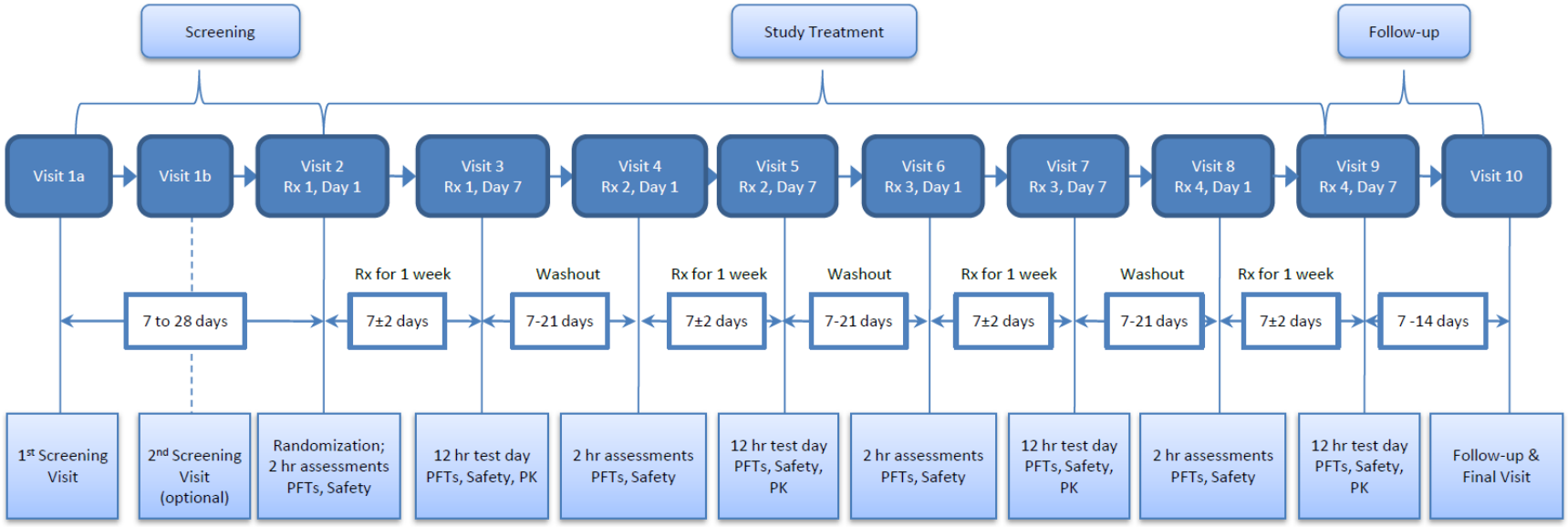
fails to appear or is unable to proceed (e.g., unable to provide adequate baseline assessments on the morning of Rx 1), the reserve patient will be enrolled, to endeavor to enroll four sentinel patients. Upon meeting randomization criteria, each sentinel patient will be randomized using the IWRS (Interactive Web Response System) to one of four treatments (Glycopyrrolate/Formoterol Fumarate [36/9.6 µg or 72/9.6 µg] or Glycopyrrolate 36 µg or Formoterol Fumarate 9.6 µg) and will be monitored for 24 hours on Day 1 of dosing and for 12 hours at the end of chronic dosing (Day 7). All sentinel patients will complete Visits 1, 2, 3 and 10 study procedures.

At Visit 2 patients will be observed for the first 2 hours as defined in the protocol with additional safety assessments obtained at 2 hour intervals for the first 12 hours. These safety assessments will include vital signs at 2 hourly intervals and ECGs conducted at 4 and 12 hours post-dose. Following the 12 hour assessments patients will be administered the second dose of study drug with vital signs and ECG obtained at 30 minutes and 2 hours post second dose. The patient will remain in the unit for overnight observation. On the following morning, the third dose of study medication will be administered at approximately the same time as Day 1. Safety assessments (i.e., vital signs and ECG) will be obtained 30 minutes and 2 hours post-dose. In addition, a CBC and CMP will be obtained prior to discharge from the unit. Patients will return for Visit 3 and follow procedures as outlined in protocol.

Following completion of Visit 3 by all sentinel patients, their safety data will be evaluated by the Principal Investigator(s) in consultation with the sponsor's Chief Medical Officer to determine whether additional patients will be enrolled in the trial. **Note:** Data from the sentinel patients will be included in the safety analyses, but not the efficacy analyses for the study.

A Study Flow Diagram is displayed in Figure 1 (following page).

Figure 1. Study Flow Diagram (Applies to both Parts A and B of this study)



PFT = pulmonary function test, Rx = treatment, PK = pharmacokinetic assessments
Sentinel patients will be observed for ~26 hours following first dose.

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

Patients 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 40-80 years of age at 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 screening, and agrees to one of the following acceptable contraceptive methods used consistently and correctly (i.e., in accordance with the approved product label and the instructions of the physician for the duration of the study - screening to until 2 weeks after Visit 9):
     - Complete abstinence from intercourse from screening until 2 weeks after Visit 9 or
     - Implants of levonorgestrel inserted for at least 1 month prior to the study drug administration but not beyond the third successive year following insertion; or
     - Injectable progestogen administered for at least 1 month prior to study drug administration and administered for 1 month following study completion; 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 occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository); 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; or
     - Estrogenic vaginal ring; or
     - Percutaneous contraceptive patches.
4. COPD Diagnosis: Patients with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) (Celli, 2004) characterized by:
   - Airflow limitation that is not fully reversible. Progressive airflow limitation associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.
5. 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).

6. Severity of Disease: Patients with an established clinical history of COPD and severity defined as:
   - Pre- and post-bronchodilator FEV_1/FVC ratio of ≤70%.
   - At Screening (Visit 1), post-bronchodilator FEV_1 must be ≤80% predicted normal value calculated using the Third National Health and Nutrition Examination Survey (NHANES III) reference equations, and must also be greater than or equal to 750 mL or 30% of predicted normal.
   - At Baseline (Visit 2), pre-bronchodilator FEV_1 must be ≤80% predicted normal value calculated using NHANES III reference equations.
7. Patient is willing and, in the opinion of the investigator, able to change current COPD therapy as required by the protocol and willing to use only albuterol/salbutamol, ipratropium or a combination thereof with or without ICS for relief of COPD symptoms for at least 1 week prior to randomization and for the duration of the study.
8. Lab tests conducted at Screening must be acceptable to investigator. ECG performed at Screening must be acceptable to investigator. Chest X-ray or CT scan within 6 months prior to Screening must be acceptable to the investigator.
9. Compliance: Patients must be willing to remain at the study center as required per protocol to complete all visit assessments.

5.2 Exclusion Criteria

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

1. Pregnancy: Women who are pregnant or lactating.
2. Asthma: Patients who have a primary diagnosis of asthma. (Note: Patients with a prior history of asthma are eligible if COPD is currently their primary diagnosis).
3. Alpha-1 Antitrypsin Deficiency: Patients who have alpha-1 antitrypsin deficiency as the cause of COPD.
4. Other Respiratory Disorders: Patients 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 severity of the disorder would impact the conduct of the study).
5. Lung Resection: Patients who have undergone lung volume reduction surgery at any time in the past.
6. Chest X-ray/CT Scan: Patients who have a chest X-ray (or CT scan) that reveal clinically significant abnormalities not believed to be due to the presence of COPD. A chest X-ray must be conducted if the most recent chest X-ray or CT scan are more than 6 months old at the time of Screening (Visit 1).
7. Hospitalization: Patients who have been hospitalized due to poorly controlled COPD within 3 months of Screening (Visit 1).

8. Poorly Controlled COPD: Patients 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.
9. Lower Respiratory Tract Infection: Patients who had lower respiratory tract infections that required antibiotics within 6 weeks prior to Screening (Visit 1).
10. Spirometry Performance: Patients who cannot perform acceptable spirometry (3 consecutive reproducible flow-volume curves).
11. Other Diseases: Patients who have clinically significant medical conditions including but not limited to cardiovascular, neurological, psychiatric, hepatic, gastrointestinal, renal (creatinine clearance ≤ 50 mL/minute), immunological, glaucoma, symptomatic prostatic hypertrophy (if treated and asymptomatic, the patient is eligible for enrollment), endocrine (including uncontrolled diabetes or thyroid disease), or hematological medical problems.
12. Clinically significant abnormal ECG: Patients who in the opinion of the investigator 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., complete right or left bundle branch block, Wolff-Parkinson-White syndrome)
    - Clinically significant arrhythmias (e.g., atrial fibrillation, ventricular tachycardia)
    - A mean corrected QT interval using Fridericia's correction factor (QTcF) value at screening >450 ms for males and >470 ms for females or an ECG that is not suitable for QT measurements (e.g., poorly defined termination of the T wave).
    - Ventricular rate <45 bpm.
    - Evidence of second degree (Mobitz Type II) or third degree atrioventricular (AV) block
    - Pathological Q waves of 1 year or less
    - ST-T wave abnormalities (excluding non-specific ST-T wave abnormalities)
13. Uncontrolled Hypertension: Patients who have clinically significant uncontrolled hypertension.
14. Patient with abnormal liver function tests defined as AST, ALT, alkaline phosphatase or total bilirubin ≥ 1.5 times upper limit of normal on repeat testing.
15. Cancer: Patients who have cancer that has not been in complete remission for at least 5 years. Note: Patients with squamous cell carcinoma and basal cell carcinoma of the skin and localized prostate cancer that in the opinion of the investigator has been adequately worked up, is clinically controlled and the patient's participation in the study would not represent a safety concern, are eligible
16. Drug Allergy: Patients who have a history of hypersensitivity to any β_2-agonists, muscarinic anticholinergics, or any component of the MDI and/or constituents of the dry powder product (lactose).
17. Milk Allergy: Patients who have a history of severe milk protein allergy.

18. Substance Abuse: Patients with a known or suspected history of alcohol or drug abuse within the last 2-year period prior to Screening.
19. Medication Prior to Spirometry: Patients 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.
20. Prohibited COPD Medications: Patients 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: Patients requiring chronic maintenance therapy with oral corticosteroids are excluded from participation in this study.
    - 6 weeks: antibiotics administered for a COPD exacerbation
    - 2 weeks: theophylline (any formulation).
21. Other Prohibited Medications:
    - Tricyclic antidepressants inhibitors for treatment of depression.
    - Monoamine oxidase (MAO) inhibitors.
    - Anticonvulsants (barbiturates, hydantoins, and carbamazepine) for the treatment of seizure disorder.
    - Non-selective beta-adrenergic antagonists.
    - Anti-tumor necrosis factor α (TNFα) antibodies (e.g., infliximab and any other members of this class of drugs).
    - Antipsychotic drugs (phenothiazines).
    - 1 month: P-glycoprotein inhibitors (e.g., ritonavir, ketoconazole), cytochrome P450 3A4 inhibitors (e.g., cimetidine).
    - Note: Benzodiazepines are not exclusionary
22. Oxygen: Patients receiving long-term-oxygen therapy (LTOT) or nocturnal oxygen therapy required for greater than 12 hours a day. As needed oxygen use is not exclusionary.
23. Pulmonary Rehabilitation: Patients who have participated in the acute phase of a Pulmonary Rehabilitation Program within 4 weeks prior to Screening (Visit 1) or who will enter the acute phase of a Pulmonary Rehabilitation Program during the study. Patients who are in the maintenance phase of a Pulmonary Rehabilitation program are not to be excluded.
24. Non-compliance: Patients 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.
25. Affiliations with Investigator Site: Study investigators, sub-investigators, study coordinators, employees of a participating investigator or immediate family members of the aforementioned are excluded from participation in this study.

26. Questionable Validity of Consent: Patients 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.
27. Investigational Drugs or Devices: Treatment with investigational study drug or participation in another clinical trial or study within the last 30 days or 5 half lives prior to Screening, whichever is longer.
28. A patient who requires the use of a spacer device to compensate poor hand-to-breath coordination with a MDI.
29. Except for sentinel patients, patients who were previously enrolled in a Pearl Therapeutics PT001 (Glycopyrrolate MDI), PT005 (Formoterol Fumarate MDI), or PT003 (Glycopyrrolate/Formoterol Fumarate MDI) studies.

5.3 Patient Identification

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

5.4 Prior, Concomitant, and Prohibited Medications

All prescription and over-the-counter (OTC) medications taken by the patient during 30 days before Screening 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 below) and are approved by the Investigator. Patients should also be instructed to contact the Investigator if they develop any illnesses.

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

Prohibited COPD Medications:

A list of prohibited medications prior to Screening is provided in Section 5.2. The following medications used for the treatment of asthma and/or COPD are not permitted during this study:

- oral β_2 agonists*
- any LABAs*
- any corticosteroid/LABA combination products*
- any theophylline preparations*

- cromoglycate or nedocromil inhalers*
- leukotriene antagonists (e.g., zafirlukast, montelukast, zileuton)*
- tiotropium*
- any formulation of oral corticosteroids (see Section 5.2). Note: For patients maintained on ICS, the dose must remain stable for the duration of the trial.
- prednisone

Patients who meet all entry criteria but are using a prohibited COPD medication will have their maintenance therapy for COPD adjusted as follows:

- Patients taking the COPD medications denoted with * in the list above at Screening (Visit 1) will discontinue these medications for the duration of the trial and be switched to short-acting bronchodilators (albuterol MDI, ipratropium MDI or albuterol/ipratropium combination MDI) per the Investigator's discretion.
- Patients receiving a maintenance dose of an ICS as part of a fixed dose combination therapy containing fluticasone and salmeterol or formoterol and budesonide will be switched to the corresponding dose of fluticasone or budesonide administered as a single agent, with short-acting bronchodilators (albuterol MDI, ipratropium MDI or albuterol/ipratropium combination MDI) per the Investigator's discretion provided they have been maintained on a stable dose for at least 4 weeks or have been switched to an equivalent dose of an alternative ICS for at least 2 weeks.
- Patients receiving a maintenance dose of an ICS that is not administered as a fixed dose combination together with a LABA will be permitted to continue the ICS provided they have been maintained on a stable dose for at least 4 weeks or have been switched to an equivalent dose of an alternative ICS for at least 2 weeks.
- All patients treated with either a LABA (salmeterol, formoterol) or long-acting anti-muscarinic agent (LAMA) (tiotropium) administered alone or as a loose combination will have these medications discontinued and replaced with short-acting bronchodilators (albuterol MDI, ipratropium MDI or albuterol/ipratropium combination MDI) per the Investigator's discretion.

Note: During study treatment (i.e., between Visits 2 and 3, Visits 4 and 5, Visits 6 and 7, and Visits 8 and 9), patients will receive study drug to be administered daily and are only allowed sponsor provided Ventolin® HFA to be used as needed for relief of symptoms. Patients are permitted to resume other short-acting bronchodilators during washout period.

Note: During the screening phase and washout periods (i.e., between Visit 3 and 4, Visit 5 and 6, and Visit 7 and 8), Albuterol, ipratropium or ipratropium/albuterol combination drugs are acceptable based on the Investigator's assessment, but must be withheld for at least 6 hours before each study visit.

Other Prohibited Medications:

- Tricyclic antidepressants for treatment of depression
- Monoamine oxidase (MAO) inhibitors
- Anticonvulsants (barbiturates, hydantoins, and carbamazepine) for the treatment of seizure disorder
- Non-selective beta-adrenergic antagonists
- Anti-tumor necrosis factor α (TNFα) antibodies (e.g., infliximab and any other members of this class of drugs)
- Antipsychotic drugs (phenothiazines).
- P-glycoprotein inhibitors (e.g., ritonavir, ketoconazole)
- cytochrome P450 3A4 inhibitors (e.g., cimetidine)
- any investigational drugs
- Note: Benzodiazepines are not exclusionary.

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 patient discontinues the study. If any illicit drugs or drugs of abuse are used by the patient during the study, the dates of use and the amount will be documented on the appropriate CRF pages.

Patients are not allowed to consume grapefruit juice throughout the study.

Patients 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.

Patients 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. Study participants may utilize various nicotine replacement treatments such as chewing gum and patches as needed (*prn)*, in accordance with recommendations from the Investigator during the entire study visit.

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

6.1 Patient Information

Clinical supplies will be packaged to support enrollment of at least 84 patients.

Study personnel will have access to an Interactive Web Response System (IWRS) to allocate patients, to assign drug to patients and to manage the distribution of clinical supplies. Clinical supplies will be packaged according to a component schedule generated by the Sponsor. Each person accessing the IWRS system must be assigned an individual unique 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

Investigational materials will be provided by the Sponsor as summarized in Table 1.

Table 1. Product Descriptions

Product Name & Potency	Dosage Form	Comments
Glycopyrrolate/Formoterol Fumarate 72/9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 36/4.8 µg per actuation strength MDI
Glycopyrrolate/Formoterol Fumarate 36/9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 18/4.8 µg per actuation strength MDI
Formoterol Fumarate 9.6 µg ex-actuator	MDI	Taken as 2 inhalations of the 4.8 µg per actuation strength MDI
Formoterol Fumarate 7.2 µg ex-actuator	MDI	Taken as 2 inhalations of the 3.6 µg per actuation strength MDI
Glycopyrrolate 36 µg ex-actuator	MDI	Taken as 2 inhalations of the 18 µg per actuation strength MDI
Placebo	MDI	Formulation does not contain active ingredient
Tiotropium inhalation powder† 18 µg	Dry Powder Inhaler (DPI)	US source: (Spiriva® delivered via Handihaler®) *Supplies are open-label.*
Formoterol Fumarate inhalation powder† 12 µg	DPI	US source: (Foradil® Aerolizer®) Each capsule contains 12 µg corresponding to 10 µg formoterol fumarate dihydrate delivered from the mouthpiece *Supplies are open-label.*
Albuterol Sulfate inhalation aerosol§ 90 µg	MDI	US source: (Ventolin® HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece *Supplies are open-label.*

† Active controls
§ Rescue medication
Note: All study drugs will be administered by oral inhalation.

All placebos were created by Pearl Therapeutics in the image of the active test product(s).

For open-label Foradil® Aerolizer® (formoterol fumarate inhalation powder, 12 µg), bulk commercial blister packs containing 6 individually sealed capsules will be provided. Manufacturer's instructions for study drug administration will be provided.

For open-label Spiriva® Handihaler® (tiotropium bromide, 18 µg), bulk commercial blister packs containing 5 individually sealed capsules will be provided. Manufacturer's instructions for study drug administration will be provided.

For open-label Ventolin® HFA (albuterol sulfate inhalation aerosol 90 µg) bulk commercial metered dose inhalers with dose counters will be provided. Manufacturer's instructions for study drug administration will be provided.

6.3 Primary Packaging and Labeling Information

Investigational materials will be packaged by the Sponsor as summarized in Table 2 below. Foradil® and Spiriva® supplies will be supplied as open-label DPI. Ventolin® HFA supplies will be supplied as open-label MDI.

Table 2. Packaging of Clinical Supplies

Interval ID	Product Name and Potency	Fill Count	Dosing Instructions
Treatment Period (Visit 2, 4, 6 and 8)	Glycopyrrolate/Formoterol Fumarate 72/9.6 µg	1 MDI 120 actuations	Take as directed in the morning and evening.
Treatment Period (Visit 2, 4, 6 and 8)	Glycopyrrolate/Formoterol Fumarate 36/9.6 µg	1 MDI 120 actuations	Take as directed in the morning and evening.
Treatment Period (Visit 2, 4, 6 and 8)	Formoterol Fumarate 9.6 µg	1 MDI 120 actuations	Take as directed in the morning and evening.
Treatment Period (Visit 2, 4, 6 and 8)	Formoterol Fumarate 7.2 µg	1 MDI 120 actuations	Take as directed in the morning and evening
Treatment Period (Visit 2, 4, 6 and 8)	Glycopyrrolate 36 µg	1 MDI 120 actuations	Take as directed in the morning and evening
Treatment Period (Visit 2, 4, 6 and 8)	Placebo	1 MDI 120 actuations	Take as directed in the morning and evening
Treatment Period (Visit 2, 4, 6 and 8)	Spiriva® HandiHaler®†	N/A	Use only with provided medication as directed.
Treatment Period (Visit 2, 4, 6 and 8)	Foradil® Aerolizer®†	N/A	Use only with provided medication as directed.
Treatment Period (Visit 2, 4, 6 and 8)	Albuterol Sulfate inhalation aerosol§ 90 µg	1 MDI 60 or 120 actuations	Use only as directed.

† Active controls

§ Rescue medication

Blinded Supplies: Each MDI will be labeled with a single label. The foil pouch will be labeled with a two-part label.

Open-label Supplies: Open-label Spiriva® supplies will be provided as individually labeled DPI (Handihaler®) device and 3 blister packs containing 5 capsules. The blister packs will be packaged together with a foil overwrap. The foil overwrap will be labeled with a two-part label

Open-label Foradil® supplies will be provided as individually labeled DPI (Foradil® Aerolizer®) and bulk labeled commercial blister packs packaged in sets of 4 blister packs per patient within a foil overwrap labeled with a two-part label. Each Foradil® Aerolizer® will have a single label.

Open-label Ventolin® HFA will be provided as individually labeled MDIs. Each MDI will contain a single label.

Both single and two-part labels will be printed with black ink and may include the following text:

• Packaging Lot Trace ID # • Space for entry of baseline # • Component ID # • Space for entry of Allocation # • Fill Count & Dosage Form • Space for entry of Interval ID (Visit # only) • Re-evaluation/Expiration date (if applicable)	• Dosing Instructions • Storage Conditions • Compound ID - Protocol # • Country regulatory requirements • Sponsor address (If applicable) • Translation Key (If applicable)

6.4 Secondary Packaging and Labeling Information (Box)

Investigational drug or placebo supplies for Visit 2, 4, 6 and 8 will be packaged in boxes as outlined in Table 3. Open-label Foradil® supplies will be provided as bulk commercial blister packs packaged in boxes as outlined in Table 3. The foiled overwrap Spiriva® HandiHaler®/blister packs and Foradil® Aerolizer® device will be packaged in boxes as outlined in Table 3.

Box configuration is subject to change as a result of packaging constraints.

Table 3. Description of Boxes

Drug Supplies	Box Contents
Blinded Foradil® Aerolizer® Device	1 MDI 1 DPI
Bulk Foradil Capsule	5 Foil Pouches Containing 4 Blister Packs Each)
Spiriva® HandiHaler®	1 DPI plus 3 Blister Packs
Bulk Ventolin® HFA	1 MDI

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

• Packaging Lot ID # • Space for entry of baseline # • Component ID # • Space for entry of Allocation # • Kit Contents (1 MDI or DPI) • Space for entry of Interval ID • Re-evaluation date (if applicable)	• Dosing Instructions (if applicable) • Storage Conditions • Compound ID - Protocol # • Country regulatory requirements • Sponsor address (If applicable) • Translation Key (If applicable)

6.5 Clinical Supplies Disclosure

The IWRS should be used in order to unblind patients and to unmask drug identity. The Sponsor will not provide a disclosure envelope with the clinical supplies. Drug identification information is to be unmasked ONLY if necessary for the welfare of the patient. Every effort should be made not to unblind the patient unless necessary. Prior to unblinding, the investigator will attempt to contact the clinical monitor. Any unblinding that occurs at the site must be documented and the Sponsor notified.

6.6 Storage Requirements

Blinded supplies: Clinical supplies should be kept in a secured location at room temperature (up to 25ºC). Do not refrigerate or freeze.

Spiriva® supplies:

Store at 25ºC (77°F). Brief storage between 59 and 86 °F (15 and 30 °C) is permitted. Do not expose the capsules to extreme temperatures or moisture. Avoid freezing. Do not store capsules in the HandiHaler device. Once the blister is opened, the capsule should be used immediately.

Foradil® supplies:

Prior to dispensing: Store in a refrigerator, 2°C-8°C (36°F-46°F). After dispensing to patient: Store at 20°C to 25°C (68°F to 77°F). Protect from heat and moisture. CAPSULES SHOULD ALWAYS BE STORED IN THE BLISTER AND ONLY REMOVED FROM THE BLISTER IMMEDIATELY BEFORE USE.

Ventolin® HFA supplies:

Store at room temperature, 59-77 °F (15-25 °C), with mouthpiece down. Do not use or store near heat or open flames. Exposure to temperatures above 120 °F (49 °C) may cause bursting. Never throw into a fire or incinerator.

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

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

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

Glycopyrrolate/Formoterol Fumarate (36/9.6 or 72/9.6 µg), Formoterol Fumarate (9.6 or 7.2 µg), Glycopyrrolate (36 µg) and placebo MDIs

Individual Glycopyrrolate/Formoterol Fumarate (36/9.6 or 72/9.6 µg), Formoterol Fumarate (9.6 or 7.2 µg), Glycopyrrolate (36 µg) and placebo MDIs will be packaged in a foil pouch and contained in an individual visit treatment box. Both the visit treatment box and the foil overwrap will have a label with a component ID number. Confirm that the identifier given by IWRS and the component ID number written on the label are the same. The foil overwrap is labeled with a two-part label. Write the patient 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's ready to use.

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.

The MDI must be primed in a separate room from the patient 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 patients, the MDIs are to be gently shaken (5-10 seconds) immediately before each actuation.

Each dose will consist of 2 puffs from the MDI. Patients will be dispensed the MDI and instructed to continue taking study medication twice daily, 2 puffs in the morning and 2 puffs in the evening approximately 12 hours apart, for 1 week at home. The MDI should be stored at room temperature by the patient, avoiding temperature extremes and storage in direct sunlight. See Appendix 4 for instructions on the administration of Glycopyrrolate/Formoterol Fumarate, Formoterol Fumarate, Glycopyrrolate and Placebo MDI

Foradil® Aerolizer® (Formoterol fumarate inhalation powder) 12 µg

Individual Foradil® Aerolizer® devices will be packaged in a foil overwrap contained in an individual visit treatment box. Both the visit treatment box and the foil overwrap will have a label with a component ID number. Confirm that the identifier given by IWRS and the component ID number written on the label are the same. The foil overwrap is labeled with a

two-part label. Write the patient 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.

For open-label formoterol fumarate inhalation powder, the bulk commercial blister packs will be stored refrigerated in a secured location within the clinic or pharmacy facilities. To ensure adequate time for equilibration (minimum 2 hours) to room temperature prior to administration, one foil pouch (containing 3 blister packs) should be kept in a secure location at room temperature. If a patient is randomized to Foradil® Aerolizer®, the equilibrated supplies will be dispensed and at an appropriate time following study drug administration, study staff will obtain new foil pouch (containing 4 blister packs) from the refrigerated bulk supplies. Retain new foil pouch at the site, stored at room temperature in a secured location for use with a subsequent patient.

Patients will take study medication twice daily for 1 week at home. Foradil® Aerolizer® should be stored at room temperature by the patient. See Appendix 5 for the manufacturer's instructions on the administration of Foradil® Aerolizer®.

Spiriva® Handihaler® (tiotropium bromide), 18 µg

Spiriva® Handihaler® device and 3 blister packs will be contained in an individual visit treatment box. Both the visit treatment box and the foil overwrap will have a label with a component ID number. Confirm that the identifier given by IWRS and the component ID number written on the label are the same. The foil overwrap is labeled with a two-part label. Write the patient 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.

Patients will be dispensed the Spiriva® Handihaler® and blister packs containing tiotropium bromide 18 µg capsules) to continue taking study medication once daily for 1 week at home. Spiriva® Handihaler® (tiotropium bromide 18 µg) should be stored at room temperature by the patient. See Appendix 6 for the manufacturer's instructions on the administration of Spiriva® Handihaler® (tiotropium bromide 18 µg).

Ventolin® HFA (albuterol sulfate inhalation aerosol), 108 µg

Bulk supplies of open-label Ventolin® HFA will be provided by the sponsor and stored in a secured location within the clinic or pharmacy facilities. Per the protocol patients will be dispensed Ventolin® HFA MDI to take as rescue medication between Visits 2 and 3, Visits 4 and 5, Visits 6 and 7 and Visits 8 and 9. Ventolin® HFA should be stored at room temperature by the patient. Ventolin® HFA should be primed per manufacturer's instructions prior to dispensing to patient. See Appendix 7 for the manufacturer's instructions on the administration of Ventolin® HFA. One Ventolin® HFA canister will be dispensed at visits 2 and returned at start of Visit 3. Study personnel will record number on the dose counter at the time of dispensing (following priming) and upon return.

This process is to be repeated on Visit 4 and 5, Visit 6 and 7, and Visit 8 and 9.

6.8 Standard Policies/Return of Clinical Supplies

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are to be dispensed only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor, the amount dispensed to and returned by the subjects/patients, and the amount remaining at the conclusion of the study. In accordance with Good Pharmacy Practices, gloves should always be worn by study personnel if directly handling tablets or capsules that are returned (i.e., when counting returns). The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned as directed by the Sponsor.

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

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

At the end of each treatment period (Day 7), patients will return to the clinic and study personnel will retrieve and account for all study drug dispensed for that treatment period. For each patient, all used study drug materials, including the foil pouch and the treatment visit box will be collected and placed in a plastic bag (Ziploc or similar type bag) and labeled with the patient number. Used patient supplies will be kept at room temperature in a secure and locked cabinet until returned to the sponsor 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 4. This table applies to both Part A and Part B of this study. Detailed schedules for pre- and post-dose procedures to be performed on Day 1 (Visits 2, 4, 6, and 8) and Day 7 (Visits 3, 5, 7, and 9) of each treatment period are provided in Table 5 and Table 6, respectively.

All assessments during Visits 2 through 9 will be conducted in the following order: tremor/dry mouth assessments, vital signs, ECGs, clinical laboratory assessments, and spirometry (IC, when conducted should be obtained prior to all other spirometry assessments).

7.1 Efficacy Assessments

Both forced expiratory spirometry for derivation of FEV_1, FVC and PEFR, and Slow Vital Capacity (SVC) maneuvers for IC determination will be assessed using a spirometer that meets or exceeds minimum performance recommendations of the ATS (See Appendix 1).

The volume accuracy of the spirometer is to be checked daily using a 3 L syringe across 3 flow ranges i.e., at <2 L/sec, 4-6 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 (Refer to Appendix 2, Spirometry Assessment Criteria).

On Day 1 of each treatment period (Visits 2, 4, 6, and 8), 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. **The baseline FEV_1 at Visits 4, 6, and 8 must be within ±15% of the baseline FEV_1 obtained at the Randomization Visit (Visit 2). If the test day FEV_1 is not within ± 15%, the visit may be rescheduled at the Investigators discretion (e.g., within one week), or the patient discontinued.** Following study drug administration, spirometry will be obtained at 15 and 30 minutes, and 1 and 2 hours post-dosing of study drug.

On Day 7 of each treatment period (Visits 3, 5, 7, and 9), spirometry will be conducted 60 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 1, 2, 4, 6, 8, 10, 11.5, and 12 hours post-dosing of study drug. Specifically, FEV_1, FVC and PEFR data will be analyzed for primary and secondary assessments.

On Day 1 of each treatment period (Visits 2, 4, 6, and 8), IC assessments will be obtained at 60 and 30 minutes prior to study drug and at 1 and 2 hours after study drug

On Day 7 of each treatment period (Visits 3, 5, 7, and 9), IC assessments will be obtained at 60 and 30 minutes prior to study drug and at 1, 2, 11.5, and 12 hours after study drug. IC assessments are to precede spirometry assessments.

All patients will be instructed on the performance of the IC maneuver. Subjects must be tested in the seated position wearing a nose clip with no air leaks between the mouth and mouthpiece. Subjects should be relaxed (shoulders down and relaxed) and asked to breathe regularly for several breaths until the end-expiratory lung volume (FRC) is stable (this usually requires at least five tidal maneuvers). They are then urged to take a deep breath to total lung capacity (TLC) with no hesitation. From at least three acceptable trials, the two largest IC measurements should agree within 5% or 100 mL, both of these IC values will be documented on the CRF. Change in peak IC is a secondary endpoint.

7.1.1 Pulmonary Function Tests

All pulmonary function tests including FEV_1, FVC, PEFR, SVC and IC as defined in ATS/ERS guidelines (Miller, 2005) 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 pulmonary function testing will receive identical, detailed training at the investigator meetings. All technicians are required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable pulmonary function tests (ATS criteria, Miller, 2005) prior to performing testing on study patients. 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 Therapeutics or designee for central data management.

Refer to Section 7.6 for specific FEV_1 criteria that prompt patients to be discontinued from the study.

7.2 Patient Diary

The study coordinator will be responsible for explaining to the patient the proper methods for completing the diary. The diary contains questions concerning actual time of dosing, rescue Ventolin® HFA use, and home peak flow measurements using a sponsor-provided home peak flow meter. Two types of diaries will be provided – one for use during Spiriva® (18 µg) study treatment and the other for use with all other treatments.

Beginning with the Screening Visit (Visit 1) and at Visits 2, 4, 6 and 8, the patient will be given a diary to be completed daily and returned at the next visit. The patient diary will not

be dispensed at Visits 3, 5, 7, 9 and 10. Before giving the diary to the patient, the study coordinator will be responsible for entering the patient's identification (baseline number [Visit 1] and allocation number [Visits 2, 4, 6, and 8]), and dates of the week(s) the diary is to be completed.

The diary should be completed on the designated dates prefilled by the study site personnel. Upon arriving at the site for Visit 2, 3, 5, 7 and 9, patients will return the diary provided at the previous visit. For example, patients returning for Visit 5 will return the diary given to them at Visit 4.

At or prior to Visit 2 only, patients must demonstrate acceptable use of the diary to be eligible for randomization. Diary data is considered acceptable if the requisite data is completed on at least 4 of 7 consecutive days. Patients who fail their first demonstration of proper diary use may at the investigator's discretion be retrained and Visit 2 rescheduled. Patients who fail to demonstrate proper diary use ≥2 times will be excluded from the study.

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 data 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 on the diary card in blue or black ink—**correction fluid or pencil should never be used**. The diary card is considered a source document and should be retained in the appropriate section of the patient binder*.

Furthermore, in conjunction with review of the diary, the patient will be prompted for missed doses of study medication and additional COPD medication. The patient should be instructed to record this information in the diary card. Missing data from >24 hours prior to the site visit should be left blank.

7.2.1 Rescue Ventolin® HFA Use

The patient will record the total number of "puffs" of rescue Ventolin® HFA used on a daily basis. The number of "puffs" of rescue Ventolin® HFA to be recorded is the number of actuations of the canister. For example, when rescue Ventolin® HFA is required and 2 actuations are inhaled, this should be recorded as 2 "puffs." In the event the patient requires 4 actuations this should be recorded as 4 "puffs." Patients requiring more than 8 puffs per day on 3 or more consecutive days with worsening symptoms should contact the site.

7.2.2 Home Peak Expiratory Flow Rate

The peak flow meter will be provided to all study patients for measurement of PEFR at home. Under supervision and with coaching from the site staff, the patient will be instructed to perform peak expiratory flow efforts using the peak flow meter at Visit 1.

The peak flow meter will be used by all patients for home measurements of AM and PM PEFR. At each study visit, the investigator will review the PEFR readings and any findings will be discussed with the patient and clinical relevance determined. Patients will bring their peak flow meter to the clinic at each visit.

On each day starting with Day 1 of each treatment, the patient will measure PEFR immediately before and 30 minutes after dosing with study medication. Note: The 30 minute post-dose PEFR on Day 1 should be obtained after spirometry assessments allowing enough time for the patient to recover from the pulmonary function test maneuvers. The patient will be instructed to forcefully exhale from total lung capacity 3 times into the peak flow meter and record the *highest value* on the diary card.

7.2.3 Medication Compliance

Time of dosing with study medication will be recorded in the patient diary for each day of treatment. Study medication compliance will be checked at all visits and any issues identified will be noted in the appropriate study files.

7.3 Safety Assessments

The safety assessments include ECGs, vital signs, physical examination findings, clinical laboratory tests, monitoring for paradoxical bronchospasm, assessment of symptoms of tremor, and dry mouth assessments, in addition to recording AEs and SAEs.

7.3.1 Medical/Surgical History and Physical Examination

Medical history will be taken at Screening (Visit 1) and updated at the Randomization Visit (Visit 2). A complete physical examination will be performed at Screening and the Final/Follow-up Visit (Visit 10). A complete physical examination will include the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system (including assessment of tremor pre-albuterol use). Weight, assessed in ordinary indoor clothing with shoes off, and height (Screening) will be recorded at the specified visits.

7.3.2 Vital Sign Measurements

Heart rate and systolic and diastolic blood pressure (‘vital signs’) will be assessed at each visit; assessments will be obtained after being supine for 5 minutes for the first 4 hours after study drug and thereafter measurements may be obtained in the supine or seated position. If in the opinion of the investigator a clinically significant vital sign change occurs, then the measurement will be repeated at medically appropriate intervals until the value returns to

within an acceptable range**.** Refer to Section 7.6 for specific criteria for heart rate and systolic and diastolic blood pressure readings that prompt patients to be discontinued from the study.

Systolic and diastolic blood pressures and heart rate will be obtained at the same times as indicated for spirometry (i.e., 60 and 30 minutes prior to study drug (all visits); 15 and 30 minutes, and 1 and 2 hours after study drug [Visits 2, 4, 6 and 8]; 15 and 30 minutes, and 1, 2, 4, 6, 8, 10, 11.5, and 12 hours after study drug on Day 7 of each treatment period [Visits 3, 5, 7 and 9]) Oral and/or tympanic temperature will be obtained at Screening and at pre-dose and 2 hours post-dose and will not be repeated at subsequent time points unless clinically indicated.

7.3.3 12-Lead Electrocardiogram (ECG)

An ECG will be obtained at Screening. On Day 1 of each treatment period (Visits 2, 4, 6, and 8), ECGs will be obtained between 1 to 2 hours and 30 minutes to 1 hour prior to study drug and at 15 and 30 minutes, and 1, and 2 hours after study drug. On Day 7 of each treatment period (Visits 3, 5, 7, and 9), ECGs will be obtained between 1 to 2 hours and 30 minutes to 1 hour prior to study drug and at 15 and 30 minutes, and 1, 2, 4, and 12 hours after study drug. Original ECGs with interval printouts and rhythm strip run at 25 mm/sec must be attached to the appropriate CRF.

If a >30 msec difference in QTcF (Fridericia's Formula) is observed between the two baseline ECGs, then the Investigator needs to make a determination as to the suitability of the patient to proceed. If the patient does proceed in the study, a third baseline ECG is to be obtained prior to dosing. In this case, all of the ECG's obtained on that test day will be over-read by a board certified cardiologist.

QT intervals and manually calculated QTcF intervals will be reviewed and checked for gross inaccuracies by the Investigator or designated ECG reviewer. If the calculated QTcF intervals are greater than 450 msec for males and 470 msec for females, and have increased by 30 msec or more over baseline value, it will be manually over-read by the Investigator or designated ECG reviewer. The ECG parameters that will be assessed include heart rate, RR interval, PR interval, QRS axis, QRS interval, and QT interval. If QTcF interval prolongation exceeding these limits is verified during treatment, the patient's medical background should be examined closely for risk factors that may have contributed to the event, including genotyping for hereditary long QT syndromes, if appropriate. Refer to Section 7.6 for specific criteria for QTcF (Fridericia's Formula) that prompt patients to be discontinued from the study.

Additional ECGs will be obtained if the patient's heart rate is less than 60 beats/minutes (bpm) and is more than 20 bpm below baseline or is greater than 100 bpm and is more than 20 bpm above the test day baseline value (where baseline is defined as the mean of the heart rate assessments obtained 60 and 30 minutes prior to study drug administration on the same test day).

Any sign of arrhythmia should be noted. During treatment, any indication of Torsade de Pointes, a polymorphic ventricular tachyarrhythmia that appears on the ECG as continuous twisting of the vector of the QRS complex around the isoelectric baseline, must be recorded as an AE and reported to the Pearl Therapeutics, Inc Medical Monitor.

The decision to continue the treatment of any patient with prolonged QT or QTcF interval must be discussed and agreed upon by the Investigator and the Pearl Therapeutics Medical Monitor. All such patients, including patients with cardiac arrhythmias, should be monitored closely. If appropriate, ECG monitoring should be performed until the QT and QTcF interval and waveform morphology have returned to normal. If the prolongation or abnormal rhythm persists, the Pearl Therapeutics, Inc Medical Monitor must be contacted.

7.3.4 AEs of Interest - Paradoxical Bronchospasm, Tremor and Dry Mouth

Paradoxical bronchospasm may occur following inhalation from either an MDI or DPI. Tremor is a known side effect following administration of a LABA and Dry Mouth is a known side effect following administration of a LAMA.

Monitoring for paradoxical bronchospasm will occur at every visit for the first 2 hours post-dose. In this study, paradoxical bronchospasm is defined as a reduction in FEV_1 of >20% from test day baseline (i.e., the mean FEV_1 values obtained 60 and 30 minutes prior to study drug administration) with associated symptoms of wheezing, shortness of breath, or cough. All AEs and SAEs will be recorded as appropriate.

Patients will be asked about symptoms of tremor (see Appendix 8 for Tremor Assessment Criteria) at baseline and at specified intervals (pre-dose and at 1 and 2 hours post-dose on Day 1 and on Day 7. On Day 7 if tremor persists at 2 hours post-dose additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day (see Table 5 and Table 6) and if present, the severity (mild, moderate, and severe, see Appendix 8 for Tremor Assessment Criteria) of tremor symptoms will be assessed. If tremor is not noted at 2 hours post study drug administration, further tremor assessments do not need to be collected. All reports of tremor exceeding baseline will be recorded as AEs.

Patients will be specifically asked about the presence of dry mouth at baseline and at specified intervals (pre-dose and at 1 and 2 hours post-dose on Day 1 and on Day 7. On Day 7 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 5 and Table 6) and 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 exceeding baseline will be recorded as AEs.

Instructions for Recording Dry Mouth and Tremor AE:

1) Investigator should assess patients for history of dry mouth and tremor at screening and prior to dosing at Visit 2 (Randomization). If yes, record dry mouth and/or tremor in the patient medical history.

2) If patient reports an event of dry mouth or tremor post-randomization capture as an AE if:

    a. Patient has a history of dry mouth or tremor at screening, and the event is considered a worsening of pre-existing tremor.

    b. Patient has no history of dry mouth or tremor at screening.

3) The investigator should follow all AEs of dry mouth or tremor to resolution. An AE of dry mouth or tremor is considered resolved when the patient reports the event has returned to baseline (absent or as described in medical history).

4) Duration is captured from onset (when first reported by patient) to resolution (when patient reports event has returned to baseline as described above).

7.3.5 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 of each treatment period (Visits 2, 4, 6, and 8), hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) 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-dosing on all patients (see Table 5).

On Day 7 of each treatment period (Visits 3, 5, 7 and 9), hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained within 60 minutes prior to dosing and at 4 hours post-dosing. In patients participating in PK sample collection, a BMP will be obtained at 30 minutes and 2 hours after dosing (see Table 6).

Serum pregnancy testing will be performed at Screening and at the Final Visit with Urine HCG testing occurring (for women of child-bearing potential only).

The following clinical laboratory parameters will be assessed:

Hematology	
Hemoglobin	Mean corpuscular hemoglobin (MCH)
Hematocrit	Mean corpuscular hemoglobin concentration (MCHC)
White Blood Cell count with differential	Mean corpuscular volume (MCV)
Red Blood Cell count	
Platelet Count	
Clinical Blood Chemistry	
Liver Enzyme and Other Function Tests	**Other Clinical Blood Chemistry**
Alanine aminotransferase (ALT)	Albumin
Aspartate aminotransferase (AST)	Blood urea nitrogen (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
	Urea

Other Tests:

Pregnancy test (women of child-bearing potential only): serum [human chorionic gonadotropin (HCG)] at Screening and Final Visit only and Urine HCG at all other visits

Creatinine clearance will be estimated by the central laboratory using a published formula.

[a] Parameters included in the Basic Metabolic Panel (BMP).

7.4 Pharmacokinetic Assessments

7.4.1 Plasma Collection and Plasma Sample Handling

Approximately 5 mL of whole blood will be collected by direct venipuncture or may be obtained from an indwelling intravenous cannula (per site SOP after review by Pearl Therapeutics Medical Monitor or designee) using a vacuum collection tube (for example Vacutainer plasma collection tube) containing EDTA tripotassium according to the Schedule

of Events (Table 4). After processing, the plasma for each sample is to be harvested, equally divided into two aliquots, and transferred into cryotubes appropriate for plasma. Aliquots are to be frozen at less than or equal to -20°C. Refer to Appendix 3 for Plasma Collection, Storage and Handling.

Samples are to be shipped frozen by overnight courier to the bioanalytical laboratory [redacted] for analysis. Plasma levels of formoterol will be determined using a validated High Performance Liquid Chromatography tandem Mass Spectrometry (LC/MS/MS) method. Refer to Appendix 3 for sample shipping details.

7.4.2 Pharmacokinetic Evaluations

Pharmacokinetics (PK) will be evaluated in approximately one-half of patients enrolled across Part A and B. Prior to study start, a subset of sites will be identified and designated for pharmacokinetic sample collection. At Visits 2, 4, 6 and 8 (Treatment Day 1) a pre-dose PK sample will be collected. At Visits 3, 5, 7, and 9 following chronic dosing (~ 1 week), pharmacokinetic sampling will be performed using the following blood sampling scheme: pre-dose (30 minutes before dosing), 2, 6, 20 minutes, and 1, 2, 4, 8, 10, and 12 hours post-dose.

7.5 Adverse Events Assessments

7.5.1 Performing Adverse Events Assessments

The Investigator is responsible for recording AEs observed during the study. In addition, certain AEs (as described in Section 7.5.7) are classified as "serious" and must be reported within one working day to Pearl Therapeutics or its designee (Sponsor).

In the case of serious adverse events, after discussing the details of the AE, the Investigator and the Medical Monitor may discontinue patients prematurely.

7.5.2 Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonization and the U.S. Code of Federal Regulations [21 CFR 312.32] and are included herein.

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.

Adverse events include, but are not limited to:

- Any symptom or condition not previously reported by the patient (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).

7.5.3 Pre-Randomization Adverse Events

Adverse events that occur between the time the patient signs the informed consent form for the study and the time when that patient is randomized will be summarized as medical history and not as a study adverse event unless the event meets the definition of an SAE as defined below.

7.5.4 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 patient to carry out usual activities or very marked discomfort; considered to be life-threatening; resulting in significant disability or incapacity; and requiring therapeutic intervention.

7.5.5 Relationship

The relationship of each adverse event 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.

7.5.6 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 BUN and creatinine in the setting of an adverse event 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)
- Other laboratory abnormality judged by the Investigator to be of any particular clinical concern (e.g., significant fall in hemoglobin not requiring transfusion)

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

7.5.7 Serious Adverse Events

A serious adverse event [serious adverse drug experience] is any adverse event [drug experience] that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect.

Significant medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event [serious adverse drug experience] when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Life-threatening is any adverse event [drug experience] that places the patient, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Unexpected adverse event means any adverse event [adverse drug experience], the specificity or severity of which is not consistent with the current Investigator's Brochure.

Reporting Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for prompt notification of SAEs to the Sponsor's Medical Monitor or designee.

All SAEs must be reported to Pearl Therapeutics no later than one working day after the Investigator recognizes/classifies the event as a serious adverse event. At a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report using the appropriate form (e.g., SAE Report Form). After the initial report, as necessary, the Investigator must provide any additional information on a serious adverse event to the Medical Monitor within two working days after he/she receives that information. This follow-up information will be a detailed written report that will include copies of hospital records, case reports, and autopsy reports, and other pertinent documents.

Post-study SAEs following the last dose of study drug must be reported to Pearl Therapeutics as described in Section 7.5.10.

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

7.5.8 Additional Adverse Events

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

7.5.9 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 patient is lost-to-follow-up.

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

7.5.10 Notification of Post-Study Serious Adverse Events

Investigators are not obligated to actively follow patients after the completion of the study. However, all post-study SAEs occurring up to 30 days following the last dose of study drug must be reported to Pearl Therapeutics, whether or not the event is attributable to study drug. In addition, if the Investigator becomes aware of a SAE beyond 30 days following the last dose of study drug, he/she should notify Pearl Therapeutics if such events are attributable to study drug. The notification to Pearl Therapeutics of a post-study SAE by the Investigator should occur within two working days of becoming aware of the SAE.

7.5.11 IRB/EC Notification of Serious Adverse Events

The Investigator is responsible for promptly notifying her/his IRB/EC of all SAEs, including any follow-up information, occurring at her/his site and any SAE regulatory report, including any follow-up reports that he/she receives from Pearl Therapeutics. Documentation of the submission to the IRB/EC must be retained for each safety report.

7.5.12 Health Authority Safety Reports

Pearl Therapeutics or its representatives will submit a safety report to the FDA and/or any other appropriate regulatory agencies, for any SAE that is unexpected and related to the study drug within the appropriate time frame. Pearl Therapeutics or its representatives will send copies of each safety report submitted to the FDA and/or other regulatory agencies to the

Investigators who are actively participating in Pearl Therapeutics-sponsored clinical studies. Safety reports must be submitted to the appropriate IRB/EC as soon as possible. Documentation of the submission to the IRB/EC must be retained for each safety report.

7.6 Reasons and Procedures for Early Termination

Patients 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.

A patient 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 >50 msec from test day baseline (QTc interval obtained from test day baseline ECGs corrected using Fridericia's correction formula) and QTcF >450 msec for males and >470 msec for females at any time after taking study drug.
- Heart rate 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 BP (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.
- FEV_1 decrease by more than 20% from test day baseline (before taking study drug) on two consecutive spirometry assessments obtained at least 15 minutes apart with associated symptoms of dyspnea at any time within the first 2-hour interval after taking study drug.

Other valid reasons for removing a patient from the study include:

- The patient does not adhere to study rules and procedures;
- The patient wishes to withdraw from the study;
- Continuation of the patient is in violation of the inclusion and exclusion criteria;
- The Investigator feels it is in the patient's best interest to terminate participation;
- The study is terminated by the Sponsor.

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

All patients 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 patients 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.

7.7 Termination of the Study

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

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

The study will be placed on hold and a safety board convened in the event of:

1. 4 or more deaths deemed to be cardiac or respiratory in origin by the end of Part A; or
2. 7 or more deaths from any cause by the end of Part A; or
3. 9 or more deaths from any cause by the end of Part B.

Stopping criteria based on deaths from any source were based on estimates of instantaneous rates of mortality taken from the TORCH (Calverley, 2007) and UPLIFT (Tashkin, 2008) studies. These criteria imply a 1% 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 4. Detailed schedules for pre- and post-dose procedures to be performed on Day 1 (Visits 2, 4, 6, and 8) and Day 7 (Visits 3, 5, 7, and 9) of each treatment period are provided in Table 5 and Table 6, respectively.

Table 4. Schedule of Events

Procedures	Screening[a]		Treatment Period 1[a]		Treatment Period 2[a]		Treatment Period 3[a]		Treatment Period 4[a]		Follow-Up/ Final
	Visit 1a	Visit 1b (optional)	Visit 2 Randomization (Rx 1, Day 1)	Visit 3 (Rx 1, Day 7)	Visit 4 (Rx 2, Day 1)	Visit 5 (Rx 2, Day 7)	Visit 6 (Rx 3, Day 1)	Visit 7 (Rx 3, Day 7)	Visit 8 (Rx 4, Day 1)	Visit 9 (Rx 4, Day 7)	Visit 10 Final Visit
Study Day[a]	**-28 to -7[a]**		**1[a]**	**7[a]**	**14[a]**	**21[a]**	**28[a]**	**35[a]**	**42[a]**	**49[a]**	**56[a]**
Informed Consent	X										
Eligibility Criteria	X	X	X								
Verify Continued Eligibility				X	X	X	X	X	X	X	
Reversibility to Albuterol[b]	X										
Demographics & Medical/Surgical History	X	X									
Concomitant Medications[c]	X	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[f]	X		X	X	X	X	X	X	X	X	X
12-Lead ECG[g]	X		X	X	X	X	X	X	X	X	X
Pregnancy Test[h]	X		X	X	X	X	X	X	X	X	X
Clinical laboratory testing[h]	X		X	X	X	X	X	X	X	X	X
Adjust COPD Medications per Protocol[i]	X									X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Inhalation Device Training	X		X		X		X		X		
Study Drug Administration[j]			X	X	X	X	X	X	X	X	
Dispense Patient Diary	X		X		X		X		X		
Collect/Review Patient Diary			X	X		X		X		X	
Study Drug Dispensing			X		X		X		X		
Study Drug Collection				X		X		X		X	
PK Blood Samples[k]			X	X	X	X	X	X	X	X	
Tremor, Dry Mouth & Paradoxical Bronchospasm	X		X	X	X	X	X	X	X	X	

See table footnotes on the following page.

Table 4. Schedule of Events (continued)

a. Screening period of at least 1 week and up to 4 weeks. Patients are to return to the clinic within 1 week following initiation of each treatment arm. If any patient exceeds 9 days of treatment for any treatment except open-label Foradil® Aerolizer® and Spiriva, the Sponsor should be notified and the patient may be withdrawn. There must also be at least 7 days (not to exceed 21 days) between Visits 3 and 4, between Visits 5 and 6, and between Visits 7 and 8 to allow for appropriate washout of study drug. The indicated Study Days are estimates calculated based on a 7-day treatment period and a 7-day washout period.

b. Assess reversibility of FEV_1 at 30 minutes following 4 puffs albuterol MDI (to characterize the patient population only; not to be used to determine eligibility to participate in the study).

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. See Table 5 for spirometry assessments and specific time points to be performed at Visits 2, 4, 6, and 8. See Table 6 for spirometry assessments and specific time points to be performed at Visits 3, 5, 7, and 9.

e. Includes evaluation of height and weight at Screening.

f. All vital signs will be obtained at Screening. SBP, DBP and HR will be obtained in the supine position at all time points preceding and including the 4 hours time point post-dose. SBP, DBP and HR measurements obtained after the first 4 hours post-dose may be obtained in either the supine or the seated position. See Table 5 for SBP, DBP, and HR assessments and specific time points to be performed at Visits 2, 4, 6, and 8. See Table 6 for SBP, DBP, and HR assessments and specific time points to be performed at Visits 3, 5, 7, and 9. At Visits 2-9, oral temperature will be obtained at pre-dose and 2 hours post-dose and will not be repeated at subsequent time points unless clinically indicated.

g. An ECG will be conducted at Screening. See Table 5 for ECG assessments and specific time points to be performed at Visits 2, 4, 6, and 8. See Table 6 for ECG assessments and specific time points to be performed at Visits 3, 5, 7, and 9.

h. All clinical laboratory tests will be obtained at Screening and Follow-up. At Visits 2 through 9, hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel) will be obtained within 60 minutes prior to dosing. At Visits 2, 4, 6, and 8 (Treatment Day 1), BMP with focus on potassium and glucose parameters will be obtained at 2 hour post-dose on all patients (see Table 5). On Treatment Day 7 (Visits 3, 5, 7, and 9), BMP with focus on potassium and glucose parameters will be obtained at 30 minutes and 2 hour post-dose only in patients participating in PK sample collection (see Table 6). An additional assessment of all laboratory parameters will performed at 4 hours post-dose at Visits 3, 5, 7, and 9 (see Table 6). Pregnancy test (women of child-bearing potential only): serum [human chorionic gonadotropin (HCG)] at Screening and Final Visit only and Urine HCG at all other visits

i. At screening, stop prohibited COPD medications and change COPD medications as specified in protocol Section 5.4 (i.e., short-acting bronchodilators with or without ICS). At the end of the Visit 9, return patient to pre-study or other appropriate inhaled maintenance COPD medications.

j. Foradil study medication must be removed from the refrigerator and allowed to equilibrate to room temperature for at least 2 hours. See Section 6.7 for additional instructions.

k. Pharmacokinetics (PK) will be evaluated in approximately one-half of patients enrolled (i.e., approximately 42 patients). Prior to study start at subset of sites will be identified and designated for pharmacokinetic sample collection. Only a pre-dose PK sample will be collected at Visits 2, 4, 6 & 8 (see Table 5). See Table 6 for PK sample collection times at Visits 3, 5, 7, and 9.

Table 5. Visit Procedures on Day 1 of Each Treatment Period (Visits 2, 4, 6, and 8)

	Pre-dosing		Post-dosing			
Clinical Variable[a]	**-1 hour**	**-30 minutes**	**15 minutes**	**30 minutes**	**1 hour**	**2 hours**
Dry Mouth, Tremor Assessments & Paradoxical Bronchospasm		X	X	X	X	X[b]
Vital Signs[c]	X	X	X	X	X	X
12- Lead ECG	X[d]	X[d]	X	X	X	X
PK Sampling[e]		X				
Clinical Laboratory Testing[f]	X[f]					X[f]
Spirometry (FEV_1, FVC, PEFR)[g]	X	X	X	X	X	X
Inspiratory Capacity	X	X			X	X
Peak Flow Meter Assessment[h]		X		X		

a. Safety assessments (tremor assessments, vital signs, ECG, and PK sampling) should be started approximately 5 - 10 minutes ahead of the specified time point to ensure that spirometry for FEV_1, FVC and PEFR determination will be conducted as close to the specified time points 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 post study drug administration; ± 15 minutes of specified time point for assessments obtained thereafter).

b. If dry mouth and/or tremor are not noted at the 2-hour time point, no further assessment is required. If dry mouth and/or tremor persist at 2 hours additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day.

c. Oral and/or tympanic temperature will be obtained pre-dose and 2 hours post-dose; no further temperature assessments required unless clinically indicated.

d. Two Baseline ECGs should be conducted, one between 60 to 120 minutes and another between 30 to 60 minutes prior to dosing. If >30 ms difference in QTcF observed between the two baseline ECGs then the Investigator will make a determination as to the suitability of the patient to proceed. If the patient does proceed in the study, a third baseline ECG is to be obtained prior to dosing. In this case, all ECG's will be over-read by a board certified cardiologist.

e. Pharmacokinetics (PK) will be evaluated in approximately one-half of patients enrolled (i.e., approximately 42 patients). Prior to study start, a subset of sites will be identified and designated for pharmacokinetic sample collection. Only a pre-dose PK sample will be collected at Visits 2, 4, 6 & 8 (Rx Day 1).

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 **on all patients**.

g. The baseline FEV_1 on each test day must be within ±15% of the baseline FEV_1 obtained at the Randomization Visit (Visit 2). If the test day FEV_1 is not within ± 15%, the visit may be rescheduled at the Investigators discretion (e.g., within one week), or the patient discontinued.

h. The 30 minute post-dose PEFR on Day 1 should be obtained after spirometry assessments allowing enough time for the patient to recover from the pulmonary function test maneuvers.

Note: Where data collection time-points are concurrent, variables must be collected in the following order: Tremor assessment, vital signs, ECG, clinical laboratory assessments, PK blood samples and spirometry (IC when conducted, should be done prior to all other spirometry assessments).

Table 6. Visit Procedures on Day 7 of Each Treatment Period (Visits 3, 5, 7, and 9)

	Pre-dosing		Post-dosing												
Clinical Variable[a]	**-1 hr**	**-30 min**	**2 min**	**6 min**	**15 min**	**20 min**	**30 min**	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**11.5 hr**	**12 hr**
Dry Mouth, Tremor Assessments & Paradoxical Bronchospasm		X[b]			X		X	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Vital Signs[c]	X	X			X		X	X	X	X	X	X	X	X	X
12- Lead ECG	X[d]	X[d]			X		X	X	X	X					X
PK Sampling[e]		X	X	X		X		X	X	X		X	X		X
Clinical Laboratory Testing[f]	X[f]						X[f]		X[f]	X[f]					
Spirometry (FEV_1, FVC, PEFR)	X	X			X		X	X	X	X	X	X	X	X	X
Inspiratory Capacity	X	X						X	X					X	X
Peak Flow Meter Assessment[g]		X					X								

a. Safety assessments (tremor assessments, vital signs, ECG, and PK sampling) should be started approximately 5 - 10 minutes ahead of the specified time point to ensure that spirometry for FEV_1, FVC and PEFR determination will be conducted as close to the specified time points 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 post study drug administration; ± 15 minutes of specified time point for assessments obtained thereafter).

b. If dry mouth and/or tremor are not noted at the 2-hour time point, no further assessment is required. If dry mouth and/or tremor persist at 2 hours additional assessments will be conducted every 2 hours until resolution of symptoms or completion of the test day.

c. Oral and/or tympanic temperature will be obtained pre-dose and 2 hours post-dose; no further temperature assessments required unless clinically indicated.

d. Two Baseline ECGs should be conducted, one between 60 to 120 minutes and another between 30 to 60 minutes prior to dosing. If >30 ms difference in QTcF observed between the two baseline ECGs then the Investigator will make a determination as to the suitability of the patient to proceed. If the patient does proceed in the study, a third baseline ECG is to be obtained prior to dosing. In this case, all ECG's will be over-read by a board certified cardiologist.

e. Pharmacokinetics (PK) will be evaluated in approximately one-half of patients enrolled (i.e., approximately 42 patients). Prior to study start, a subset of sites will be identified and designated for pharmacokinetic sample collection.

f. All clinical laboratory parameters will be obtained within 60 minutes prior to study drug administration and at 4 hours after study drug. BMP with focus on potassium and glucose parameters will be obtained at 30 minutes and 2 hour post-dose **only in patients participating in PK sample collection.**

g. The 30 minute post-dose PEFR on Day 1 should be obtained after spirometry assessments allowing enough time for the patient to recover from the pulmonary function test maneuvers

Note: Where data collection time-points are concurrent, variables must be collected in the following order: Tremor assessment, vital signs, ECG, clinical laboratory assessments, PK blood samples and spirometry (IC when conducted, should be done prior to all other spirometry assessments).

8.1 Screening Visit (Visit 1a-1b)

- Obtain informed consent.
- Check inclusion/exclusion criteria.
- Obtain demographic data, including age, race, smoking history, medical/surgical history including tremor, dry mouth, glaucoma and age of onset of COPD.
- Obtain medication history, including COPD medications.
- Conduct a serum pregnancy test for all female patients unless it is documented in the medical history that the patient 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 [including assessment of tremor pre-albuterol use]).
- Obtain height, weight, and vital signs (heart rate and blood pressure after being supine for 5 minutes, and oral temperature).
- Obtain a 12-lead ECG.
- Conduct baseline spirometry assessments.
- Administer 4 puffs albuterol:
    - Confirm patient's ability to use MDI correctly (provide coaching as needed).
    - Repeat spirometry assessments 30 minutes following 4 puffs albuterol (to characterize the patient population only; not to be used to determine eligibility to participate in the study).

If patient still meets inclusion/exclusion criteria perform the following:

- Obtain laboratory samples (hematology and chemistry).
- Complete an eye examination for glaucoma if not performed within the last 2 years (New Zealand Sites Only).
- Complete Chest X-ray or CT scan if not performed within the last 6 months.
- Stop prohibited COPD medications and change concurrent COPD medications as specified in protocol (see Section 5.4).

- Arrange date of Visit 1b or Visit 2 as appropriate.
- Complete Screening Log (basic demographics, spirometry, medications and reasons for screen failure) for patients who do not meet eligibility criteria.
- Adverse events must be recorded during the screening period, that is, from the time of consent to the start of study treatment.
- Dispense patient diary, peak flow meter and provide instructions on use of peak flow meter and diary completion.

8.2 Randomization Visit (Visit 2; Rx 1, Day 1)

- Review inclusion/exclusion criteria to confirm protocol eligibility.
- Obtain patient treatment assignment information from IWRS.
- Collect and review patient diary (if diary is not completed, re-train patient and Visit 2 must be rescheduled).
- Review of clinical laboratory results from Visit 1. Please note whether the results are clinically significant and include comments where applicable.
- Record adverse events (if any).
- Review concomitant medications to ensure adherence to COPD regimen.
- Note time of last dose of short-acting bronchodilator and other COPD medications on the CRF (if <6 hours, Visit 2 must be rescheduled).
- Perform urine pregnancy test (women of child-bearing potential only).
- Perform all pre-dose assessments (refer to Table 5).
- At 15-30 minutes prior to dosing, the seal around the study day treatment box is to be opened and the instructions for administration of study drug on the inner flap of the study day treatment box are to be followed.
- The patient is to be considered randomized and will contribute to the intent-to-treat (ITT) population after receiving study medication.
- 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.

- Patient will administer first dose of newly assigned study drug at the clinic. Perform all post-dosing assessments (refer to Table 5).
- Schedule Visit 3 and ensure patient has adequate supply of study drug and rescue Ventolin HFA.
- Dispense patient diary and provide instructions on use of peak flow meter and diary completion if appropriate.

8.3 Visit 3 (Rx 1, Day 7)

- Confirm eligibility to continue.
- Record adverse events (if any).
- Collect and review patient diary.
- Review concomitant medications and ensure adherence to COPD regimen.
- Note time of last dose of short-acting bronchodilator and other COPD medications on CRF (if <6 hours, reschedule visit).
- Perform urine pregnancy test (women of child-bearing potential only).
- Perform all pre-dose assessments (refer to Table 6).
- Patient will administer final dose of previously dispensed study drug at the clinic under supervision.
- Perform all post-dosing assessments (refer to Table 6).
- Collect previously dispensed study drug.
- Schedule next visit (following a washout period of at least 1 week but no longer than 3 weeks) and ensure patient has adequate supply of COPD medication.

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

- Confirm eligibility to continue.
- Obtain patient treatment assignment information from IWRS.
- Record adverse events (if any).
- Review concomitant medications and ensure adherence to COPD regimen.

- Note time of last dose of short-acting bronchodilator and other COPD medications on CRF (if <6 hours, reschedule visit).
- Perform urine pregnancy test (women of child-bearing potential only).
- Perform all pre-dose assessments (refer to Table 5).
- At 15-30 minutes prior to dosing, the seal around the study day treatment box is to be opened and the instructions for administration of study drug on the inner flap of the study day treatment box are to be 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.
- Patient will administer first dose of newly assigned study drug at the clinic.
- Perform all post-dosing assessments (refer to Table 5).
- Schedule next visit and ensure patient has adequate supply of study drug and rescue Ventolin® HFA.
- Dispense patient diary and provide instructions on use of peak flow meter and diary completion if appropriate.

8.5 Visits 5, 7, and 9 (Day 7 of Rx 2, Rx 3, and Rx 4)

- Confirm eligibility to continue.
- Record adverse events (if any).
- Collect and review patient diary.
- Review concomitant medications and ensure adherence to COPD regimen.
- Note time of last dose of short-acting bronchodilator and other COPD medications on CRF (if <6 hours, reschedule visit).
- Perform urine pregnancy test (women of child-bearing potential only).
- Perform all pre-dose assessments (refer to Table 6).
- Patient will administer final dose of previously dispensed study drug at the clinic.
- Perform all post-dosing assessments (refer to Table 6).

- Collect previously dispensed study drug.
- **At Visit 5 and 7 only**: Schedule next visit (following a washout period of at least 1 week but no longer than 3 weeks) and ensure patient has adequate supply of COPD medications.
- **At Visit 9 only**: Schedule the final/follow-up visit at least 1 week but no longer than 2 weeks from Visit 9.

8.6 Follow-Up (Final) Visit/Premature Discontinuation (Visit 10)

- Record adverse events (if any).
- Review concomitant medications
- Conduct a physical examination, including vital signs.
- Perform ECG and collect blood samples for hematology and chemistry.
- Collect a blood sample for pregnancy test for women of child bearing potential.
- Inform patient about reporting all SAEs up to 30 days following the last dose of study drug.
- Return patient to pre-study or appropriate inhaled maintenance COPD medications.
- Complete study completion page.

8.7 Completion of the Study

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

- Patient discretion (document reason)
- Investigator considers it to be in the best interest of the patient
- Intolerable adverse events(s)
- Administrative reasons (e.g., early termination of the study)
- Patient lost-to-follow-up
- Major protocol violation (with approval by the Sponsor)
- Death

- QTc prolongation, heart rate, systolic or diastolic blood pressure, or FEV_1 changes (see Section 7.6)
- Completion of the study.

9 QUALITY CONTROL AND ASSURANCE

9.1 Source Documentation

All data obtained in this study are source data. The clinical site study staff members will record the data on source documents immediately, except for data that are available on original printouts or as data files. If printouts are available, each copy of the printouts will be attached to the patient's CRF.

All clinical work conducted under this protocol will be conducted according to GCP. This includes an inspection by the Sponsor and/or health authority representatives at any time. The Investigator will agree to the inspection of study-related records by health authority representatives and/or the Sponsor.

Representatives of Pearl Therapeutics (or designee) will periodically review source documents (e.g., hospital records, office records, etc.) and will perform source data verification of all data captured in the CRFs as outlined in the data management plan for this study.

9.2 Data Entry in Database

All protocol specified data documented on CRFs will be entered into a clinical database. Data captured in an electronic format will be compiled and reconciled with CRF data, as applicable.

All spirometry tracings will be over-read by qualified personnel and data entered into the database as defined in the protocol specific over-read SOP.

9.3 Check of Queries

The raw data will be checked by appropriate programs for consistency and plausibility according to previously defined study edit checks documented in a data management plan. Data Clarification Forms will be provided to the Investigator or appropriate clinical site study staff for clarification.

9.4 Coding of Adverse Events, Drugs, and Diseases

After data entry, the AEs and medical history diseases will be coded according to the MedDRA dictionary. Concomitant medications will be coded according to the World Health Organization Drug Reference List.

9.5 Study Language & Translations

The primary study materials (protocol, correspondence, study report) will be prepared in English. However, where the first language of the study personnel, or others involved in the study (such as Ethics Committees) is not English, appropriate arrangements will be made to

have translations of the documents in the local language. The patients' ICF, if changed, will then be translated back into English to allow the Sponsor and English speaking regulatory agency staff to ensure that the ICF meets the applicable standards.

Additional documents may need to be translated into English (e.g., transcripts of necessary additional hospital tests that may occur), and others (e.g., new safety information) may need to be translated into the local language. The Sponsor, or designee (e.g., CRO), will make arrangements for such translations to occur promptly.

10 PLANNED STATISTICAL METHODS

10.1 Introduction

This study will be undertaken in two Parts: Part A and Part B. Part A will be completed before Part B, but the analysis of data from Part A will make use of data from Part B. Similarly, the analysis of data from Part B will also make use of data from Part A. Despite the distinct parts, this study is not adaptive. Progression to Part B is not dependent on the results from Part A, and the treatments administered in Part B will not be affected by the results of Part A.

Part A will be conducted as a 4-period, 8-treatment, incomplete block cross-over design evaluating the following 8 treatments in approximately 48 patients:

- Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg ex-actuator twice daily
- Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg ex-actuator twice daily
- Glycopyrrolate MDI 36 µg ex-actuator twice daily
- Formoterol Fumarate MDI 9.6 µg ex-actuator twice daily
- Formoterol Fumarate MDI 7.2 µg ex-actuator twice daily
- Placebo MDI twice daily
- Foradil® Aerolizer® 12 µg twice daily
- Spiriva® Handihaler® 18 µg (Tiotropium) once daily

The objective of Part A is to investigate the efficacy and pharmacokinetics of two doses of Glycopyrrolate/Formoterol Fumarate MDI (72/9.6 µg and 36/9.6 µg ex-actuator) administered in a fixed combination. The primary efficacy objective is to assess the improvement in FEV_1 AUC_{0-12} of Glycopyrrolate/Formoterol Fumarate MDI (72/9.6 µg ex-actuator) administered in a fixed combination compared with administration of Formoterol Fumarate MDI (9.6 µg ex-actuator) and Glycopyrrolate MDI (36 µg ex-actuator) as single agents. Superiority to both components must be demonstrated in order to satisfy the primary objective of this part of the study.

The Pharmacokinetic evaluation of Part A is of equal importance. It is necessary to establish whether or not Glycopyrrolate/Formoterol Fumarate MDI, delivered as a fixed combination, at 36/9.6 µg or 72/9.6 µg results in a higher systemic exposure to Formoterol Fumarate than Foradil® Aerolizer® 12 µg twice daily.

No sequence will have a Glycopyrrolate component in more than 2 treatment periods regardless of whether given as fixed combination or as a single agent (e.g., a sequence can have no more than 2 of the following glycopyrrolate treatment possibilities: Glycopyrrolate/Formoterol Fumarate 36/9.6 µg, Glycopyrrolate/Formoterol Fumarate 72/9.6 µg and Glycopyrrolate 36 µg). In addition, no sequence will have a Formoterol Fumarate MDI component in more than 2 treatment periods regardless of whether given as fixed

combination or as a single agent (e.g., a sequence can have no more than 2 of the following Formoterol Fumarate treatment possibilities: Glycopyrrolate/Formoterol Fumarate 36/9.6 µg, Glycopyrrolate/Formoterol Fumarate 72/9.6 µg, Formoterol Fumarate 7.2 µg and Formoterol Fumarate 9.6 µg).

Of the 70 possible choices of 4 treatments from 8, only 50 do not violate this constraint. The treatment selections in Part A are a subset of 6 of these 50 selections, chosen to provide higher power for comparisons associated with the primary efficacy objectives, and important secondary objectives. Those selections are shown in Table 7. Each of the selections is replicated 8 times.

Table 7. Treatment Selections for Part A

Selection	*Treatments*			
1	GP MDI 36 µg	GP/FF MDI 36/9.6 µg	Spiriva® 18 µg	FF MDI 9.6 µg
2	GP MDI 36 µg	GP/FF MDI 36/9.6 µg	Spiriva® 18 µg	FF MDI 7.2 µg
3	GP/FF MDI 72/9.6 µg	GP MDI 36 µg	Spiriva® 18 µg	FF MDI 7.2 µg
4	GP/FF MDI 72/9.6 µg	GP MDI 36 µg	Spiriva® 18 µg	FF MDI 9.6 µg
5	GP/FF MDI 72/9.6 µg	GP/FF MDI 36/9.6 µg	Spiriva® 18 µg	Foradil® 12 µg
6	GP/FF MDI 72/9.6 µg	GP/FF MDI 36/9.6 µg	Spiriva® 18 µg	Placebo MDI

FF MDI=Formoterol Fumarate MDI; GP MDI=Glycopyrrolate MDI; GP/FF MDI= Glycopyrrolate/Formoterol Fumarate MDI.

Part B will be conducted as a 4-period, 4-treatment complete block crossover design in 36 patients. The treatments administered to each patient will be:

- Formoterol Fumarate MDI 9.6 µg ex-actuator twice daily
- Formoterol Fumarate MDI 7.2 µg ex-actuator twice daily
- Placebo MDI twice daily
- Foradil® Aerolizer® 12 µg twice daily

The objective of Part B is to investigate the efficacy of Formoterol Fumarate MDI at two doses (7.2 and 9.6 µg ex-actuator). The primary objective is to establish whether or not Formoterol Fumarate MDI administered twice daily at 9.6 µg ex-actuator is superior to placebo.

Following Part B, the replication for each treatment is shown in Table 8.

Table 8. Replication of Each Treatment

Treatment	*Replication*
GP MDI 36 µg	32
GP/FF MDI 72/9.6 µg	32
FF MDI 7.2 µg	52
GP/FF MDI 36/9.6 µg	32
FF MDI 9.6 µg	52
Spiriva® 18 µg	48
Foradil® 12µg	44
Placebo MDI	44

FF MDI=Formoterol Fumarate MDI; GP MDI=Glycopyrrolate MDI;
GP/FF MDI= Glycopyrrolate/Formoterol Fumarate MDI.

10.2 Protocol Variables

The safety, efficacy and pharmacokinetic endpoints are identical for Parts A and B (although, of course, the treatment comparisons using these endpoints differ).

10.2.1 Efficacy Endpoints

All efficacy assessments are relative to baseline, and will be compared with individual agents and/or placebo where appropriate. Baseline is defined as the average of pre-dose values obtained prior to dosing with study medication at randomization (Visit 2).

10.2.1.1 Primary Efficacy Endpoint

Primary Efficacy Endpoint Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing)

- Forced expiratory volume in 1 second (FEV_1) AUC_{0-12} relative to baseline following chronic dosing (1 week) with each treatment administered.

10.2.1.2 Secondary Efficacy Endpoints

Secondary Endpoints Evaluated on Treatment Day 1 (Visits 2, 4, 6 and 8):

- Peak FEV_1 (defined as peak improvement in FEV_1)
- Time to onset of action (≥10% improvement in mean FEV_1)
- Proportion of patients achieving ≥ 12% improvement in FEV_1.
- Peak improvement in Inspiratory Capacity (IC) (mean of 1 and 2 hour post-dose)

Secondary Endpoints Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing):

- Improvement in morning pre-dose FEV_1
- Peak FEV_1 (defined as peak improvement in FEV_1)
- Peak improvement in IC (mean of 1 and 2 hours post-dose)
- Trough FEV_1 (trough FEV_1 is defined as the mean of the FEV_1 assessments taken at 11.5 and 12 hours post-dose)
- Mean daily peak flow readings taken by patients and recorded in patient diaries, during each treatment sequence.

10.2.1.3 Exploratory Endpoints Evaluated on Treatment Day 1 (Visits 2, 4, 6 and 8)

- Creatinine clearance (relative to Visit 2 pre-dose)

10.2.1.4 Exploratory Endpoints Evaluated on Treatment Day 7 (Visits 3, 5, 7 and 9, following chronic dosing)

- Peak expiratory flow rate (PEFR)
- Forced vital capacity (FVC)
- Trough IC (mean of 11.5 and 12 hours post-dose assessments)
- Mean number of puffs of rescue medication recorded in patient diaries, during each treatment sequence
- Creatinine clearance (relative to Visit 2 pre-dose)

10.2.2 Pharmacokinetic Endpoints

The pharmacokinetic endpoints for this study are as follows:

AUC_{0-12}	Area under the whole blood or plasma concentration versus time curve from time 0 to 12 hours post-dose where time 0 is the pre-dose measurement
$AUC_{0-tlast}$	Area under the whole blood or plasma concentration versus time curve from time 0 to time of last quantifiable concentration, where time 0 is the pre-dose measurement
AUC_{0-inf}	Area under the whole blood or plasma concentration versus time curve from time 0 to infinity, where time 0 is the pre-dose measurement
C_{max}	Maximum whole blood or plasma concentration
T_{max}	Time to C_{max}
$t_{1/2}$	Apparent terminal elimination half-life

k_e	The terminal elimination rate
CL/F	Apparent systemic clearance after oral administration
Vz/F	Apparent volume of distribution during the terminal phase after oral administration.

The terminal elimination rate constant (k_e), the apparent terminal elimination half-life ($t_{1/2}$) and the area under the plasma concentration versus time curve from time 0 to infinity (AUC_{0-inf}) will be calculated if the data permit.

10.2.3 Exploratory Pharmacodynamic Endpoints

The major objective of these analyses will be to define an optimal therapeutic ratio based on outcomes from pharmacodynamic (FEV_1)/pharmacokinetic (AUC or C_{max}) determinants.

Details will be defined prospectively in a separate Statistical Analysis Plan.

10.2.4 Safety Endpoints

The safety endpoints for this study include:

1. **Adverse Events:** The safety measurements include both the numbers of adverse events as observed by the investigational team or reported by the patient, and the numbers of patients experiencing adverse events. Adverse events will be collected from the time of study enrolment at Screening, that is, once informed consent is obtained until the time of study termination or exit. Adverse events will be characterized by severity and relationship to study drug.
2. **Paradoxical Bronchospasm, Dry Mouth and Tremor** will be regarded as adverse events of special significance, and tabulated separately.
3. **12 Lead ECG:** Change from baseline heart rate, RR interval, PR interval, QRS axis, QRS interval, QT intervals and QTcF (Fridericia Corrected QT) intervals, where baseline is defined as the average of the values prior to dosing at the start of each treatment sequence.
4. **Concomitant Medications:** All medications (including complementary medicines and other health supplements) that were used to treat acute or chronic conditions will be recorded at screening (Visit 1).
5. **Clinical Laboratory Testing:** Full clinical laboratory testing at every visit including hematology and clinical chemistry, characterized by change from baseline, where the baseline is defined as the value prior to dosing at the start of each treatment sequence.
6. **Vital Sign Measurements:** Change from baseline values where baseline is defined as the average of the values prior to dosing at the start of each treatment sequence.

10.3 Analysis for Part A

There will be a first stage data base lock on completion of Part A. Following that lock, statistical analysis of certain of efficacy comparisons will be undertaken. Other comparisons will be deferred until final data base lock on completion of Part B. No comparison will be repeated; that is none of the comparisons scheduled to be performed at completion of Part A will be repeated at completion of Part B, and none of the comparisons undertaken on completion of Part B will also be performed on completion of Part A. The statistical comparisons scheduled for completion of Part A, and those scheduled for completion of Part B are described below. Only those comparisons that have essentially full information will be performed at completion of Part A.

Since no comparison is repeated, and since the scheduling of comparisons is defined *a priori,* no group sequential adjustments to p values are required.

10.3.1 Primary Efficacy Analysis

The primary efficacy analysis will involve two a priori comparisons between treatments for the primary endpoint: FEV_1 $AUC_{0\text{-}12}$:

1. Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg vs. Glycopyrrolate MDI 36 µg[1]

2. Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg vs. Formoterol Fumarate MDI 9.6 µg.

At the completion of Part A the proportion of total information available[2] for Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg vs. Glycopyrrolate MDI 36 µg will be 98.3%. This comparison will therefore be analyzed *only* at the end of Part A and not re-analyzed at the end of Part B. The analysis of this comparison is therefore **not** sequential. It will be conducted with a significance level of 0.05.

At the completion of Part A the proportion of total information available[2] for Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg vs. Formoterol Fumarate MDI 9.6 µg will be 57.1%, and analysis of this comparison will be deferred until completion of Part B.

These comparisons will be achieved with a linear mixed effects model, including fixed effect terms for treatment and period. Point and interval estimates will be obtained using the REML algorithm (Patterson and Thompson, 1971), under three models for the within subjects covariance matrix: unstructured (for period), compound symmetry and first order autoregressive (Pinheiro and Bates, 2000). The covariance model yielding the smallest value

[1] We note the concentration of Glycopyrrolate in the Glycopyrrolate/Formoterol Fumarate fixed combination is twice that in the Glycopyrrolate alone treatment. This is because of the reduced bioavailability of .Glycopyrrolate in fixed combination.
[2] That is. the Fisher information for the contrast at the end of Phase A divided by the Fisher information at the end of Phase B.

of Akaike's information criterion (Akaike, 1974) will be selected for tabulation. Testing for unequal carryover effects will be performed.

Two-sided 95% confidence intervals will be tabulated.

Efficacy claims will only be advanced if **both** these primary comparisons are statistically significant.

10.3.2 Secondary Efficacy Analysis

Secondary efficacy analyses will involve the primary efficacy comparisons applied to secondary efficacy endpoints (*vide supra*) except time to onset of effect, and secondary efficacy comparisons applied to all efficacy endpoints except time to onset of effect.

Secondary efficacy comparisons for Part A are:

1. Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg vs. open-label tiotropium bromide 18 µg (Spiriva® Handihaler®). On completion of Part A more than 99% of the information[3] will be available for this comparison. The comparison will be performed on completion of Part A, and not repeated on completion of Part B;

2. Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg vs. open-label tiotropium bromide 18 µg (Spiriva® Handihaler®). On completion of Part A more than 99% of the information[3] will be available for this comparison. The comparison will be performed on completion of Part A, and not repeated on completion of Part B;

3. Glycopyrrolate vs. open-label tiotropium bromide 18 µg (Spiriva® Handihaler®). On completion of Part A more than 99% of the information[3] will be available for this comparison. The comparison will be performed on completion of Part A, and not repeated on completion of Part B;

4. Non-inferiority of Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg vs. Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg. On completion of Part A more than 99% of the information[3] will be available for this comparison. The comparison will be performed on completion of Part A, and not repeated on completion of Part B;

5. Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg vs. Formoterol Fumarate MDI 7.2 µg . On completion of Part A, only 57% of the information[3] will be available for this comparison. Statistical analysis will be deferred until completion of Part B.

[3] As defined by the ratio of Fisher's information for the comparison on completion of Part A to Fisher's information on completion of Part B

6. Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg vs. open-label Foradil® Aerolizer® (12 µg). On completion of Part A, only 38% of the information[3] will be available for this comparison. Statistical analysis will be deferred until completion of Part B.

7. Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg vs. open-label Foradil® Aerolizer® (12 µg). On completion of Part A, only 38% of the information[3] will be available for this comparison. Statistical analysis will be deferred until completion of Part B.

8. Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg vs. Formoterol Fumarate MDI 7.2 µg . On completion of Part A, only 57% of the information[3] will be available for this comparison. Statistical analysis will be deferred until completion of Part B.

9. Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg vs. Formoterol Fumarate MDI 9.6 µg . On completion of Part A, only 57% of the information[3] will be available for this comparison. Statistical analysis will be deferred until completion of Part B.

10. Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg vs. Glycopyrrolate. On completion of Part A, only 98% of the information[3] will be available for this comparison. This comparison will be performed at the end of Part A.

These secondary comparisons include non-inferiority comparisons. For all non-inferiority comparisons the margin will be 0.1L. This margin has been selected because a change in pre-dose FEV_1 of approximately 0.1L can be perceived by patients, correlates with fewer relapses following exacerbations, and correlates with two year decline in lung function (Donohue, 2005).

The statistical model, and tabulations will be exactly as for the primary objectives, except that no tests for unequal carryover effects will be performed.

10.3.3 Primary Pharmacokinetic Analysis

The primary pharmacokinetic analysis will be a relative bioavailability analysis on log $\mathbf{AUC_{0\text{-}inf}}$ of Formoterol Fumarate between Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg vs. open-label Foradil® Aerolizer® (12 µg). Log $\mathbf{AUC_{0\text{-}12}}$ may be substituted for log $\mathbf{AUC_{0\text{-}inf}}$ at the discretion of the study pharmacokineticist (if, for example, estimates of terminal elimination are considered unreliable). The margin will be a 1.2 fold change, and the test will be conducted to provide assurance that the Formoterol Fumarate $\mathbf{AUC_{0\text{-}inf}}$ for Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg is no more than 1.2 times that of open-label Foradil® Aerolizer® (12 µg).

The statistical model and tabulations will be essentially the same as that adopted for the primary efficacy objective; except that all significance tests will be performed at the 10% level, and 90% confidence intervals will be calculated.

All pharmacokinetic comparisons will be performed on completion of Part B; there will be no interim analysis on completion of Part A.

10.3.4 Secondary Pharmacokinetic Analysis

Secondary pharmacokinetic analyses will involve the primary pharmacokinetic comparison (Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg vs. open-label Foradil® Aerolizer® (12 µg).) applied to all pharmacokinetic end points other than log $\mathbf{AUC_{0\text{-}inf}}$ of Formoterol Fumarate, and the following comparisons applied to log $\mathbf{AUC_{0\text{-}inf}}$ and log Cmax:

1. Relative bioavailability (based on log $AUC_{0\text{-}inf}$ and log Cmax only) of Glycopyrrolate concentrations for Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg vs. Glycopyrrolate MDI (36 µg ex-actuator);

2. Relative bioavailability (based on log $AUC_{0\text{-}inf}$ and log Cmax only) of Glycopyrrolate concentrations for Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg vs. . Glycopyrrolate MDI (36 µg ex-actuator);

3. Relative bioavailability (based on log $AUC_{0\text{-}inf}$ and log Cmax only) of Formoterol Fumarate concentrations for Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg vs. Formoterol Fumarate MDI 9.6 µg;

4. Relative bioavailability (based on log $AUC_{0\text{-}inf}$ and log Cmax only) of Formoterol Fumarate concentrations for Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg vs. Formoterol Fumarate MDI 9.6 µg;

5. Relative bioavailability (based on log $AUC_{0\text{-}inf}$ and log Cmax only) of Formoterol Fumarate concentrations for Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg vs. open-label Foradil® Aerolizer® (12 µg).

Relative bioavailability calculations will be performed with a margin of 1.2.

The statistical model and tabulations will be identical to those adopted for the primary efficacy objective; except that tests will be performed at the 10% significance level, and 90% confidence intervals will be tabulated.

In addition, omnibus F tests for treatment differences followed by pairwise comparisons between all eight treatments will be performed for $\mathbf{T_{max}}$, $t_{1/2}$, $\mathbf{k_e}$,**CL/F and** Vz/F. These tests will be performed with an alpha of 0.05. There will be no group sequential adjustments to p values for the secondary pharmacokinetic objectives.

10.3.5 Safety Analysis for Part A

There will be no interim analysis for safety objectives. All analyses will be performed at the termination of Part B.

10.3.5.1 Adverse Events for Part A

Adverse events during each treatment regime will be summarized by the number of patients experiencing an event. They will be tabulated at the level of the MedDRA preferred term, and the MedDRA System Organ Class. The version of MedDRA current at the time the first subject is randomized will be used throughout the study. Tabulations will be broken down by severity and by relationship to study drug. No hypothesis tests will be performed. Tables will show the overall incidence of adverse events, and the incidence broken down by each of the 8 treatment selections in Part A. That is, adverse events will be tabulated for the entire patient history, rather than for the treatment during which they occurred.

10.3.5.2 Paradoxical Bronchospasm for Part A

Paradoxical Bronchospasm will be considered as an adverse event of special interest, and will be tabulated separately. Bronchospasm will be summarized by the number of patients experiencing the event, during a particular treatment period. We note that tabulations for bronchospasms differ from those for general adverse events, since the tabulation involves the treatment period during which bronchospasm arose. Bronchospasm that occurs outside a treatment period will be listed separately. No hypothesis tests will be performed, but an appropriate confidence interval may be provided.

10.3.5.3 Tremor and Dry Mouth for Part A

The incidence of tremor and dry mouth will be summarized by the number of patients experiencing the event, during a particular treatment period. We note that tabulations for tremor and dry mouth differ from those for general adverse events, since the tabulation involves the treatment period during which Tremor and dry mouth arose. Tremor and dry mouth that occur outside a treatment period will be listed separately. No hypothesis tests will be performed, but an appropriate confidence interval may be provided.

10.3.5.4 Clinical Laboratory Measurements for Part A

Summary statistics (mean, median, standard deviation and range) of 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 value prior to dosing at the start of each treatment sequence. Male and female patients will be tabulated separately.

10.3.5.5 Vital Signs for Part A

Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment and each assessment time. For vital signs, baseline values will be defined by the value prior to dosing at the start of each treatment sequence.

10.3.5.6 ECGs for Part A

Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment period and each assessment time. For ECG parameters, baseline values will be defined by the value prior to dosing at the start of each treatment sequence.

10.3.6 Pharmacodynamic Analysis for Part A

All pharmacodynamic endpoints are considered exploratory.

Pharmacodynamic endpoints will be analyzed using a linear mixed model in which treatment will be a fixed effect and within subject errors are correlated, but between subject errors are independent. Unstructured (for period), compound symmetry and first order autoregressive error models will be considered, and the appropriate model selected using Akaike's information criterion (Akaike, 1974). Fixed and random effect (subject) parameter estimates will be obtained using the REML algorithm (Patterson and Thompson, 1971). Ratios will be log-transformed before analysis.

10.4 Analysis for Part B

There is no interim analysis for any of the objectives defined for Part B.

10.4.1 Primary Efficacy Analysis for Part B

The primary efficacy analysis will involve a comparison of the primary endpoint: FEV_1 $AUC_{0\text{-}12}$ between Formoterol Fumarate MDI 9.6 µg vs. Placebo MDI. This comparison will be achieved with a linear mixed effects model, including fixed effect terms for treatment and period. Point and interval estimates will be obtained using the REML algorithm (Patterson and Thompson, 1971), under three models for the within subjects covariance matrix: unstructured (for period), compound symmetry and first order autoregressive (Pinheiro and Bates, 2000). The covariance model yielding the smallest value of Akaike's information criterion (Akaike, 1974) will be selected for tabulation. Two-sided 95% confidence intervals for this comparison will be tabulated, in addition to tail area probabilities. Tests for unequal carry over effects will be performed.

No efficacy claims will be advanced unless the primary efficacy comparison is statistically significant at the 5% level.

Part B comparisons will be made using data collected from both Part A and Part B.

10.4.2 Secondary Efficacy Analysis for Part B

Secondary efficacy analyses will involve the primary efficacy comparison (Formoterol Fumarate MDI 9.6 µg vs. Placebo MDI) applied to secondary efficacy endpoints (*vide supra*) except time to onset of effect, and secondary efficacy comparisons applied to all efficacy endpoints except time to onset of effect

Secondary efficacy comparisons for Part B are:

1. For FEV_1 AUC_{0-12} only, non-inferiority of Formoterol Fumarate MDI 9.6 µg to open-label Foradil® Aerolizer® (12 µg). For other endpoints a comparison of Formoterol Fumarate MDI 9.6 µg with open-label Foradil® Aerolizer® (12 µg);

2. For FEV_1 AUC_{0-12} only, non-inferiority of Formoterol Fumarate MDI 7.2 µg to open-label Foradil® Aerolizer® (12 µg). For other endpoints a comparison of Formoterol Fumarate MDI 7.2 µg with open-label Foradil® Aerolizer® (12 µg);

3. Formoterol Fumarate MDI 7.2 µg vs. Placebo MDI.

These secondary comparisons include non-inferiority comparisons. For all non-inferiority comparisons the margin will be 0.1L. This margin has been selected because a change in pre-dose FEV_1 of approximately 0.1L can be perceived by patients, correlates with fewer relapses following exacerbations and correlates with two year decline in lung function (Donohue, 2005).

The statistical models and tabulations will be identical to those used for the primary efficacy objective, with all tests conducted at the 5% level and 95% confidence intervals will be calculated\; except that no tests for unequal carry over effects will be performed.

There will be no interim analysis for these comparisons conducted at the end of Part A.

No multiplicity adjustment will be made to secondary efficacy analyses, since no efficacy claim will be based on the results of these analyses.

Secondary efficacy analysis for the time to onset of effect will be based on Kaplan-Meier analyses, adjusted for the assumed correlation structure of measurements on the same patient (a within-patient correlation estimate will be assumed (to be determined). Secondary efficacy analyses for the proportion of patients achieving $\geq$ 12% improvement in FEV_1 will be based on pairwise comparisons between treatment means, achieved using McNemar's test.

Part B comparisons will be made using data collected from both Part A and Part B.

10.4.3 Safety Analysis for Part B

10.4.3.1 Adverse Events for Part B

Adverse events during each treatment regime will be summarized by the number of patients experiencing an event. They will be tabulated at the level of the MedDRA preferred term, and the MedDRA System Organ Class. The version of MedDRA current at the time the first subject is randomized will be used throughout the study. Tabulations will be broken down by severity and by relationship to study drug. No hypothesis tests will be performed. Tables will show the overall incidence of adverse events, and will be based only on data collected during Part B.

10.4.3.2 Paradoxical Bronchospasm for Part B

Paradoxical bronchospasm will be considered as an adverse event of special interest, and will be tabulated separately. Events will be tabulated for each treatment. No hypothesis tests will be performed. Tabulations will be based only on data collected during Part B.

10.4.3.3 Tremor and Dry Mouth for Part B

The incidence of tremor and dry mouth will be summarized for each treatment, selection, by the number of patients experiencing an event. Events will be tabulated for each treatment. No hypothesis tests will be performed. Tabulations will be based only on data collected during Part B.

10.4.3.4 Clinical Laboratory Measurements for Part B

Summary statistics (mean, median, standard deviation and range) for change from baseline values will be tabulated for each treatment. For clinical laboratory measurements, baseline values will be defined by the value prior to dosing at the start of each treatment sequence. Male and female patients will be tabulated separately. Tabulations will be based only on data collected during Part B.

10.4.3.5 Vital Signs for Part B

Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment. For vital signs, baseline values will be defined by the value prior to dosing at the start of each treatment sequence. Tabulations will be based only on data collected during Part B.

10.4.3.6 ECGs for Part B

Summary statistics (mean, median, standard deviation and range) of change from baseline values will be tabulated for each treatment period and each assessment time. For ECG parameters, baseline values will be defined by the value prior to dosing at the start of each treatment sequence. Tabulations will be based only on data collected during Part B.

10.4.4 Pharmacokinetic Analysis for Part B

10.4.4.1 Primary Pharmacokinetic Analysis for Part B

The primary pharmacokinetic analysis will be a relative bioavailability analysis on **$AUC_{0\text{-}inf}$** of Formoterol Fumarate between Formoterol Fumarate MDI 9.6 µg vs. open-label Foradil® Aerolizer® (12 µg). **$AUC_{0\text{-}12}$** may be substituted for **$AUC_{0\text{-}inf}$** at the discretion of the study pharmacokineticist (if, for example, estimates of terminal elimination are considered unreliable). The margin will be a 1.2 fold change, and the test will be conducted to provide assurance that the Formoterol Fumarate **$AUC_{0\text{-}inf}$** for Formoterol Fumarate MDI 9.6 µg is no more than 1.2 times that of open-label Foradil® Aerolizer® (12 µg).

The comparison will be performed using a linear mixed model for log **$AUC_{0\text{-}inf}$** in which treatment and period will be fixed effects and within subject errors are correlated, but between subject errors are independent. Unstructured (for period), compound symmetry and first order autoregressive error models will be considered, and the appropriate model selected using Akaike's information criterion (Akaike, 1974). Fixed and random effect parameter estimates will be obtained using the REML algorithm (Patterson and Thompson, 1971). AUC and C_{max} will be log-transformed before analysis. Testing for unequal carryover effects will be performed.

No interim analysis will be conducted for this comparison.

10.4.4.2 Secondary Pharmacokinetic Analysis for Part B

Secondary pharmacokinetic analyses will involve:

Relative bioavailability (using $AUC_{0\text{-}inf}$ and Cmax) of Formoterol Fumarate concentrations for Formoterol Fumarate MDI 7.2 µg vs. open-label Foradil® Aerolizer® (12 µg);

For all other pharmacokinetic parameters, pairwise comparisons will be made among Formoterol Fumarate MDI 9.2 µg, Formoterol Fumarate MDI 7.2 µg, Foradil® Aerolizer® (12 µg) and Placebo MDI.

The statistical model and tabulations will be identical to those used for the primary pharmacokinetic objective, except that no testing for unequal carryover effects will be performed.

Relative bioavailability (ratio) calculations will be performed with a margin of 1.2, and tests will be conducted with a significance level of 0.1.

10.4.5 Pharmacodynamic Analysis for Part B

All pharmacodynamic endpoints are considered exploratory.

The statistical analysis and tabulation procedures will be identical to those adopted for the primary efficacy objective. Ratios will be log-transformed before analysis.

Pairwise comparisons will be made among Formoterol Fumarate MDI 9.2 µg, Formoterol Fumarate MDI 7.2 µg, Foradil® Aerolizer® (12 µg) and Placebo MDI.

10.5 Sample Size Consideration

Power calculations were based on the primary endpoint, FEV_1 $AUC_{0\text{-}12}$.

Estimates of within subject standard deviation of FEV_1 $AUC_{0\text{-}12}$ were obtained from published studies (D'Urzo et al, 2001; van Noord et al, 2005, Maesen et al 1995). A composite within subjects variance component of 0.13L was adopted. A between subjects variance component of FEV_1 $AUC_{0\text{-}12}$ was obtained from Dahl et al, 2001 and from

Calverley et al, 2003. A composite value of 0.13 was adopted. This represents a total standard deviation of 0.18. Note that variance components here are expressed as the standard deviation of the relevant random effect (not the variance).

For the efficacy comparisons, power was calculated as follows:

1. Between and within patients variance components were assumed to have standard deviations of 0.13L.

2. The standard error of each contrast was calculated, assuming a generalized least squares analysis in which the ratio of between and within patient variance components was known. The generalized least squares estimates also assumed spherical errors. This is an approximation to the standard error of the REML estimates. It was assumed that there are no carryover effects.

3. The non centrality parameter of the t test was calculated, assuming the standard error from the generalized least squares analysis, and a difference of 0.1L (the minimally clinically significant difference).

Because the design is an unbalanced incomplete block design, power varies between the comparisons. With these variance components, and a clinically relevant difference of 0.1L, we obtain the power for the primary comparisons: shown in Table 9.

Table 9. Power for Primary Comparisons on FEV_1 AUC_{0-12}

Part	Comparison	Power (%)
A	Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg vs. open-label Spiriva® (18 µg)	86
A	Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg vs. open-label Spiriva® (18 µg)	86
A	Non-inferiority of Glycopyrrolate MDI (36 µg ex-actuator) vs. open-label Spiriva® (18 µg)	90
A	Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg vs. Formoterol Fumarate MDI 9.6 µg.	86
A	Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg vs. Glycopyrrolate MDI (36 µg ex-actuator)	82
A	Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg vs. Glycopyrrolate MDI (36 µg ex-actuator)	82
A	Superiority of Glycopyrrolate/Formoterol Fumarate MDI 36/9.6 µg vs. open-label Foradil® Aerolizer® (12 µg);	83
A	Superiority of Glycopyrrolate/Formoterol Fumarate MDI 72/9.6 µg vs. open-label Foradil® Aerolizer® (12 µg);	83
B	Formoterol Fumarate MDI 7.2 µg vs. Placebo	95
B	Formoterol Fumarate MDI 9.6 µg vs. Placebo	95
B	Non-inferiority of Formoterol Fumarate MDI 9.6 µg vs. open-label Foradil® Aerolizer® (12 µg);	95
B	Non-inferiority of Formoterol Fumarate MDI 7.2 µg vs. open-label Foradil® Aerolizer® (12 µg);	95

10.6 Randomization

The first 48 patients recruited will be allocated to Part A; the final 36 will be allocated to Part B. Separate randomization schemes will be generated for Part A and Part B. Also, the sentinel patients will be randomized separately using an IWRS.

10.6.1 Part A Randomization Scheme

Part A comprises six selections of four treatments chosen so as not to violate toxicity constraints, and to provide high power for the comparisons of greatest clinical relevance. These selections are shown in Table 7. The treatment sequences will be generated using two complementary Williams' square designs for each of the six selections, giving 48 sequences in total.

Each treatment occur an equal number of times in each period. The low replication of Foradil 12 µg, Placebo, Formoterol Fumarate MDI 9.6 µg and Formoterol Fumarate MDI 7.2 µg treatments is mitigated by the inclusion of data from Part B (which contains only these treatments).

Patients will be randomly assigned to each of the treatment sequences in Part A using an IWRS.

10.6.2 Part B Randomization Scheme

There are 24 possible orderings of the four treatments administered to each patient. Each of these 24 sequences will be allocated to at least one patient. Twelve of these sequences will be allocated to two patients. The twelve sequences allocated to two patients will be selected as a set of three Williams' squares.

Patients will be randomly assigned to each of the treatment sequences in Part B using an IWRS.

10.7 Analysis Plan

All analyses will be specified in a detailed Statistical Analysis Plan that will include table and data listing shells with mock graphical representations. The analysis plan will be signed before database lock.

10.8 Study Populations

The following analysis populations are defined in this study:

- The Intent-To-Treat (ITT) Population: defined as all subjects who are randomized to treatment and receive at least one dose of the study treatment.
- A Modified ITT (MITT) Population used for analysis of pharmacokinetic and efficacy variables; where subjects must have remained in the study for minimally 6 hours post-dosing. A more detailed description of the MITT Population will be provided in the Statistical Analysis Plan.

The Per-Protocol (PP) Population is defined as all subjects who completed all treatment periods of the study as specified in the protocol. The PP Population will be used for sensitivity analyses. For efficacy measurements, the PP Population will also exclude any measurements excluded from the efficacy MITT Population.

Analyses will be performed as follows:

- Demographics and Safety Analyses will be performed for both the Intent-To-Treat (ITT) and Per-Protocol (PP) patient populations, with the ITT Population being considered the primary population for these analyses.

- Efficacy Analyses will be performed for both the Modified Intent-To-Treat (MITT) and Per-Protocol (PP) patient populations, with the MITT Population being considered the primary population for these analyses.

In the event of documented mis-dosings (that is, situations in which a patient is known to have received a dose different from that scheduled in the protocol) efficacy analyses will be based on the dose actually received, rather than the dose scheduled.

10.9 Handling of Missing Data

Missing data will not be imputed.

For efficacy data based on AUCs, inclusion criteria are as follows:

- If two or more consecutive time periods are missing, or if the data obtained are deemed to be invalid by the study investigator, AUCs will not be calculated for the visit;

- If spirometry measurements close in time to the anticipated peak effect (0.5 hours) are missing, then AUCs will not be calculated for the visit;

- If the final spirometry measurement (12 hours) is missing, AUCs will be calculated using last-one-carried forward;

- If other spirometry measurements are missing, AUCs will be calculated using trapezoidal integration on the available time points.

If either the 11.5 or 12-hour spirometry measurements is missing, but not both, trough values will be calculated using the other non-missing measurement (11.5 or 12 hour).

If both the 11.5 and 12-hour measurements are missing, trough values will be considered missing.

10.10 Statistical Software

Data processing, statistical screening, descriptive reporting and analysis of the efficacy and safety data will be performed using SAS (Version 8.2 or higher). The pharmacokinetic data will be analyzed using WinNonLin (Version 5.1 or higher).

11 ETHICS

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

- Guideline for Good Clinical Practice (E6(R1): Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR parts 50, 54, 56, and 312).
- Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects, Declaration of Helsinki amendments through to Edinburgh 2000 and subsequent clarification 2001 [http://www.wma.net/e/home.html].
- The Australian NH&MRC National Statement on Ethical Conduct in Human Research (2007)
- Any additional local or state requirements.

The ethical requirements of Institutional Review Boards/Ethics Committees (IRB/ECs) and the Informed Consent Forms (ICFs) are discussed in Section 12, Administrative Considerations.

12 ADMINISTRATIVE CONSIDERATIONS

12.1 Investigator Responsibilities for General Study Conduct

It is the Investigator's responsibility to ensure that:

- The protocol, the proposed ICF and any advertisement for patient recruitment is reviewed and approved by the appropriate IRB/EC, prior to the start of the study.
- The proposed ICF and any proposed advertisement are agreed to by Pearl Therapeutics.
- A copy of the IRB/EC approval letter of the protocol, any amendments, the ICF and any advertisements are supplied to Pearl Therapeutics prior to starting the study.
- During the course of the study, that timely and accurate reports are submitted to the IRB/EC on the progress of the study, at intervals not exceeding one year, as well as satisfying any other local IRB/EC regulations regarding reporting.
- Copies of all reports to and correspondence with and from the IRB/EC is provided to Pearl Therapeutics.
- At the completion or early termination of the study, a final report is made to the IRB/EC within the applicable IRB/EC time frames.
- Any significant deviation in the study protocol or any change that may alter patient risk is approved by Pearl Therapeutics (and applicable regulatory agency review and/or approval is obtained if required) and is approved in writing by the IRB/EC prior to implementation.
- A written notice of approval from Pearl Therapeutics is obtained prior to initiating changes to the study protocol.

A protocol deviation intended to eliminate an apparent immediate hazard may be implemented immediately provided that Pearl Therapeutics is notified and an amendment is subsequently provided by Pearl Therapeutics and approved by the IRB/EC. Such deviations, and their rationale, should be documented.

It is the Investigator's obligation to maintain an IRB/EC correspondence file, and to make this available for review by representatives of Pearl Therapeutics and applicable regulatory agencies as part of the study monitoring process.

12.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

The investigator (or 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 IEC/IRB. The investigator agrees to allow the IEC/IRB direct

access to all relevant documents. The IEC/IRB must be constituted in accordance with all applicable regulatory requirements.

Pearl Therapeutics will provide the investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study. Before investigational product(s) and CRFs can be shipped to the site, Pearl Therapeutics must receive copies of the IEC/IRB approval, the approved ICF, and any other information that the IEC/IRB has approved for presentation to potential subjects. If the protocol, the ICF, or any other information that the IEC/IRB has approved for presentation to potential subjects is amended during the study, the investigator is responsible for ensuring the IEC/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 IEC/IRB approval of the amended form before new subjects consent to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to Pearl Therapeutics promptly.

12.3 Patient Information and Consent

The proposed ICF, which must be in compliance with applicable regulations, must be reviewed and approved by Pearl Therapeutics prior to initiation of the study. The proposed ICF must contain a full explanation of the purpose and nature of the study, a description of the procedures, the possible advantages, risks, alternate treatment options, and a statement of confidentiality of patient study records, a statement regarding compensation and availability of treatment in the case of injury, an explanation of whom to contact about the research, the patient's rights, and notification that participation is voluntary and refusal will involve no penalty or loss of medical benefits. These requirements are in accordance with the Federal Regulations as detailed in the 21CFR50.25 and the most current revision of the Declaration of Helsinki. It should also indicate by signature that the patient, or where appropriate, legal guardian/representative, permits access to relevant medical records by the Sponsor and/or the Sponsor's duly appointed agent and by representatives of applicable regulatory agencies and permits their data to be used in publications.

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

12.4 Laboratory Accreditation

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

12.5 Confidentiality

All information provided by Pearl Therapeutics and all data and information generated by the site as part of the study (other than a subjects medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described Section 12.13. If a written contract for the conduct of the study that includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

12.6 Required Documents

The Investigator must provide the Sponsor with the following documents before the enrollment of any patient (copies should be kept by the Investigator in the Investigator's regulatory document binder):

- Signed copy (original) of the approved protocol
- Completed and signed statement of Investigator (Form FDA 1572)
- Financial disclosure
- Curriculum vitae of the Investigator and sub-Investigators
- Composition (names and representation) of IRB/EC
- Letter of approval from the IRB/EC for both protocol and ICF
- Copy of the stamped IRB/EC-approved written ICF to be used
- Name and location of the laboratory utilized for laboratory assays, and other facilities conducting tests, including a copy of the laboratory certificate
- List of normal laboratory values

In case a laboratory certification is not available, a written statement as to how the laboratory complies with quality assurance should be provided. The Sponsor's monitor must be notified if the laboratory is changed.

12.7 Study Monitoring

Prior to commencement of the study, representatives of Pearl Therapeutics or designee will visit the study site to assure adequacy of facilities to conduct the protocol, and to discuss with the Investigator the general obligations regarding studies with investigational new drugs.

Upon satisfactory receipt of all required documentation (see Section 12.6), representatives of Pearl Therapeutics will arrange for all study material to be delivered to the study site and for the scheduling of a mutually convenient appointment for an initiation visit. Patient entry must not begin until this initiation visit by representatives of Pearl Therapeutics has been made. At this meeting, all personnel expected to be involved in the conduct of the study will undergo an orientation to include review of the study protocol, instructions for CRF completion and specific responsibilities including those for drug accountability and study file maintenance.

Throughout the course of the study, the Investigator shall make every reasonable effort to maintain the enrollment rate of appropriate patients at a level previously determined with Pearl Therapeutics. Should the enrollment rate lag or significant numbers of clearly non-evaluable patients be entered, Pearl Therapeutics may elect to terminate the study. Pearl Therapeutics also has the right to terminate the study for non-adherence to protocol, unavailability of the Investigator or his/her study staff for the Sponsor or its designee's monitoring personnel, or for administrative reasons, at any time. Investigators will be compensated for reasonable expenses incurred if it is necessary to terminate the study. Pearl Therapeutics will not compensate the Investigator for evaluation of cases in which the procedures and evaluations are conducted in a manner other than that specified by the protocol.

Throughout the course of the study, representatives of Pearl Therapeutics will make frequent contacts with the Investigator. This will include telephone and/or on-site visits at appropriate and necessary intervals. During these visits, CRFs will be reviewed for completeness and for adherence to the protocol. As part of the data review it is expected that source documents (e.g., hospital records, office records, etc.) will be made available for review by the representatives of Pearl Therapeutics. The representatives will also perform drug accountability checks, and may periodically review the Investigator's study file to assure completeness of documentation in all aspects of the conduct of the study.

The Investigator or appointed delegate will be available to the representatives of Pearl Therapeutics during these on-site visits and will provide necessary study documents for inspection and will respond to all inquiries that may arise as part of this review. On completion of the study, the representatives of Pearl Therapeutics will arrange for a final review of the study files after which the file should be secured for the appropriate time period as specified in Section 12.10. 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.

12.8 Case Report Forms and Study Records

Case report forms will be provided by Sponsor or Sponsor's designee for the collection of all study data. One copy is to be retained in the Investigator's files. The original copy will be collected by the representatives of Pearl Therapeutics. The forms should be firmly printed or written legibly, using an indelible ball-point pen. Forms should be completed in a timely manner, and appropriate efforts should be made to have forms completed and up-to-date

prior to visits by the representatives of Pearl Therapeutics. It is the obligation of the Investigator to review each page of the CRFs and to sign the designated and appropriate forms as the study's authority. Case report form completion may be formally delegated to other study personnel. However, Pearl Therapeutics must be informed in writing of the name of such persons and the scope of their authority.

In event the sponsor switches to EDC format data will be captured in compliance with ICH/GCP guidelines and described in detail in the data management plan.

12.9 Drug Accountability

The study drug is to be prescribed only by the Principal Investigator or physician sub-Investigators named on the Form FDA 1572.

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

The Investigator must maintain accurate records accounting for the receipt of the study drug supplies and for the disposition of the drug. Documentation of the disposition of the drug should consist of a dispensing record including the identification of the person to whom the drug is dispensed, the quantity and the date of dispensing, and any unused drug returned. This record is in addition to any drug accountability information recorded on the CRFs. At the termination of the study or at the request of the Sponsor, the Investigator must return any unused study drug and all partially dispensed or empty containers to the Sponsor or its designee according to applicable local and country regulations. If return of drug is not feasible, the Sponsor will supply instructions as to how the supplies may be destroyed. Drug supply destruction must be clearly documented. Any study drug return will be documented at Pearl Therapeutics. The Investigator will also provide a written explanation for any missing study drug.

12.10 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 period of time these documents must be maintained is governed by applicable regulations. International requirements specify that these documents are to be maintained for 15 years or longer after a drug is approved for marketing. Pearl Therapeutics or its designee will inform the Investigator when these documents may be destroyed. The Sponsor or its designee must be notified in writing *at least 6 months* prior to the intended date of disposal of any study record related to this protocol to allow the Sponsor to make alternate storage arrangements.

12.11 Financial Disclosure

The Principal Investigator or physician sub-Investigators named on the Form FDA 1572 will need to complete a financial disclosure form prior to study initiation.

12.12 Investigator's Final Report

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

12.13 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 (Seoul revision 2008 [http://www.wma.net]). 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 the Sponsor 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 for clinical studies that are appropriate for this study.

Key issues include:

1. **Responsibility:** Each Principal Investigator is responsible for the accuracy and completeness of all data from their site. The Sponsor (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.
2. **Authorship and Publication Committee:** The Sponsor, in collaboration with the investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE. It is anticipated that a publication committee will be formed to assume oversight of these activities. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
3. **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted at least 30 days prior to submission for publication or presentation to the Sponsor for review, approval, and to ensure consistency with the policy in this protocol. The Sponsor will have the right to request appropriate modification to correct facts and to represent its opinions, or the opinions of the publication committee, if these differ with the proposed publication.
4. **Confidentiality:** Investigators will conduct all interactions with the Sponsor and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of nonclinical studies, or chemical formulae) may still need to remain confidential.
5. **Medical Journal Review:** Consistent with the intention of the Sponsor to publish the study in a fair and accurate manner, the Sponsor 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, *etc*. The journal and reviewers will need to make arrangements to maintain the confidentiality of such supplemental information, where relevant, and the Sponsor will make suitable arrangements to ensure that the identity of journal reviewers is kept confidential. Records will be maintained of reviewers and the respective documents and datasets that were reviewed by each of them.

6. **Internet Clinical Trial Listing:** In addition, also consistent with the recommendations of the ICMJE, the Sponsor 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.

13 REFERENCE LIST

Akaike H. A new look at the statistical model identification. IEEE Transactions on Automatic Control. 1974;19(6):716–723.

Calverley P, Lee A, Towse L, et al. Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease. Br Medical J. 2003b;58(10):855–860.

Calverley P, Anderson J, Celli B, Ferguson G, Jenkins C, Jones P, Yates J, and Vestbo J, Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease: New England Journal of Medicine 2007;356:775-89

Casaburi R, Briggs D, Donohue J, Serby C, Menjoge S, and Witek T, The Spirometric Efficacy of Once-Daily Dosing With Tiotropium in Stable COPD : A 13-Week Multicenter Trial: Chest 2000;118;1294-1302.

Casaburi R, Kukafka D, Cooper CB, Witek TJ Jr, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest 2005;127:809–817.

Celli B, MaNee W, Agusti A, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004; 23:932-946.

Criee CP, Meyer T, et al. In vitro comparison of two delivery devices for administering formoterol: Foradil P and formoterol ratiopharm single-dose capsule inhaler. J Aerosol Med. 2006;19(4):466-472.

Dahl R, Greefhorst LA, Nowak D, et al. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2001; 164:778–84.

Dellamary LA, Tarara TE, Smith, et al. Hollow Porous Particles in Metered Dose Inhalers. Pharmaceutical Research. 2000;17(2):168-174.

Donohue JF. Minimally clinically important differences in COPD lung function. COPD. 2005;2(1):111-124.

D'Urzo A, Salvo M D, Ramirez-Rivera A, et al. In patients with copd, treatment with a combination of formoterol and ipratropium is more effective than a combination of salbutamol and ipratropium a 3-week, randomized, double-blind, within-patient, multicenter study. Chest. 2001;119(5):1347–1356.

Feenstra TL, van Genugten ML, Hoogenveen RT, et al. The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease: a model analysis in the Netherlands. Am J Respir Crit Care Med 2001;164:590-596.

Ferrer, Alonso J,Morera J, et al. Chronic obstructive pulmonary disease Part and health-related quality of life. Ann Intern Med. 1997;127:1072-1079.

GOLD (Global Initiative for Chronic Obstructive Lung Disease). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. National Institutes of Health, updated 2008 (www.goldcopd.com). Accessed February 16, 2009.

Halbert RJ, Isonaka S, George D, Iqbal A. Interpreting COPD prevalence estimates: what is the true burden of disease? Chest 2003;123:1684-1692.

Halbert RJ, Natoli JL, Gano A, et al. Global burden of COPD: systemic review and meta-analysis. Eur Respir J 2006;28:523-532.

Hansel TT, Barnes PJ. Tiotropium bromide: a novel once daily anticholinergic bronchodilator for the treatment of COPD. Drugs Today 2002; 38: 585–600

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

Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J. 2005 Aug;26(2):319-38.

MIMS Online Australia, 2008. CMPMedica Australia Pty Ltd.

Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997;349:1498-1504.

Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JA Jr, Korducki L, Cassino C, Kesten S. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med 2005;143:317–326.

Noord JAV. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. European Respiratory Journal. 2005;26(2):214–222.

Patterson H and Thompson R. Recovery of inter-block information when block sizes are unequal. Biometrika, 1971; 58:545–554

Pinheiro JC, Bates DM. Mixed Effects Models in S and S-Plus. Springer Verlag, 1st Edition, 2000.

Sullivan SD, Ramsey SD, Lee TA. The economic burden of COPD. Chest 2000;117:5S-9S.

Tashkin D, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, and Decramer, M : A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease. New Engl J Med 2008;359:1543-54.

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 Therapeutics), central training provided, qualification will be required, and specific operating instruction will also be provided.

Series "ATS/ERS Task Force: Standardization of Lung Function Testing: Number 2 in Series. European Respiratory Journal 2005;26(2):319-338.

FEV_1 AND FVC MANEUVERS

Equipment Requirements

The spirometer must be capable of accumulating volume for $\geq$15 s (longer times are recommended) and measuring volumes of $\geq$8 L (body temperature (i.e., 37°C), ambient pressure, saturated with water vapor, BTPS) with an accuracy of at least $\pm$3% of reading or $\pm$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 s) of the FVC maneuver. Since this portion of the maneuver, particularly the peak expiratory flow (PEF), 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 trials, the sequencing of the blows should be apparent to the user. For the start of test display, the volume–time display should include $\geq$0.25 s, and preferably 1 s, 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 s 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 $\geq$10 mm L^{-1} (BTPS). For a screen display, 5 mm L^{-1} is satisfactory (Table A1-1).

Table A1-1. 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*	0.050 L	5 mm-L^{-1}	0.050 L
Flow*	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

*The correct aspect ratio for flow versus volume display is two units of flow per one unit of volume

The time scale should be $\geq$20 mm-s^{-1}, and larger time scales are preferred ($\geq$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 A1-1). 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 (see Test signals for spirometer testing section).

Quality control

Attention to equipment quality control and calibration is an important part of good laboratory practice. 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 A1-2.

Table A1-2. Summary of Equipment Quality Control

Test	Minimal Interval	Action
Volume	Daily	Calibration check with a 3 L syringe
Leak	Daily	2 cm H_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., $\pm$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 $\pm$15 mL or $\pm$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 cmH2O (0.3 kPa) with the spirometer outlet occluded (preferably at or including the mouthpiece). Any observed volume loss of .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., 0–1,1–2, 2–3,…6–7 and 7–8 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., 0–3, 1–4, 2–5, 3–6, 4–7 and 5–8 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 s and 0.5 s). 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 patient 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%.

VC AND IC MANEUVERS

Equipment

For measurements of VC and IC, 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 or, ideally, both inspiratory and expiratory maneuvers should be included in the display of VC maneuver. Regardless of whether the inspiratory or 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 A1-1, but must meet the recommendations for those that are measured. Accuracy and repeatability recommendations apply over the entire volume range of the instrument.

Table A1-3. 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 cm H_2O L^{-1} s^{-1} (0.15 kPa $L^{-1}s^{-1}$)	24 ATS waveforms, 3-L Cal Syringe
FEV_1	0.5–8 L, +3% of reading or ±0.050 L, whichever is greater	0-14	1	<1.5 cm H_2O L^{-1} s^{-1} (0.15 kPa $L^{-1}s^{-1}$)	24 ATS waveforms
Time Zero	The time point from which all FEV_t measurements are taken.			Back extrapolation	

FEVt: forced expiratory volume in t seconds

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 $\pm$1°C. In situations where the ambient air temperature is changing rapidly (>3°C in <30 min), 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

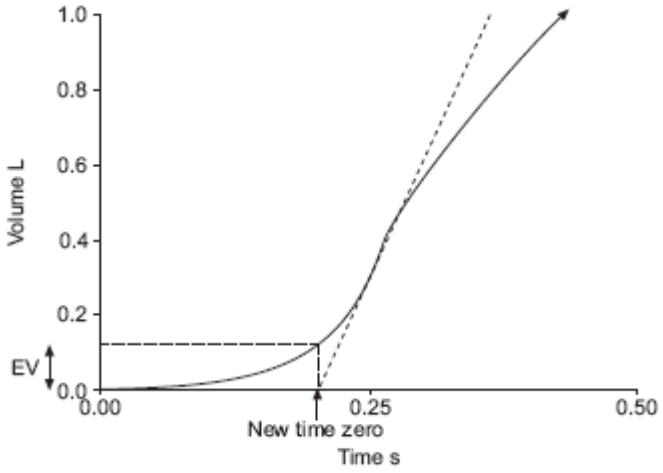
***Acceptable* Tests must meet the following 7 Criteria:**

7. Acceptable start of exhalation with brisk upstroke, no hesitation or false start, and back extrapolation volume (EV) < 5% of FVC or 0.150 L, whichever is the greater. (See example in Figure A2-1 below)
8. No cough during the first second.
9. No valsalva maneuver.
10. No leak.
11. No obstruction of mouthpiece.
12. No extra breaths.
13. Plateau achieved, i.e., the volume-time curve shows no change in volume (<0.025 L) for ≥ 1s, and the patient has tried to exhale for at least 6 seconds.

An acceptable test meets all 7 criteria listed. This is to be considered the "gold standard".

Useable spirometry tracings are those that only meet criteria 1 and 2. When this occurs, repeat testing up to 8 attempts in an effort to obtain 3 acceptable spirograms. If only Usable tests are obtained, report results based on the 3 best Usable trials with observed limitations.

Figure A2-1. Example of a Usable Spirogram



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 peak expiratory flow (PEF), to determine the new "time zero". Forced vital capacity (FVC)-4.291 L; back extrapolated volume (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 time-point may conclude. The highest FEV_1 and the highest FVC obtained at each testing time-point (even if from different reproducible tracings), will be recorded on the CRF.

If acceptability criteria are not met, continue testing until they are met or the patient cannot/ should not continue (Maximum of 8 attempts). Under the latter circumstance, place a check mark in the "Spirometry does not meet acceptability criteria" box on the CRF and record values from the traces with the highest FEV_1 and the highest FVC. Save as a minimum the three satisfactory maneuvers.

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

- Collect approximately 5 mL of blood in a tube containing EDTA tripotassium (4×10^{3}M in PBS). Care should be taken to minimize hemolysis during sample collection.
- Place all tubes on wet ice immediately after collection.
- Centrifuge the blood within 30 minutes of collection at >1000 x g (~2500 rpm) for 10 – 15 minutes. The rotor chamber of the centrifuge must be refrigerated to maintain a temperature of approximately 4^{o}C.
- Transfer approximately equal aliquots (Aliquot A and Aliquot B) of plasma into duplicate labeled polypropylene test tubes with a snap or screw cap. Care should be taken to minimize contamination with red blood cells during transfer of plasma.
- Securely cap the labeled tubes. Please ensure the following when labeling the plasma aliquots.
- Sample vials must be clearly and accurately labeled using a solvent resistant ink (do not use ballpoint pen) or using supplied labels.
- The information on the labels should correspond to the information recorded on the PK Sample Log worksheet for each patient.
- The actual date and clock time (24 hour clock) of sample collection should be entered on the PK Sample Log worksheet.
- The plasma samples should then be placed in a freezer capable of maintaining a temperature of at least -20°C as soon as possible after aliquoting for storage. Store Aliquot A samples separate from Aliquot B samples as these will be shipped separately.
- Ship frozen plasma samples within dry ice using a supplied cooler and labeling according to the procedure provided by the courier service.
- Ship samples only on a Monday, Tuesday or Wednesday or at least three days prior to a holiday via priority overnight delivery.
- Ship Aliquot A samples first.
- Aliquot B samples should be retained frozen until receipt of Aliquot A samples is confirmed and then shipped according to instruction.

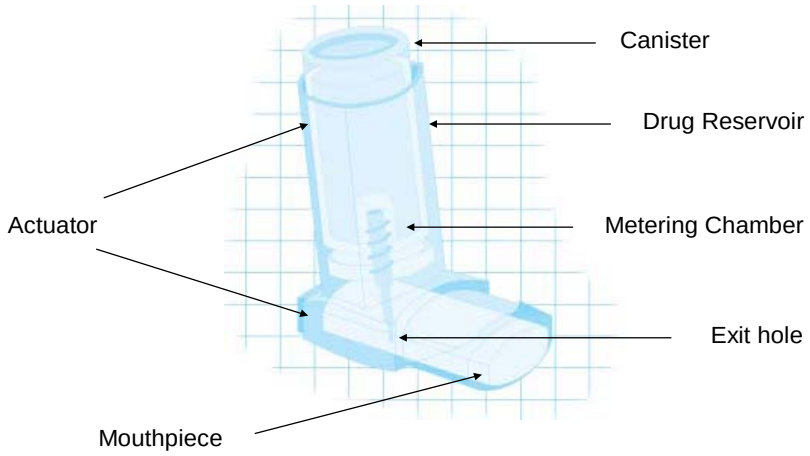
Shipping Address:

[redacted]

Appendix 4 Patient Instructions for Use of Glycopyrrolate/Formoterol Fumarate, Formoterol Fumarate, Glycopyrrolate and Placebo MDI 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 (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's ready to use. 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.
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 4 to 6, with gentle shaking for 5-10 seconds prior to each spray.
10. Put the cap back on the mouthpiece after every time the inhaler is used.

METERED DOSE INHALER SCHEMA



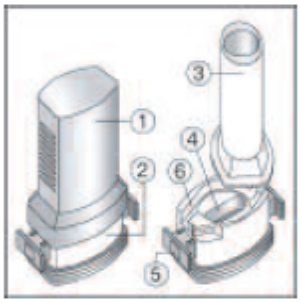
Appendix 5 Instructions for Use of Foradil Aerolizer Device

FORADIL AEROLIZER

- **FORADIL AEROLIZER consists of FORADIL capsules and a AEROLIZER Inhaler.**
- **FORADIL capsules come on blister cards and are wrapped in foil pouches. Do not open a foil pouch until you are ready to use FORADIL AEROLIZER.**
- **Keep your FORADIL and AEROLIZER Inhaler dry. Handle with DRY hands.**

Aluminum pouch covering the foil blister cards

Foil blister card



The Aerolizer consists of the following parts:
1. A cap to protect the mouth-piece of the base
2. A base that allows the proper release of medicine from the capsule

The base consists of:
3. A mouth piece
4. A capsule chamber
5. A button with "winglets" (projecting side pieces) and pins on each side
6. An air inlet channel.

With each new prescription of FORADIL AEROLIZER or refill, your pharmacist should have written the "Use by" date on the sticker on the outside of the FORADIL AEROLIZER box. Remove the "Use by" sticker on the box and place it on the AEROLIZER Inhaler cover that comes with FORADIL. If the sticker is blank, count 4 months from the date you got your FORADIL AEROLIZER from the pharmacy and write this date on the sticker. Also, check the expiration date stamped on the box. If this date is less than 4 months from your purchase date, write this date on the sticker.

Do not use FORADIL capsules with any other capsule inhaler, and do not use the AEROLIZER inhaler to take any other capsule medicine.

Taking a dose of FORADIL AEROLIZER requires the following steps:

1. Open the foil pouch containing a blister card of FORADIL capsules. Do not remove a FORADIL capsule until you are ready for a dose.

2. Pull off the AEROLIZER Inhaler cover. (Figure 1)

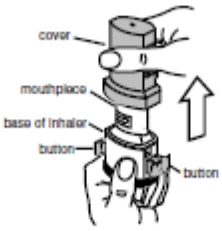


Figure 1

3. Hold the base of the AEROLIZER Inhaler firmly and twist the mouthpiece in the direction of the arrow to open. (Figure 2) Push the buttons in on each side to make sure that you can see 4 pins in the capsule well of the AEROLIZER Inhaler.

Figure 2

4. Separate one FORADIL capsule blister by tearing at the pre-cut lines. (Figure 3)

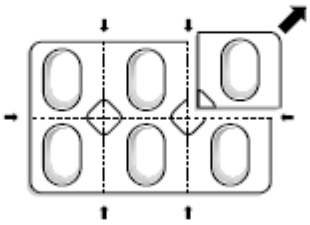


Figure 3

5. Peel the paper backing that covers one FORADIL capsule on the blister card. Push the FORADIL capsule through the foil. (Figure 4)

Figure 4

6. Place the FORADIL capsule in the capsule-chamber in the base of the AEROLIZER Inhaler. **Never place a capsule directly into the mouthpiece.** (Figure 5)

Figure 5

7. Twist the mouthpiece back to the closed position. (Figure 6)

Figure 6

8. Hold the mouthpiece of the AEROLIZER Inhaler upright and press both buttons at the same time. Only press the buttons **ONCE**. You should hear a click as the FORADIL capsule is being pierced. (Figure 7)

Figure 7

9. Release the buttons. If the buttons stay stuck, grasp the wings on the buttons and pull them out of the stuck position before the next step. Do not push the buttons a second time. This may cause the FORADIL capsule to break into small pieces. There is a screen built into the AEROLIZER Inhaler to hold these small pieces. It is possible that tiny pieces of a FORADIL capsule might reach your mouth or throat when you inhale the medicine. This will not harm you, but to avoid this, only pierce the capsule once. The FORADIL capsules are also less likely to break into small pieces if you store them the right way (See "How do I store FORADIL AEROLIZER?").

10. Breathe out (exhale) fully. **Do not exhale into the AEROLIZER mouthpiece.** (Figure 8)

Figure 8

11. Tilt your head back slightly. Keep the AEROLIZER Inhaler level, with the blue buttons to the left and right (**not up and down**). Place the mouthpiece in your mouth and close your lips around the mouthpiece. (Figures 9 and 10)

Figure 9

Figure 10

12. Breathe in quickly and deeply (Figure 11). This will cause the FORADIL capsule to spin around in the chamber and deliver your dose of medicine. You should hear a whirring noise and experience a sweet taste in your mouth. If you do not hear the whirring noise, the capsule may be stuck. If this occurs, open the AEROLIZER Inhaler and loosen the capsule allowing it to spin freely. **Do not try to loosen the capsule by pressing the buttons again.** (You will have to repeat steps 10 to 12 again to get your dose.)

Figure 11

13. Remove the AEROLIZER Inhaler from your mouth. Continue to hold your breath as long as you can and then exhale.

14. Open the AEROLIZER Inhaler to see if any powder is still in the capsule. If any powder remains in the capsule repeat steps 10 to 13. Most people are able to empty the capsule in one or two inhalations.

15. After use, open the AEROLIZER Inhaler, remove and discard the empty capsule. Do not leave a used capsule in the chamber.

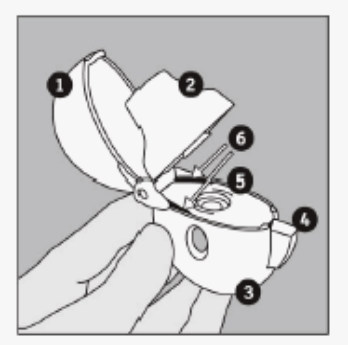
16. Close the mouthpiece and replace the cover.

Appendix 6 Instructions for Use of Spiriva Handihaler Device

Taking your dose of SPIRIVA, requires four main steps: Open the blister and the HandiHaler device, insert the SPIRIVA capsule, press the HandiHaler button, and inhale your medication. (See below for details.)

Become familiar with the components of the HandiHaler inhalation device:

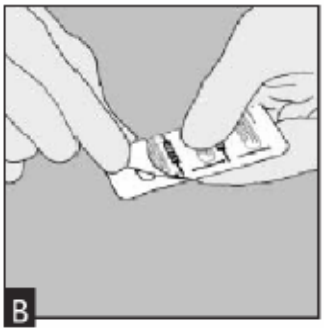
1. dust cap
2. mouthpiece
3. base
4. piercing button
5. center chamber
6. Air intake vents



Removing the SPIRIVA capsule from the blister.

A) SPIRIVA capsules are packaged in a blister card. Each blister card consists of one blister strip, containing 5 capsules. Prior to removing the first capsule from the blister card, separate the blister strips by tearing along the perforation.

B) The blister should be carefully opened to expose only one capsule at a time. Immediately before you are ready to use your dose of SPIRIVA, peel back the aluminum foil using the tab at the rounded edge until one capsule is fully visible. The foil lidding should only be peeled back as far as the *STOP* line printed on the blister foil to prevent exposure of more than one capsule. (Figure B) Turn the blister strip upside down and tip the capsule out, tapping the back of the blister pack, if necessary. DO NOT CUT THE FOIL OR USE SHARP INSTRUMENTS TO REMOVE THE CAPSULE FROM BLISTER.



Capsules should always be stored in the sealed blisters and only removed immediately before use. The drug should be used immediately after the packaging over an individual capsule is opened, or else its effectiveness may be reduced.

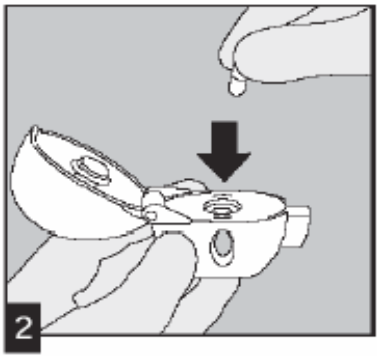
If additional capsules are inadvertently exposed to air, they should not be used and should be discarded.

Do not store capsules in the HandiHaler device.

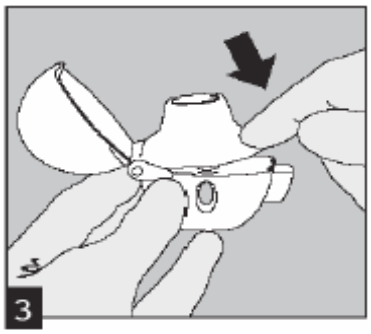
Opening the HandiHaler device and inserting the SPIRIVA capsule.

1) OPEN: Open the dust cap by pulling it upwards. Then open the mouthpiece. (Figure 1)

2) INSERT: Place the capsule in the center chamber. It does not matter which end of the capsule is placed in the chamber. (Figure 2)

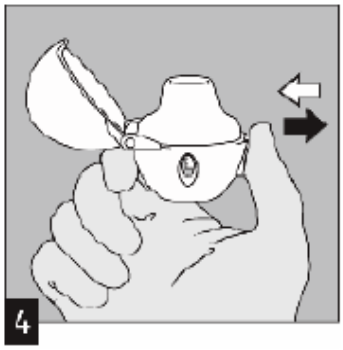


3) Close the mouthpiece firmly until you hear a click, leaving the dust cap open. Check to see that the mouthpiece is completely closed. Be sure that the mouthpiece sits firmly against the gray base so that there is no gap between the mouthpiece and the base. (Figure 3)

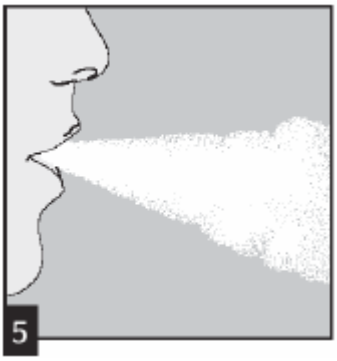


Taking your dose of SPIRIVA.

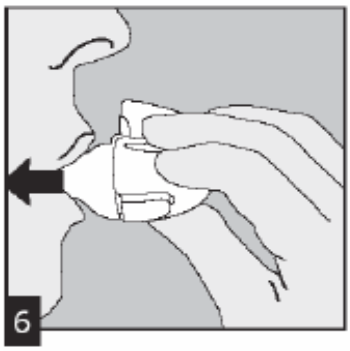
4) PRESS: Hold the HandiHaler device with the mouthpiece upwards and press the piercing button completely in once until it is flush against the base, and release. This makes holes in the capsule and allows the medication to be released when you breathe in. (Figure 4)



5) Breathe out completely. (Figure 5) Important: Do not breathe (exhale) into the HandiHaler mouthpiece at any time.



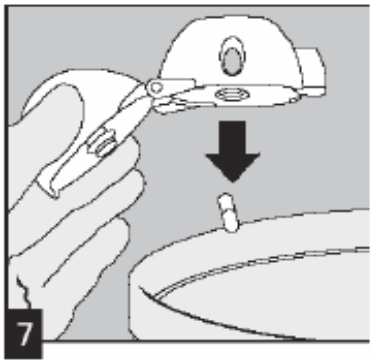
6) INHALE: Holding the HandiHaler by only the gray base and without blocking the air intake vents, raise the HandiHaler device to your mouth and close your lips tightly around the mouthpiece. Keep your head in an upright position and breathe in slowly and deeply but at a rate sufficient to hear or feel the capsule vibrate. Breathe in until your lungs are full; then hold your breath as long as is comfortable and at the same time take the HandiHaler device out of your mouth. Resume normal breathing. (Figure 6)



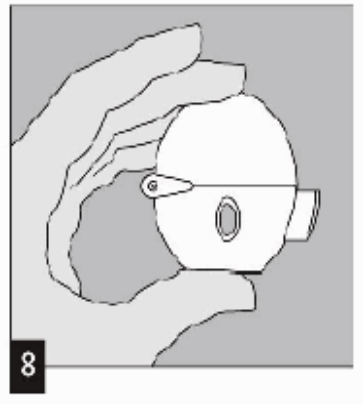
To ensure you get the full dose of SPIRIVA, you must repeat steps 5 and 6 once again.

If you do not hear or feel the capsule vibrate, DO NOT PRESS THE GREEN BUTTON AGAIN, but instead tap the HandiHaler gently on a table, holding it in an upright position. Check to see that the mouthpiece is completely closed. Then breathe in again – slowly and deeply. If you still do not hear or feel the capsule vibrate after repeating the above steps please consult your physician.

7) After you have finished taking your daily dose of SPIRIVA, open the mouthpiece again. Tip out the used capsule and discard. (Figure 7)



8) Close the mouthpiece and dust cap for storage of your HandiHaler device. (Figure 8)



Appendix 7 Instructions for Use of Ventolin HFA Inhaler

The Parts of Your VENTOLIN HFA Inhaler

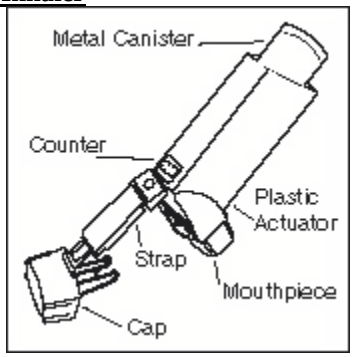


Figure 1

There are 2 main parts to your VENTOLIN HFA inhaler:

1. The metal canister that holds the medicine and
2. The blue plastic actuator that sprays the medicine from the canister (see Figure 1).
    a. The inhaler also has a cap that covers the mouthpiece of the actuator.
    b. The strap on the cap will stay attached to the actuator.
    c. The canister has a counter to show how many sprays of medicine you have left. The number shows through a window in the back of the actuator.

The counter starts at 204, the number will count down by 1 each time you spray the inhaler. The counter will stop counting at 000.
Never try to change the numbers or take the counter off the metal canister. The counter cannot be reset, and it is permanently attached to the canister.

Do not use the actuator with a canister of medicine from any other inhaler. And do not use a VENTOLIN HFA canister with an actuator from any other inhaler.

How to Use Your VENTOLIN HFA

Before using your VENTOLIN HFA:

1. Take the inhaler out of the foil pouch. Safely throw away the pouch and the drying packet that comes inside the pouch. The counter should read 204. *The inhaler should be at room temperature before you use it.*
2. Check each time to make sure the canister fits firmly in the plastic actuator. Also look into the mouthpiece to make sure there are no foreign objects there, especially if the strap is no longer attached to the actuator or if the cap is not being used to cover the mouthpiece.

Priming your VENTOLIN HFA:

- You must prime the inhaler to get the right amount of medicine. Prime the inhaler before you use it for the first time, if you have not used it for more than 14 days, or if it has been dropped.
    1. To prime the inhaler, take the cap off the mouthpiece of the actuator.
    2. Then shake the inhaler well, and spray it into the air away from your face.
    3. Shake and spray the inhaler like this 3 more times to finish priming it.
    4. The counter should now read 200, or 60 if you have a sample or institutional canister.

Instructions for taking a dose from your VENTOLIN HFA:

Read through the 6 steps below before using VENTOLIN HFA. If you have any questions, ask your study doctor.

1. Take the cap off the mouthpiece of the actuator. **Shake the inhaler well** before each spray.

2. Hold the inhaler with the mouthpiece down (see Figure 2). **Breathe out through your mouth** and push as much air from your lungs as you can. Put the mouthpiece in your mouth and close your lips around it.

3. **Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth** (see Figure 3). Right after the spray comes out, take your finger off the canister. After you have breathed in all the way, take the inhaler out of your mouth and close your mouth.

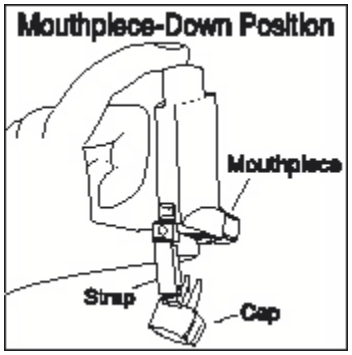


Figure 2

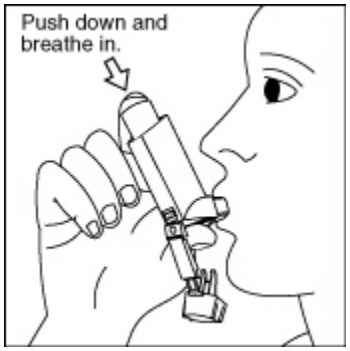


Figure 3

4. **Hold your breath as long as you can**, up to 10 seconds, then breathe normally.

5. If your doctor has prescribed more sprays, wait 1 minute and **shake** the inhaler again. Repeat steps 2 through 4.

6. Put the cap back on the mouthpiece after every time you use the inhaler, and make sure it snaps firmly into place.

When to Replace Your VENTOLIN HFA

- **When the counter reads 020**, you should refill your prescription or ask your doctor if you need another prescription for VENTOLIN HFA.
- **Throw the inhaler away** when the counter reads 000 or 6 months after you have taken the inhaler out of the foil pouch, whichever happens first. You should not keep using the inhaler when the counter reads 000 because you will not receive the right amount of medicine.
- **Do not use the inhaler** after the expiration date, which is on the packaging it comes in.

How to Clean Your VENTOLIN HFA

It is very important to keep the plastic actuator clean so the medicine will not build-up and block the spray. Do not try to clean the metal canister or let it get wet. The inhaler may stop spraying if it is not cleaned correctly.

Wash the actuator at least once a week.

Cleaning instructions:

1. Take the canister out of the actuator, and take the cap off the mouthpiece. The strap on the cap will stay attached to the actuator.
2. Wash the actuator through the top with warm running water for 30 seconds (see Figure 4). Then wash the actuator again through the mouthpiece (see Figure 5).

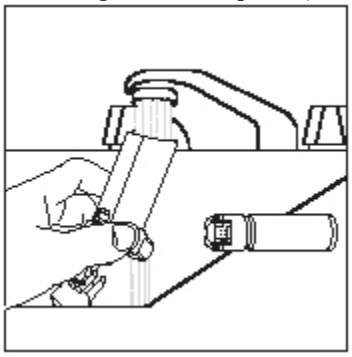


Figure 4

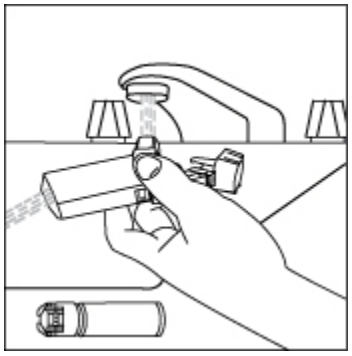


Figure 5

3. Shake off as much water from the actuator as you can. Look into the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat step 2.
4. Let the actuator air-dry completely, such as overnight (see Figure 6).

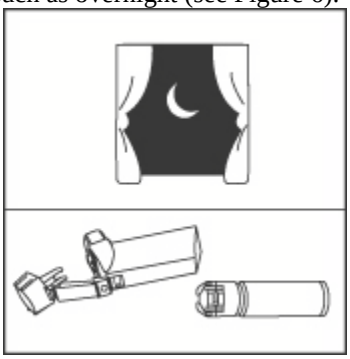


Figure 6

5. When the actuator is dry, put the canister in the actuator and make sure it fits firmly. Shake the inhaler well and spray it once into the air away from your face. (The counter will count down by 1.) Put the cap back on the mouthpiece.

If your actuator becomes blocked:

Blockage from medicine build-up is more likely to happen if you do not let the actuator air-dry completely. If the actuator gets blocked so that little or no medicine comes out of the mouthpiece (see Figure 7), wash the actuator as described in cleaning steps 1-5.

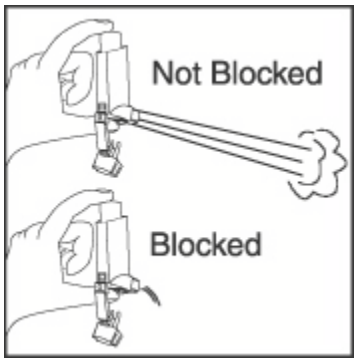


Figure 7

If you need to use your inhaler before the actuator is completely dry, shake as much water off the actuator as you can. Put the canister in the actuator and make sure it fits firmly. Shake the inhaler well and spray it once into the air away from your face. Then take your dose as prescribed. Then clean and air-dry it completely.

Storing Your VENTOLIN HFA

Store at room temperature with the mouthpiece down. Keep out of reach of children.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw into fire or incinerator

Appendix 8 Criteria for Tremor Assessment

Grade	1 (mild)	2 (moderate)	3 (severe)
Definition	Tremor is present but transient, causing minimal discomfort and no impact on ability to conduct fine motor task	Tremor is present, causing moderate discomfort and minor impact on ability to conduct fine motor tasks,	Tremor is present had has a severe impact on fine motor tasks, e.g. unable to writer
Example	Mild impact on writing skills	Moderate impact on writing skills	Unable to write

Appendix 9 Investigator's Signature

Study Title: A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (7 Days), Four-Period, Eight-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Two Doses of PT003, Two Doses of PT005 and One Dose of PT001 in Patients With Moderate to Very Severe COPD, Compared With Foradil® Aerolizer® (12 µg, Open-Label) and Spiriva® Handihaler® (18 µg, Open-Label) as Active Controls

Study Number: PT0031002

Final Date: [redacted]

Amendment 3 Date: [redacted]

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

I agree to:

- Implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Accurately transfer all required data from each patient's source document to the case report forms (CRFs). The original CRFs will be submitted to the sponsor in a timely manner at the completion of the study, or as otherwise specified by the sponsor.
- Keep a complete and accurate accounting during and at the completion of the study of all procedures performed with the drug provided by the sponsor.
- Allow authorized representatives of Pearl Therapeutics Inc. or regulatory authority representatives to conduct on-site visits to review, audit and copy study documents. I will personally meet with these representatives at mutually convenient times to answer any study-related questions.
- Provide the sponsor with an Investigator's summary within 90 days of completion of the final study visit for the last patient enrolled, or as designated by sponsor.
- Maintain all information supplied by the sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethical Review Committee (ERC), or another group, it will be submitted with a designation that the material is confidential.

Signature:_____ Date:_____

Name:_____

Affiliation:_____

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