Clinical Trial Protocol: PT001101-01

Study Title:	A Randomized, Double-Blind, Chronic-Dosing (14 days), 5-Period, 7-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-center, Dose-ranging Study to Assess the Efficacy and Safety of PT001 Relative to Placebo MDI and Open-Label Serevent® Diskus® in Adult Subjects With Intermittent Asthma or Mild to Moderate Persistent Asthma
Study Number:	PT001101-01
Study Phase:	II
Product Name:	Glycopyrronium Inhalation Aerosol; PT001
IND Number:	101985
Indication:	Asthma
Investigators:	Multi-center
Sponsor:	[redacted]
Sponsor Contact:	[redacted]

	Version Number	Date
Original Protocol	Version 1.0	[redacted]
Amended Protocol	Version 2.0	[redacted]

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

The amended study protocol, PT0011001-01(Version 2.0), includes the following edits: Newly added text is shown in **red bold font** and deleted text is shown as ~~strikethrough font~~. Minor typographical errors were also corrected in the protocol. These are not displayed below.

No.	Description of Change	Rationale
1	Synopsis, Study Population This multi-center study will be conducted at approximately 45 sites, contributing approximately 5 subjects per site. Across these sites, it is planned that approximately ~~200~~ **224** subjects with intermittent asthma or mild to moderate persistent asthma will be randomized into the study to provide approximately ~~160~~ **180** subjects to complete the study. Randomization will be stratified by ICS use at the time of Screening such that **approximately** 1**12**~~00~~ subjects treated with ICS and **approximately** 1**12**~~00~~ subjects not treated with ICS will be included.	Sample size was increased due to the potential for increased variability that the initial drug supplies may have introduced. This is consistent with the administrative letter dated [redacted]
2	Synopsis, Test Product, Dose, and Mode of Administration; and Table 4 [a] Placebo MDI will be ~~used for training purposes and also~~ administered as a randomized treatment. All placebos are created by Pearl Therapeutics in the image of the active test product. Table 9 ~~[e] Sites should use Sponsor-provided Placebo MDIs to train subjects on the use of MDIs.~~ Section 8.1 Screening Visit (Visit 1a) • Train subjects on use of Sponsor-provided inhalation devices~~, using Placebo MDIs~~.	Correction to the protocol as Placebo MDI is not used for training purposes.
3	Synopsis, Duration of Treatment To standardize asthma maintenance medications and to determine disease severity, eligible subjects will undergo a Screening period of a minimum of ~~14~~ **7** days and up to a maximum of 28 days. This will be followed by 5 Treatment Periods of 14 days and a Washout Period of at least 7 days (up to 14 days) between Treatment Periods. A telephone follow-up will be conducted in 7 to 14 days after the last dose. The entire study is scheduled to be	Updated typographical error in synopsis to be consistent with Section 4.1 of the protocol that indicates the screening period is a minimum of 7 days.

	approximately 24 weeks for each individual subject from the time of Screening (Visit 1a).	
4	Synopsis, Statistical Methods, Sample Size Determination; and Section 9.7 Power calculations are based on the properties of the primary endpoint, peak change in FEV_1 on Day 15. An estimate for the within-subject standard deviation (SD) is obtained from a Phase II study with tiotropium (Beeh, 2014). A within-subject SD of 210 mL **and an intra-class correlation of 64%** ~~is~~**are** assumed. It is further assumed that **approximately** ~~200~~ **224** subjects will be randomized and **approximately** ~~160~~ **180** subjects will complete the study and be included in the modified intent-to-treat (mITT) Population. The power was also updated in table following the revised text above.	Sample size was increased due to the potential for increased variability that the initial drug supplies may have introduced. Based on the new assumptions the power was updated in the table.
5	Synopsis, Study Design; Section 4.1, Overall Study Design and Plan, Paragraph 2; Table 9, footnote q; Table 10, footnote i; Table 11 footnote 1; and Section 8.1 Screening Visit (Visit 1a) Subjects that meet the eligibility criteria at Screening (Visit 1a) will enter a Screening Period of at least 7 days and not to exceed 28 days. During the Screening Period, subjects previously treated with an inhaled corticosteroid (ICS) ~~alone~~ will be switched to Sponsor-provided open-label Pulmicort® Flexhaler® (Budesonide) 180 or 360 µg BID.	Corrected typographical error to make statement consistent with inclusion criterion #7.
6	Section 4.1, Overall Study Design and Plan, General Guidance for Treatment During In-clinic Visits 3 through 12, Bullets 5 and 9 • The in-clinic dosing time for the MDIs will be recorded as the time of administration of the *second* puff of study medication. **For subjects assigned to open label Serevent, the first puff is the recorded time of dose, as Serevent is only 1 puff.** • **Subjects will undergo a study medication Washout Period of 7 to 14 days, prior to initiating the next treatment period.**	Updated to clarify that open label Serevent dosing is only 1 puff and to provide clarification on the Washout Period requirements
7	Section 4.1, Study Flow Diagram in Figure 1, Footnote 2 [2] *Subjects who do not meet the FEV_1 criteria at Screening may, at the Investigator's discretion, be*	Removed typographical error to align text with all other references to Visit 1b where there is no condition on the number of days

	retested at Visit 1b ~~within the next 2 days~~.	
8	Section 6.7, Instructions for Preparation of Treatments for Administration and Dispensing, Serevent Diskus Individual open-label Serevent Diskus DPIs labeled with a component ID number for IWRS assignment and tracking will be provided by Pearl Therapeutics. Sites will use IWRS to dispense Serevent Diskus to subjects. ~~during Screening and Washout Periods throughout the study~~.	Updated to correct an error in the protocol. Serevent is not used during the Screening and Washout Periods of the study.
9	Section 7.1.2, Characterization of Reversibility, Bullet 1 Perform pre-bronchodilator PFTs prior to administration of Ventolin HFA (albuterol). **Note**: A single pre-dose bronchodilator PFT is collected at Visit 1a **or 1b**. At visit 2a or 2b, pre-bronchodilator PFTs will be performed within 60 minutes prior to administration of Ventolin HFA.	Updated to be consistent with rest of protocol and clarify that the single pre-dose bronchodilator PFT is collected at Visit 1a or 1b, not just at Visit 1a.
10	Section 7.1.2, Characterization of Reversibility, Bullet 3 Perform post-bronchodilator PFT at ~~15~~ **30** minutes after the administration of Ventolin HFA. If the criterion is not met ~~at 15 minutes~~, a repeat post-bronchodilator PFT may be performed at ~~30~~ approximately **60** minutes **post-dose** to assess reversibility.	Updated to reflect the correct timeframe for reversibility assessment consistent with the administrative letter dated [redacted]

11	Table 10 Footnote g and Table 11 Footnote g Subjects must have a diagnosis of asthma confirmed at Visit 1a/b with bronchodilator reversibility (~~15~~**30** to ~~30~~**60** minutes after 4 puffs of salbutamol/albuterol) defined as an FEV_1 increase of at least 12% and at least 200 mL. Pre-bronchodilator FEV_1 must be ≥60% and <90% of predicted normal value at Screening (Visit 1a/b) and Visit 2.	Updated to reflect the correct timeframe for reversibility assessment consistent with the administrative letter dated [redacted].
12	Section 8.8, Visit 12 (Final Study Visit/Day 15 of Treatment Period 5) • **Obtain treatment assignment information from IWRS.** – **To allow for proper preparation of study drug, it is recommended that the seal around the treatment box is opened 15 to 30 minutes prior to dosing, and the instruction for the administration of study drug are followed. Refer to Section 6.7 for detailed instructions for preparation of treatment for administration, including priming of the MDI prior to subject use.** • **Subject will administer in-clinic dosing from the newly assigned MDI dispensed via IWRS**. ~~Subject will administer in-clinic dosing from MDI dispensed at previous visit (Day 1 of Treatment Period 5).~~	Updated to clarify that the subjects should administer the in-clinic dosing on Visit 12 from a newly assigned MDI via IWRS.
13	Section 9.1 Introduction This study will be conducted as a 5-period, 7-treatment, incomplete block cross-over design evaluating the following 7 treatments in approximately 2~~00~~**24** subjects:	Sample size was increased due to the potential for increased variability that the initial drug supplies may have introduced. Based on the new assumptions the power was updated in the table. This is consistent with the administrative letter dated [redacted]

SYNOPSIS

Pearl Therapeutics, Inc. (Pearl) [redacted]
Names of Finished Products: Glycopyrronium Inhalation Aerosol; PT001, Glycopyrronium Metered Dose Inhaler (GP MDI) Salmeterol Xinafoate Inhalational Powder; Serevent® Diskus® Placebo MDI
Name of Active Ingredients: Glycopyrronium Salmeterol Xinafoate
Study Title: A Randomized, Double-Blind, Chronic Dosing (14 days), 5-Period, 7-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-center, Dose-ranging Study to Assess the Efficacy and Safety of PT001 Relative to Placebo MDI and Open-Label Serevent Diskus in Adult Subjects With Intermittent Asthma or Mild to Moderate Persistent Asthma
Study Number: PT001101-01
Study Phase: II
Study Objectives: The overall objective of this study is to assess the efficacy and safety of 5 dose levels of GP MDI (28.8, 14.4, 7.2, 3.6 and 1.9 μg) twice-daily (BID) compared with Placebo MDI and Serevent Diskus 50 μg [salmeterol (SAL)] BID over 14 days in adult subjects with intermittent asthma or mild to moderate persistent asthma. **Primary Objective:** The primary objective of this study is to compare the efficacy of GP MDI to Placebo MDI and SAL on lung function, based on peak forced expiratory volume in 1 second (FEV_1). **Secondary Objectives:** • To characterize the dose-response curve for GP MDI based on lung function assessments • To compare the effects of GP MDI relative to Placebo MDI and SAL on other measures of lung function and symptoms
Safety Objective: To assess the safety and tolerability of GP MDI relative to Placebo MDI and SAL.

Study Design:

This is a randomized, double-blind, chronic-dosing (14 days), 5-period, 7-treatment, incomplete block, cross-over, multi-center study to assess the efficacy and safety of 5 dose levels of GP MDI (28.8, 14.4, 7.2, 3.6 and 1.9 µg) delivered from the mouthpiece BID compared with Placebo MDI BID and open-label SAL 50 µg BID, in adult subjects with intermittent asthma or mild to moderate persistent asthma.

Subjects that meet the eligibility criteria at Screening (Visit 1a) will enter a Screening Period of at least 7 days and not to exceed 28 days. During the Screening Period, subjects previously treated with an inhaled corticosteroid (ICS) will be switched to Sponsor-provided open-label Pulmicort® Flexhaler® (Budesonide) 180 or 360 µg BID. Those subjects on low-dose ICS will be switched to Pulmicort Flexhaler 180 µg BID and those subjects on medium- or high-dose ICS will be switched to Pulmicort Flexhaler 360 µg BID. Subjects who are on non-ICS maintenance therapy (ie., Leukotriene Receptor Antagonist [LTRA]) will be allowed to continue that therapy. All subjects also will receive Sponsor-provided open-label rescue Ventolin® Hydrofluoroalkane (HFA) Inhalation Aerosol (Ventolin HFA) as needed to control symptoms.

At Screening (Visit 1a), subjects must have a pre-bronchodilator FEV_1 between ≥60 and ≤90% predicted normal and demonstrate an improvement in FEV_1 of 12% and 200 mL post-bronchodilator. Those subjects who do not meet this FEV_1 entry criteria at Visit 1a may, at the discretion of the Investigator, be retested at Visit 1b. Those who do not meet the necessary criteria at Visit 1b will be considered screen failures.

Subjects who are on non-ICS maintenance therapy at Screening (Visit 1a) and who meet all entry criteria will be allowed to proceed directly to the Randomization Visit (Visit 3) within 7 to 28 days from Visit 1a.

All subjects switched to Pulmicort Flexhaler at Screening (Visit 1a/b) will complete Screening Visit 2a following 14 days on Pulmicort Flexhaler, to ensure that they meet the spirometry entry criteria. Subjects on Pulmicort Flexhaler 180 µg BID who do not meet the spirometry criteria at Visit 2a will be considered screen failures.

At the discretion of the Investigator, subjects on Pulmicort Flexhaler 360 µg BID who do not meet the spirometry criteria at Visit 2a may have their open-label Pulmicort Flexhaler reduced to 180 µg BID and proceed to Screening Visit 2b following 7 to14 days on Pulmicort Flexhaler 180 µg BID. Subjects who do not meet the spirometry entry criteria at Visit 2b will be considered screen failures.

Visits 1b and 2b are to be used only for repeat spirometry; all other repeat assessments, if needed, will be captured as an unscheduled visit. Subjects who meet all entry criteria at Visit 2a or 2b will proceed to Randomization (Visit 3).

Subjects will be issued and trained on the use of an electronic diary (eDiary) and peak flow meter at Screening and will be instructed to collect data during the Screening Period (between Visit 1a and Visit 3). At Visit 3, subject eDiary compliance will be reviewed and asthma symptom scores assessed. Subjects with eDiary compliance of <70% in the last

7 days preceding Visit 3 will be considered screen failures.

At Visit 3, eligible subjects will be randomized to 1 of 24 pre-defined treatment sequences. Each sequence will include GP MDI 14.4 µg and GP MDI 7.2 µg, 75% of sequences will include Placebo MDI and/or SAL, and 50% of the sequences will include GP MDI 28.8 µg, GP MDI 3.6 µg, and/or GP MDI 1.9 µg. Randomization will be stratified by background therapy, either ICS or non-ICS (subjects not previously treated with ICS).

Subjects will continue to use Pulmicort Flexhaler 360 or 180 µg BID or no ICS as assigned at the end of the Screening Period, for the remainder of the study during both the Treatment Periods and Washout Periods. Subjects who are on non-ICS maintenance therapy (ie., LTRA) will be allowed to continue that therapy for the remainder of the study during both the Treatment Periods and the Washout Periods. Subjects also will continue to receive Sponsor-provided open-label rescue Ventolin HFA, to be used as needed to control symptoms.

The first day of treatment in each Treatment Period is Day 1. Each of the Treatment Periods will be 14 days between the first and last dose, corresponding to a span of 15 calendar days. Therefore, assessments collected on Day 15 will occur after 14 days of treatment in each treatment period. There will be a Washout Period of at least 7 days (up to 14 days) between Treatment Periods. After the last Treatment Period or following a Premature Discontinuation Visit, subjects will be scheduled for a post-study follow-up telephone call 7 to 14 days from the date of the last study dose.

Study Population:
This multi-center study will be conducted at approximately 45 sites, contributing approximately 5 subjects per site. Across these sites, it is planned that approximately 224 subjects with intermittent asthma or mild to moderate persistent asthma will be randomized into the study to provide approximately 180 subjects to complete the study. Randomization will be stratified by ICS use at the time of Screening such that approximately 112 subjects treated with ICS and approximately 112 subjects not treated with ICS will be included.

Test Product, Dose, and Mode of Administration:
Investigational materials will be provided by Pearl Therapeutics as summarized below.

Drug/Product Name & Dose	Product Strength	Dosage Form/Fill Count	Comments
Blinded Study Medications			
GP MDI (PT001) 28.8 µg ex-actuator	GP MDI 14.4 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations BID
GP MDI (PT001) 14.4 µg ex-actuator	GP MDI 7.2 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations BID
GP MDI (PT001) 7.2 µg ex-actuator	GP MDI 3.6 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations BID
GP MDI (PT001) 3.6 µg ex-actuator	GP MDI 1.8 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations BID
GP MDI (PT001) 1.9 µg ex-actuator	GP MDI 0.96 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations BID
Placebo			
Placebo MDI[a]	Formulation does not contain active ingredient	1 MDI 120 inhalations	Taken as 2 inhalations, BID
Open-label Products			
Salmeterol xinafoate inhalation powder 50 µg	Serevent® Diskus® 50 µg per inhalation	1 DPI 60 inhalations	Taken as 1 inhalation, BID
Budesonide Inhalation Powder 360 µg	Pulmicort® Flexhaler® 180 µg per inhalation	1 DPI 60 or 120 inhalations	Taken as 2 inhalations, BID
Budesonide Inhalation Powder180 µg[b]	Pulmicort Flexhaler 90 µg per inhalation	1 DPI 60 or 120 inhalations	Taken as 2 inhalations, BID
Albuterol Sulfate Inhalation Aerosol 90 µg[c] ex-actuator	US source: (Ventolin® HFA) Each actuation contains 108 µg corresponding to 90 µg albuterol base per actuation	1 MDI 60 or 200 actuations	Taken as directed Supplies are open-label

BID=twice daily; DPI=dry powder inhalation ; ex-actuator=dose delivered from the actuator (ie., mouthpiece) of the MDI; GP MDI=Glycopyrronium Inhalation Aerosol; HFA=hydrofluoroalkane; MDI=Metered Dose Inhaler; US=United States

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

[a] Placebo MDI will be administered as a randomized treatment. All placebos are created by Pearl Therapeutics in the image of the active test product.

[b] For subjects currently treated with ICS monotherapy at Screening, open-label Pulmicort Flexhaler DPI 180 µg or 360 µg will be provided by the Sponsor as controller therapy during the study.

[c] Rescue medication

Duration of Treatment:
To standardize asthma maintenance medications and to determine disease severity, eligible subjects will undergo a Screening period of a minimum of 7 days and up to a maximum of 28 days. This will be followed by 5 Treatment Periods of 14 days and a Washout Period of at least 7 days (up to 14 days) between Treatment Periods. A telephone follow-up will be conducted in 7 to 14 days after the last dose. The entire study is scheduled to be approximately 24 weeks for each individual subject from the time of Screening (Visit 1a).

Efficacy Assessments:

The first day of treatment in each Treatment Period is Day 1. Each treatment period will be 14 days between the first and last dose, corresponding to a span of 15 calendar days. Therefore, assessments collected on Day 15 will occur after 14 days of treatment in each treatment period. Baseline will be calculated using the average of the pre-dose values (-60 and -30 minutes) from Day 1 of all treatment periods.

Primary Efficacy Endpoint

- Peak change from baseline in FEV_1 within 3 hours post-dosing on Day 15

Secondary Efficacy Endpoints:

- Change from baseline in morning pre-dose trough FEV_1 on Day 15
- Forced expiratory volume in 1 second area under the curve from time 0 to 3 hours (AUC_{0-3}) on Day 15
- Change from baseline in average daily pre-dose peak expiratory flow rate (PEFR) over 14 days
- Change from baseline in average daily post-dose PEFR over 14 days
- Change from baseline in average daily rescue medication use over 14 days
- Change from baseline in Asthma Control Questionnaire-5 on Day 15

Other Efficacy Endpoints

- Forced vital capacity, PEFR, and forced expiratory flow from 25 to 75% will be evaluated using AUC_{0-3} and peak change from baseline on Day 15

Safety Endpoints

The safety endpoints for this study include:

- Adverse Events
- 12-Lead electrocardiograms
- Clinical laboratory testing
- Vital sign measurements

Statistical Methods:

Sample Size Determination:

Power calculations are based on the properties of the primary endpoint, peak change in FEV_1 on Day 15. An estimate for the within-subject standard deviation (SD) is obtained from a Phase II study with tiotropium (Beeh, 2014). A within-subject SD of 210 mL and an intra-class correlation of 64% are assumed. It is further assumed that approximately 224 subjects will be randomized and approximately 180 subjects will complete the study and be included in the modified intent-to-treat (mITT) Population. Under these assumptions, the power to demonstrate a difference of 75 or 100 mL for each comparison is provided in the table below:

Difference in Peak FEV_1	**GP MDI 14.4 µg versus GP MDI 7.2 µg**	**GP MDI 14.4 or 7.2 µg versus Placebo**	**GP MDI 14.4 or 7.2 µg versus GP MDI 1.9, 3.6, or 28.8 µg**	**GP MDI 1.9, 3.6, or 28.8 µg versus Placebo**	**GP MDI 1.9, 3.6, or 28.8 µg versus GP MDI 1.9, 3.6, or 28.8 µg**
Overall mITT Population					
75 mL	93%	90%	88%	84%	78%
100 mL	99%	99%	99%	97%	95%
Subgroups (ICS User or Non-ICS User)					
75 mL	67%	63%	59%	54%	49%
100 mL	89%	87%	83%	79%	73%

FEV_1=Forced expiratory volume in 1 second; GP=glycopyrronium; ICS=inhaled corticosteroid; MDI=metered-dose inhaler; mITT=modified intent-to-treat

Primary Efficacy Analyses:

The peak change from Baseline in FEV_1 will be calculated using the largest FEV_1 value measured during the 3 hours post-dosing. Baseline will be calculated using the average of the pre-dose values from Day 1 of all treatment periods. The primary efficacy analysis will be based on a mixed model with covariates of treatment, baseline FEV_1, period, ICS use subgroup, and treatment-by-subgroup interaction. The model will not include treatment sequence, unless that term is determined to be important ($p<0.10$). Intra-subject correlation across treatment periods will be modeled by including subject as a random effect.

A 2-sided alpha level of 0.05 will be employed for comparisons of the GP MDI dose levels to Placebo MDI. Multiplicity will be controlled using a sequential approach. Comparisons to SAL will be non-inferiority using a margin of 100 mL, and will follow a similar sequential approach. Comparisons between doses will also be made. The mITT Population will be considered primary, and the ITT Population will be considered supportive.

Date of Original Approved Protocol: [redacted]

Date of Protocol Amendment 01 (Version 2.0): [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ACQ-5	Asthma Control Questionnaire 5
AESI(s)	Adverse event(s) of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC_{0-3}	Area under the curve from time 0 to 3
BID	Bis in die, twice daily
CFR	Code of Federal Regulations
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DPI	Dry powder inhaler
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
FEF_{25-75}	Forced expiratory flow from 25-75%
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GP	Glycopyrronium
hCG	Human chorionic gonadotropin
HFA	Hydrofluoroalkane
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-treat
IWRS	Interactive Web Response System
LABA	Long-acting beta agonist

LAMA	Long-acting muscarinic antagonist
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified ITT
OTC	Over-the-counter
PEFR	Peak expiratory flow rate
PFT	Pulmonary function test
PIN	Personal identification number
QTcF	QT corrected using Fridericia's formula; $QT/(RR^{1/3})$
SABA	Short-acting beta agonist
SAE	Serious Adverse Event
SAL	Salmeterol
SAP	Statistical Analysis Plan
SD	Standard deviation
US/USA	United States

TRADEMARK INFORMATION

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Advair

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Combivent

Dulera

Pulmicort

Flexhaler

Seretide

Spiriva

Symbicort

Ventolin

1 INTRODUCTION

The World Health Organization (WHO) estimates that 235 million people currently suffer from asthma (World Health Organization , 2013). In the United States, asthma is responsible for almost 15 million physician office and hospital visits, and nearly 2 million visits to emergency departments, every year (Akinbami, 2012). People with asthma may experience wheezing, coughing, increased mucous production, and difficulty breathing. These symptoms are due to inflammation and/or obstruction of the airways, which transport air from the nose and mouth to the lungs. While many people develop asthma during childhood, asthma symptoms can also appear at any time in an individual's lifespan (GINA, 2014). Those individuals who develop asthma as adults are said to have adult-onset asthma.

A basic principle of asthma therapy is that the intensity of treatment should match the severity of asthmatic symptoms. As a result, patients with infrequent and mild symptoms of asthma should be treated intermittently with the goal of quick symptom relief, mainly using rescue inhalers up to maximum 4 to 6 times in 24 hours. Patients with mild symptoms that are persistent or present regularly also should receive a long-term controller medication. For all types of asthma, effective communication, ongoing patient education, and regular reassessment of asthma control are crucial for long-term success. The principal goals of treatment of moderate persistent asthma are to minimize symptoms, normalize pulmonary function, prevent exacerbations, and improve health-related quality of life. A theoretical goal is to prevent the putative long-term consequences of airway inflammation, particularly airway remodeling and chronic persistent airway obstruction. (NHLBI EPR-3, 2007)

The current National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report-3 (EPR-3) [NHLBI EPR-3, 2007]) recommends long-term treatment with inhaled corticosteroids (ICS) because of their superior effectiveness in managing the chronic airway inflammation that characterizes persistent asthma. Long-acting beta agonists (LABAs) including salmeterol, have a bronchodilation of at least 12 hours duration after a single dose. Use of LABA added to low-to-medium doses of ICS leads to improvements in lung function and symptoms and reduced need for quick relief short-acting beta agonists (SABAs [National Asthma Education and Prevention Program EPR Update, 2002]). In asthma, LABAs are not to be used as monotherapy for long-term control and are most effective when combined with ICS (NHLBI EPR-3, 2007).

The NHLBI EPR-3 Guidelines recommend a stepwise approach to asthma treatment: ICS monotherapy as first-line controller treatment for persistent asthma (mild, moderate, and severe). If asthma remains uncontrolled with low-dose ICS monotherapy, only then should physicians consider prescribing a medium-dose ICS or adding a LABA to a low-dose ICS regimen (NHLBI EPR-3, 2007).

Regular treatment with ICS improves symptoms, lung function, and quality of life, and reduces the frequency of exacerbations in asthma patients with forced expiratory volume in 1 second (FEV_1) <60% of predicted. Withdrawal from treatment of ICS may lead to exacerbations in some patients. When combined with a LABA, an ICS is more effective than the individual components in improving lung function, quality of life, and reducing exacerbations in patients with moderate to very severe asthma (GINA, 2014).

Budesonide is approved for use in children and adults. Since its introduction in the 1980's, it has been widely used and is generally acknowledged to have a favorable benefit to risk ratio. The benefit of budesonide is afforded by its potent anti-inflammatory action at the site of the mucosal inflammatory response characteristic of asthma, combined with limited systemic availability. A large number of studies have been conducted to assess the effects of budesonide when used to treat chronic asthma, and a large range outcome measures have been used to assess its efficacy and safety.

The use of long-acting, muscarinic antagonists (LAMAs) are well-established in the treatment of chronic obstructive pulmonary disease (COPD), but to date, their use in the treatment of asthma has been limited to acute management. More recently, the potential of LAMAs in the treatment of asthma has been explored. Accumulating evidence supports the use of inhaled LAMAs as an add-on therapy in patients with asthma who remain symptomatic despite therapy with ICS, with or without LABAs (Lipworth, 2014, Rogers, 2015). In clinical studies, LAMAs have shown a significant improvement in FEV_1, quality of life, and dyspnea, and reduced the number of exacerbations in COPD and more recently in asthma (Alagha et al, 2014).

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

An inhaled formulation of glycopyrronium (Seebri® Breezhaler® Inhalation Powder, glycopyrronium bromide; also referred to as NVA237) was recently approved throughout the European Union (EU) and in Canada, Australia, and Japan. In the EU, Seebri Breezhaler is approved as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

1.1 Background

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 distearoylphosphatidylcholine and calcium chloride that are cosuspended with crystalline active drug substances and formulated into suspension-based hydrofluoroalkane (HFA) metered dose inhalers (MDIs). The safety of porous particles has been demonstrated previously in Phase I studies in healthy volunteers and in Phase II studies in over 1000 subjects with COPD.

Pearl Therapeutics is developing a broad range of MDI-based inhalation aerosols using its porous particle-technology platform. Glycopyrronium (GP [GP MDI PT001]), Formoterol Fumarate (FF [FF MDI, PT005]), and a combination product comprising GP and FF in a fixed-dose metered dose inhaler (GFF MDI, PT003) are currently being evaluated in Phase III studies in subjects with COPD. In addition, Pearl Therapeutics has initiated a Phase II dose-ranging study in adults with mild to moderate persistent asthma with Budesonide Inhalation Aerosol (BD MDI, PT008). The present study is intended to evaluate the dose response of GP MDI in adult subjects with asthma to support the further

development of glycopyrronium as a monotherapy (GP MDI) and in combination products, in subjects with asthma.

1.2 Study Rationale

There are currently no study data available in subjects with asthma for GP MDI. This study is being conducted to characterize the dose response and lung function benefit of GP MDI delivered in a porous-particle MDI platform in adult subjects with intermittent asthma or mild to moderate persistent asthma.

2 STUDY OBJECTIVES

The overall objective of this study is to assess the efficacy and safety of 5 dose levels of GP MDI (28.8, 14.4, 7.2, 3.6 and 1.9 μg) twice-daily (BID) compared with Placebo MDI and Serevent Diskus 50 μg [salmeterol (SAL)] BID over 14 days in adult subjects with intermittent asthma or mild to moderate persistent asthma.

2.1 Primary Objective

To compare the efficacy of GP MDI to Placebo MDI and SAL on lung function based on peak FEV_1

2.2 Secondary Objective

- To characterize the dose response curve for GP MDI based on lung function assessments
- To compare the effects of GP MDI relative to Placebo MDI and SAL on other measures of lung function and symptoms

2.3 Safety Objective

- To assess the safety and tolerability of GP MDI relative to Placebo MDI and SAL.

3 STUDY ENDPOINTS

3.1 Efficacy Assessments

The first day of treatment in each Treatment Period is Day 1. Each treatment period will contain 14 days between the first and last dose, corresponding to a span of 15 calendar days. Therefore, assessments collected on Day 15 will occur after 14 days of treatment in each treatment period. Baseline will be calculated using the average of the pre-dose values (-60 and -30 minutes) from Day 1 of all treatment periods.

3.1.1 Primary Efficacy Endpoint

- Peak change from Baseline in FEV_1 within 3 hours post-dosing on Day 15

3.1.2 Secondary Efficacy Endpoints

- Change from Baseline in morning pre-dose trough FEV_1 on Day 15
- Forced Expiratory Volume in 1 second area under the curve from time 0 to 3 hours (AUC_{0-3}) on Day 15
- Change from Baseline in average daily pre-dose peak expiratory flow rate (PEFR) over 14 days
- Change from Baseline in average daily post-dose PEFR over 14 days
- Change from Baseline in average daily rescue medication use over 14 days
- Change from Baseline in Asthma Control Questionnaire 5 (ACQ-5) score on Day 15

3.1.3 Other Efficacy Endpoints

- Forced vital capacity (FVC), PEFR, and forced expiratory flow from 25 to 75% (FEF_{25-75}) will be evaluated using AUC_{0-3} and peak change from baseline on Day 15

3.1.4 Safety Endpoints

The safety endpoints include:

- Adverse events (AEs)
- 12-lead electrocardiograms (ECGs)
- Vital sign measurements
- Clinical laboratory tests

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind, chronic-dosing (14 days), 5-period, 7-treatment, incomplete block, cross-over, multi-center study to assess the efficacy and safety of 5 dose levels of GP MDI (28.8, 14.4, 7.2, 3.6 and 1.9 µg) delivered from the mouthpiece (ex-actuator) BID compared with Placebo MDI BID and open-label SAL 50 µg BID, in adult subjects with intermittent asthma or mild to moderate persistent asthma.

Subjects that meet the eligibility criteria at Screening (Visit 1a) will enter a Screening Period of at least 7 days and not to exceed 28 days. During the Screening Period, subjects previously treated with an ICS will be switched to Sponsor-provided open-label Pulmicort® Flexhaler® (Budesonide) 180 or 360 µg BID. Those subjects on low-dose ICS will be switched to Pulmicort Flexhaler 180 µg BID and those subjects on medium- or high-dose ICS will be switched to Pulmicort Flexhaler 360 µg BID. Subjects who are on non-ICS maintenance therapy (ie., Leukotriene Receptor Antagonist [LTRA]) will be allowed to continue that therapy for the remainder of the study during both the Treatment Periods and Washout Periods. All subjects also will receive Sponsor-provided open-label rescue Ventolin® Hydrofluoroalkane Inhalation Aerosol (Ventolin HFA) as needed to control symptoms.

At Screening (Visit 1a), subjects must have a pre-bronchodilator FEV_1 between ≥60 and ≤90% predicted normal and demonstrate an improvement in FEV_1 of 12% and 200 mL post-bronchodilator. Those subjects who do not meet this FEV_1 entry criteria at Visit 1a may, at the discretion of the Investigator, be retested at Visit 1b. Those who do not meet the necessary criteria at Visit 1b will be considered screen failures.

Subjects who are on non-ICS maintenance therapy at Screening (Visit 1a) and who meet all entry criteria, will be allowed to proceed directly to the Randomization Visit (Visit 3) within 7 to 28 days from Visit 1a.

All subjects switched to Pulmicort Flexhaler at Screening (Visit 1a/b) will complete Screening Visit 2a following a minimum of 14 days on Pulmicort Flexhaler, to ensure that they meet the spirometry entry criteria. Subjects on Pulmicort Flexhaler 180 µg BID who do not meet the spirometry criteria at Visit 2a will be considered screen failures.

At the discretion of the Investigator, subjects on Pulmicort Flexhaler 360 µg BID who do not meet the spirometry criteria at Visit 2a may have their open-label Pulmicort Flexhaler reduced to 180 µg BID and proceed to Screening Visit 2b following 7 to14 days on Pulmicort Flexhaler 180 µg BID. Subjects who do not meet the spirometry entry criteria at Visit 2b will be considered screen failures.

Visits 1b and 2b are to be used only for repeat spirometry; all other repeat assessments, if needed, will be captured as an unscheduled visit. Subjects who meet all entry criteria at Visit 2a or 2b will proceed to Randomization (Visit 3).

Subjects will be issued and trained on the use of an electronic diary (eDiary) and peak flow meter at Screening and will be instructed to collect data during the Screening Period (between Visit 1a and Visit 3). At Visit 3, subject eDiary compliance will be reviewed and the compliance requirement of ≥70% in the last 7 days preceding the visit must be met. Subjects also must meet the FEV_1 entry criteria to be eligible for Randomization. Subjects who do not meet the eDiary compliance requirement and/or FEV_1 entry criteria must be screen failed at Visit 3.

All eligible subjects at Visit 3 (Randomization Visit; Treatment Period 1, Day 1) will be randomized to 1 of 24 pre-defined treatment sequences. Each sequence will include GP MDI 14.4 µg and GP MDI 7.2 µg, 75% of sequences will include Placebo MDI and/or SAL, and 50% of the sequences will include GP MDI 28.8 µg, GP MDI 3.6 µg, and/or GP MDI 1.9 µg. Randomization will be stratified by background therapy, either ICS or non-ICS (subjects not previously treated with ICS). The 24 treatment sequences are illustrated in Section 9.5.

With the exception of SAL administration, the subject, clinical site personnel, and Pearl Therapeutics will be blinded to the treatment sequence assigned to each subject.

Subjects will continue to receive Sponsor-provided open-label rescue Ventolin HFA, to be used as needed to control symptoms.

The first day of treatment in each Treatment Period is Day 1. Each of the Treatment Periods will be 14 days between the first and last dose, corresponding to a span of 15 calendar days. Therefore, assessments collected on Day 15 will occur after 14 days of treatment in each treatment period. There will be a Washout Period of at least 7 days (up to 14 days) between Treatment Periods. After the last Treatment Period or following a Premature Discontinuation Visit, subjects will be scheduled for a post-study follow-up telephone call 7 to 14 days from the date of the last study dose.

During Visit 3 (Treatment Period 1, Day 1), site staff must confirm that the subject met all inclusion/exclusion criteria and must ensure adequate washout (≥6 hours) of short-acting bronchodilators and other asthma medications. The study site staff will prime the study drug MDI for subject use, the subjects will be dispensed study medication, and they will self-administer their first dose at the clinic under site personnel supervision before 10 AM.

Subjects will be required to remain at the clinic until completion of all protocol-defined visit assessments up to and including the 3-hour post-dose assessment (see Section 8.5). Subjects will then be discharged from the clinic and will continue to administer study medication and complete their eDiary entries at home until Visit 4 (Treatment Period 1, Day 15).

At Visit 4 (Treatment Period 1, Day 15) subjects will return to the clinic following approximately 14 days of Treatment 1 dosing at home and complete Visit 4 procedures (see Section 8.7). On discharge, subjects will undergo a study medication Washout Period of 7 to 14 days, prior to initiating Treatment 2 in their assigned treatment sequence at Visit 5.

Following the Washout Period, subjects will repeat a similar pattern of visits and assessments described above for Treatment 1 for the next 4 treatments in their assigned sequence.

Subjects will continue to use the Pulmicort Flexhaler 360 or 180 µg, or no ICS as assigned at the end of the Screening Period, for the remainder of the study during both the Treatment Periods and Washout Periods. Subjects also will continue to receive Sponsor-provided open-label rescue Ventolin HFA, to be used as needed to control symptoms.

After the last Treatment Period or following a Premature Discontinuation Visit, subjects will be scheduled for a post-study follow-up telephone call 7 to 14 days from the date of the last study dose.

General Guidance for Treatment During In-clinic Visits 3 through 12

- At the start of each treatment visit, prior to any study procedures being performed, site personnel must confirm the subject withheld all asthma medications, including withheld study medication and rescue medications (eg., Ventolin HFA [albuterol]) for at least 6 hours, by confirming the last time of dosing for all asthma medication[s]).

Note: Subjects who inadvertently took rescue medication within 6 hours of the start of study procedures must be rescheduled as soon as is practical, but within the specified visit window. In addition, before the in-clinic dose is administered, the site must confirm the subject met all other protocol-specified requirements (eg., FEV_1 baseline stability). Subjects will remain in the clinic until 3 hours post-dose, for observation (safety).

- Subjects must not ingest xanthine-containing foods and beverages for at least 4 hours prior to and for the duration of each study visit. Decaffeinated beverages are acceptable during this window.
- To ensure standardization of dosing times, it is recommended that sites encourage subjects to maintain an at-home dosing schedule consistent with their in-clinic dosing time.
  - Subjects will be required to take their study medication BID: once in the morning between 6:00 and 10:00 AM (breakfast time), and once in the evening between 6:00 and 10:00 PM (dinner time).
  - In order to minimize diurnal variance, sites should make every effort to assess subjects at the same time throughout the study and to discuss the importance of dosing in a timely manner, every 12 hours.
  - Subjects will be required to return to the clinic at approximately the same time as Visit 3 for all treatment visits (± 2 hours), but no later than 10:00 AM, and will be required to remain at the clinic until completion of all protocol-defined visit assessments.

  Note: Sites should make every effort to ensure that the in-clinic dosing time is before 10:00 AM and within 12 ± 2 hours of the prior at-home evening dosing time.

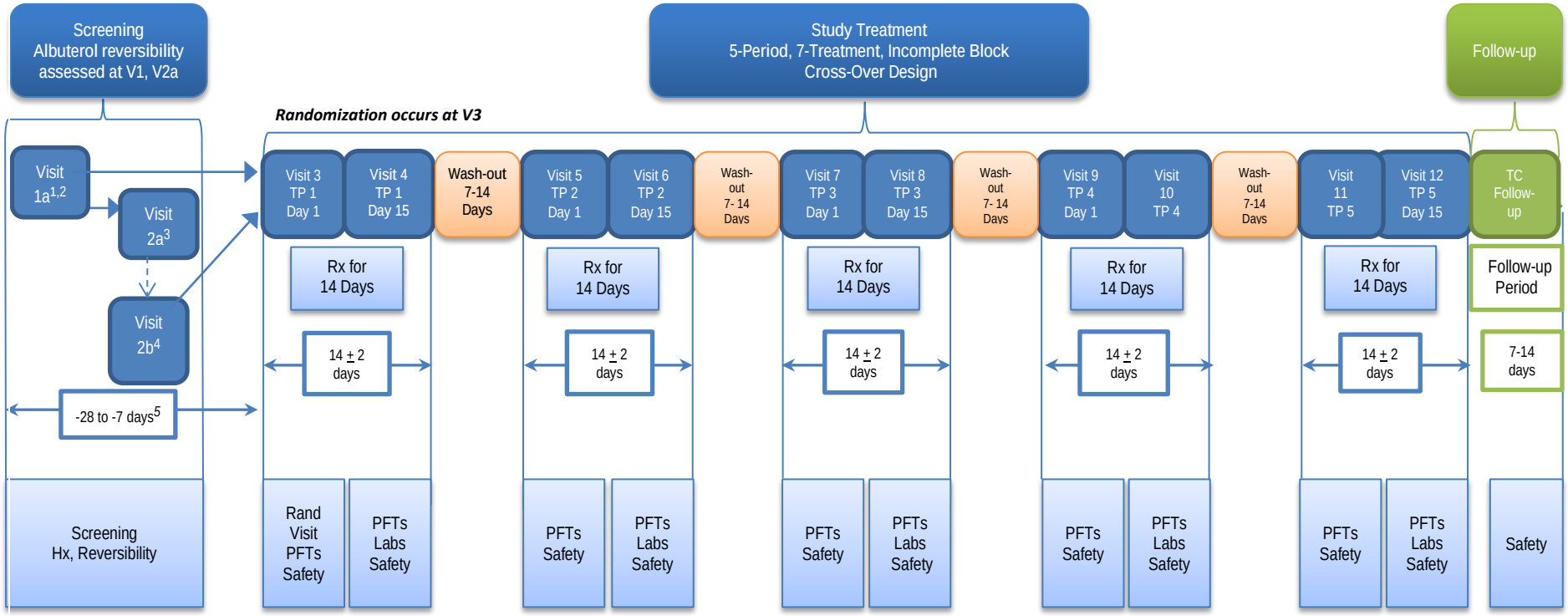
- Sites are encouraged to call the subject on the day before a scheduled visit to remind the subject to:
  - Take their last dose the evening before (12 ± 2 hours) prior to the scheduled visit.
  - Bring their study medications with them to the clinic

  - Withhold short-acting bronchodilators and other asthma medications for at least 6 hours prior to pulmonary function test (PFTs).
  - Refrain from ingesting xanthine-containing foods and beverages for at least 4 hours prior to each study visit and for the duration of each study visit.

- The in-clinic dosing time for the MDIs will be recorded as the time of administration of the *second* puff of study medication. For subjects assigned to open label Serevent, the first puff is the recorded time of dose, as Serevent is only 1 puff.
- Site personnel will instruct subjects not to take any non-study asthma medications without site personnel permission during a visit, until all study procedures have been completed and the subject is discharged. Site personnel should take every precaution to prevent use of non-study asthma medications during the test day. Site personnel may request that the subject surrender all non-study asthma medications prior to the start of the visit before performing any study procedures, and return to the subject at the end of the visit when all study procedures are completed.
- If a subject is experiencing severe symptoms and requires Ventolin HFA for relief of asthma symptoms at any time during a test day, site personnel must note the time and justification for use in the subject's chart and all subsequent spirometry and PEFR assessments should be stopped during the current treatment visit. However, safety assessments should be continued at the discretion of the Investigator.
- Every effort must be made to ensure that subjects return to the clinic on Day 15 (2 weeks) following initiation of each treatment arm. To accommodate scheduling conflicts, a window of 14 ± 2 days from Treatment Day 1 is permitted (ie.,Treatment Day 15 procedures must be performed between Treatment Day 13 and Treatment Day 17, inclusive).
- Subjects will undergo a study medication Washout Period of 7 to 14 days, prior to initiating the next treatment period.

A Study Flow Diagram is displayed in Figure 1.

Figure 1. Study Flow Diagram



GP=glycopyrronium; Hx=Medical History; ICS=Inhaled Corticosteroids; PFTs =Pulmonary Function Tests Rx=Treatment; SAL=salmeterol; TC=telephone call; TP=Treatment Period

[1] *Subjects who are on non-ICS maintenance therapy and meet the spirometry entry criteria at Screening (Visit 1a) will be able to proceed directly to the Randomization Visit (Visit 3) within 7-28 days from Visit 1a .*

[2] *Subjects who do not meet the FEV1 criteria at Screening may, at the Investigator's discretion, be retested at Visit 1b.*

[3] *All subjects switched to Pulmicort Flexhaler at Screening (Visit 1a/b) will complete Screening Visit 2a following a minimum of 14 days on Pulmicort Flexhaler, to ensure that they meet the spirometry entry criteria.*

[4] *Subjects who receive Pulmicort Flexhaler 360 µg BID and have a pre-dose FEV1 > 90% predicted or who do not meet the post-bronchodilator FEV1 requirements, may have Pulmicort Flexhaler reduced to 180 µg BID at the discretion of the Investigator.*

[5] *Subjects who have Pulmicort Flexhaler reduced to 180 µg BID will proceed to Visit 2b following an additional 7-14 day Screening period from Visit 2a on Pulmicort Flexhaler 180 µg BID.*

Randomized, placebo-controlled, incomplete block, design in subjects with intermittent asthma or mild to moderate persistent asthma
N=200
Treatments: GP MDI: 28.8 µg, 14.4 µg, 7.2 µg, 3.6 µg, 1.9 µg; SAL 50 µg; Placebo MDI

Each subject will receive 14 days (2 weeks) of study treatment with each of their assigned treatments for a total of 5 separate Treatment Periods.

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

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

1. Give their signed written informed consent to participate
2. Males and females ranging in age between 18 to 70 years, inclusive, before Screening (Visit 1a)
3. A female is eligible to enter and participate in the study if she is of:

- Non-child bearing potential (ie., 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 (Visit 1a), and agrees to 1 of the following acceptable contraceptive methods used consistently and correctly (ie., in accordance with the approved product label and the instructions of the physician for the duration of the study, from Screening [Visit 1a] until 14 days after Visit 12):
  - Complete abstinence from intercourse; 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 1 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 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. Asthma History: Have a diagnosis of intermittent asthma or mild to moderate persistent asthma, diagnosed at least 6 months prior to Screening (Visit 1a) as presented in Table 1.

Table 1. Classification of Asthma Severity

		Persistent	
	Intermittent	**Mild**	**Moderate**
Symptoms	≤2 days/week	>2 days/week but not daily	Daily
Nighttime awakenings	≤2 days/month	3-4x/month	>1x/week but not nightly
SABA use for symptom control (not prevention of EIB)	≤2 days/week	>2 days//week but not >1x/day	Daily
Interference with normal activity	None	Minor limitation	Some limitation

EIB=exercise-induced bronchospasm; SABA=short-acting beta antagonist

Source: GINA, 2014

5. Reversibility: Diagnosis of asthma confirmed at Screening (Visits 1 and 2) with demonstration of reversibility to a bronchodilator defined as an FEV_1 increase of at least 12% and at least 200 mL, 30 to 60 minutes after the inhalation of 4 puffs of salbutamol/albuterol (Ventolin HFA)
6. Pulmonary Function: Must have a pre-bronchodilator FEV_1 ≥60% and ≤90% of predicted normal value at Visit 1a/b and Visit 2a/b
7. Asthma Maintenance Therapy: For those subjects receiving asthma maintenance therapy, they must be on a stable dose of ICS or non-ICS therapy (eg., LTRA) for at least 4 weeks prior to Screening (Visit 1a).
8. Results of clinical laboratory tests conducted at Screening (Visit 1a) must be acceptable to the Investigator.

5.2 Exclusion Criteria

The following subjects will be excluded from the study if any of the following criteria apply:

1. Life-Threatening Asthma: A subject must not have life-threatening asthma. Life-threatening asthma is defined as a history of significant asthma episode(s) requiring intubation associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma-related syncopal episode(s) within the 12 months prior to Visit 1a (Screening).
2. Worsening Asthma: A subject must not have experienced a worsening of asthma that involved an emergency department visit, hospitalization, or use of oral/parenteral corticosteroids within 6 weeks of Screening (Visit 1a).
3. Seasonal or Exercise-Induced Asthma Alone: Subjects with only seasonal or exercise-induced asthma are excluded from participation.
4. Concurrent Respiratory Disease: A subject must not have current evidence or diagnosis of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, chronic bronchitis, emphysema, COPD, or other respiratory abnormalities other than asthma.
5. Concurrent Conditions/Diseases: A subject with historical or current evidence of any clinically significant, or comorbid or uncontrolled condition or disease state that, in the opinion of the Investigator, would put the safety of the subject at risk through study participation or would confound the interpretation of the results if the condition/disease exacerbated during the study.
6. Smoking History: Current smokers or former smokers who have stopped smoking within 6 months prior to enrollment or with a >10 pack year history of cigarettes, cigars, or pipe smoking. E-cigarettes and inhaled marijuana should be treated in the same manner as tobacco products.
7. Inhaled Anticholinergic Use: Subjects must not have used inhaled anticholinergics for at least the 2 weeks prior to Screening (Visit 1a).
8. Pregnant women or nursing mothers
9. Respiratory Tract Infection: Subjects who have had a respiratory tract infection within 6 weeks prior to Screening (Visit 1a). Subjects who develop a respiratory tract infection during the Screening Period must discontinue from the trial, but will be permitted to re-

enroll at a later date (at least 6 weeks after the resolution of the respiratory tract infection).

10. Uncontrolled Hypertension: Subjects who, in the opinion of the Investigator, have clinically significant uncontrolled hypertension.
11. Liver Function: Subjects with abnormal liver function tests defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or total bilirubin ≥1.5 times the upper limit of normal on repeat testing.
12. Renal:
    a. Subjects with symptomatic prostatic hypertrophy that is clinically significant in the opinion of the Investigator (if treated and asymptomatic, the subject is eligible for enrollment). Subjects with a trans-urethral resection of prostate or full resection of the prostate within 6 months prior to Visit 1a are excluded from the study.
    b. Subjects with bladder neck obstruction or urinary retention that is clinically significant in the opinion of the Investigator.
    c. Subjects with a calculated creatinine clearance ≤30 mL/minute using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [Levey, 2009] at Visit 1a and on repeat testing prior to Visit 3.

    - **Note:** Subjects with overactive bladder syndrome treated with oral anticholinergics that have been on treatment for at least 1 month are allowed in the study.
13. Glaucoma: Subjects with a diagnosis of angle closure glaucoma will be excluded, regardless of whether or not they have been treated. Subjects with a diagnosis of glaucoma (non-angle closure), that in the opinion of the Investigator, has not been adequately treated will also be excluded. Subjects with previously diagnosed glaucoma who have intraocular pressure controlled with medication(s) are eligible. All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective β-blockers such as betaxolol, carteolol, levobunolol, metipranolol, or timolol.
14. Cancer: Subjects who have cancer that has not been in complete remission for at least 5 years.

    Note: Subjects with squamous cell carcinoma and basal cell carcinoma of the skin that have been resected for cure are not considered exclusionary. Subjects with localized prostate cancer that in the opinion of the Investigator, has been adequately worked up, is clinically controlled, and the subject's participation in the study would not represent a safety concern, are eligible.
15. Drug Allergy: Subjects who have a history of hypersensitivity to lactose, milk proteins, or to any component of the MDI or dry powder inhaler (DPI)
16. Substance Abuse: Subjects with a known or suspected history of alcohol or drug abuse within the last 2-year period prior to Screening (Visit 1a).
17. Cardiac Conditions/Disease: Subjects with documented myocardial infarction within a year from the Screening (Visit 1a) are to be excluded. Subjects with a recent history of acute coronary syndrome, or who have undergone percutaneous coronary intervention or coronary artery bypass graft within 3 months of Screening (Visit 1a) are to be excluded.

18. Clinically significant abnormal ECG: A clinically significant abnormal ECG is defined as (but not limited to) any of the following:
- Clinically significant conduction abnormalities (eg., left bundle branch block, Wolff-Parkinson-White syndrome or evidence of second degree [Mobitz Type II] or third degree atrioventricular [AV] block).
- Clinically significant arrhythmias (eg., 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 (eg., poorly defined termination of the T wave).
- Bradycardia with rate <45 bpm.
- Pathological Q waves of 1 year or less
- ST-T wave abnormalities (excluding non-specific ST-T wave abnormalities)
- Subjects who, in the opinion of the Investigator, have a clinically significant abnormal 12-lead ECG

19. Medication prior to Spirometry: Subjects who are medically unable to withhold their short-acting bronchodilators and other asthma medications for the 6-hour period required prior to spirometry testing at each study visit will be excluded.
20. Prohibited Asthma Medications: Subjects taking the following medications within the specified time intervals prior to Screening (Visit 1a) are to be excluded:
- 3 months: depot corticosteroids, intra-articular corticosteroids
- 6 weeks: parenteral and oral corticosteroids administered for an asthma exacerbation

Note: Subjects requiring chronic maintenance therapy with oral corticosteroids are excluded from participation in this study.
- Subjects treated chronically with oral or systemic corticosteroids are excluded from the study.
- Subjects treated with an antibiotic for an upper or lower respiratory tract infection need to have completed the course of antibiotics for 6 weeks prior to Screening (Visit 1a).
- Subjects treated chronically with antibiotics are excluded from the study.

21. Other Diseases: Subjects who have clinically significant medical conditions, as deemed by the Investigator, including but not limited to cardiovascular, neurological, psychiatric, hepatic, gastrointestinal, chronic renal, immunological, endocrine (including uncontrolled diabetes, hypokalemia or thyroid disease), hematological medical problems, with clinical evidence of oral thrush, and ocular opacity due to steroid usage are excluded. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the subject at risk through study participation or would affect the efficacy analysis if the disease/condition exacerbated during the study.
22. Spirometry Performance:
    a. Acceptability Criteria: Subjects who cannot perform acceptable spirometry, (ie., meet American Thoracic Society/European Respiratory Society [ATS/ERS] acceptability criteria)
    b. Repeatability Criteria: Subjects who cannot perform technically acceptable spirometry with at least 3 acceptable flow-volume curves with 2 or more meeting ATS repeatability criteria for FEV_1 during the pre- and post-bronchodilator assessments at Visit 1a/b

23. Non-compliance: Subjects unable to comply with study procedures, including non-compliance with eDiary completion (ie., <70% subject completion of eDiary assessment in the last 7 days preceding Visit 3 (Randomization Visit).
24. 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.
25. Questionable Validity of Consent: Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol), or other conditions that will limit the validity of informed consent to participate in the study.
26. 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.
27. Spacer Devices: A subject who requires the use of a spacer device to compensate for poor hand-to-breath coordination with a MDI.

5.3 Subject Identification

All subjects who undergo Screening will be assigned a unique screening identification number at Screening (Visit 1a). Only subjects who continue to meet entry inclusion/exclusion criteria at Visit 3 (Randomization) will be assigned a unique subject randomization number.

5.4 Prior, Concomitant, and Prohibited Medications

Prescription and Over-the-Counter Medications:

All prescription and over-the-counter (OTC) medications taken by the subject during 30 days before Screening will be recorded on the Concomitant Medications electronic case report form (eCRF) page. Any additions, deletions, or changes in the dose of these medications while in the study should be entered on the eCRF.

Any current ongoing medications, including OTC drugs and herbal supplements, will be allowed provided they are not prohibited by the protocol (see Table 3) and are approved by the Investigator. Subjects 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 eCRF page with indication, total daily dose, and dates of drug administration.

Asthma Medications:

The definitions of the doses of ICS considered "low", "medium", and "high" are provided below in Table 2.

Table 2. Estimated Equipotent Daily Doses of Inhaled Glucocorticosteroids

Drug	Low Dose (µg)	Medium Daily Dose (µg)[a]	High Daily Dose (µg)[a]
Beclomethasone dipropionate (CFC)	200 - 500	>500 - 1000	>1000
Beclomethasone dipropionate (HFA)	100 - 200	>200 - 400	>400
Budesonide (DPI)	200 - 400	>400 - 800	>800
Ciclesonide (HFA)	80 - 160	>160 - 320	>320
Fluticasone propionate (DPI)	100 - 250	>250 - 500	>500
Fluticasone propionate (HFA)	100 - 250	>250 - 500	>500
Mometasone furoate	110-220	>220-440	>440
Triamcinolone acetonide	400 - 1000	>1000 - 2000	>2000
Fluticasone Furoate[b]	--	100	200

CFC = chlorofluorocarbons; DPI=dry powder inhaler; HFA = hydrofluoroalkanes

[a] Subjects who have been clinically stable and on a stable dose for a minimum of 3 months can be stepped down to a lower dose, at the discretion of the Investigator.

[b] Fluticasone Furoate is newly approved. See Arnuity-Ellipta (fluticasone furoate inhalation powder) Package Information

Note: Comparisons are based on efficacy data.

Source: GINA, 2014

Prohibited Medications:

The use of any of the medications listed in Table 3 is not permitted during this study. If any prohibited medication is initiated after Screening, the subject must be discontinued immediately. If the subject had been prescribed any of the prohibited medications and the medication was discontinued recently, but before Screening, the minimum Washout Period prior to Screening is presented in Table 3.

Table 3. Prohibited Medications

Prohibited Medications	Minimum Cessation Period Prior to Screening (Visit 1a)
Other investigational drugs	30 days or 5 half-lives whichever is longer
Non-selective beta-blocking agents	7 days
Immunosuppressants (Methotrexate, Cyclosporins, etc.)	7 days
Anticonvulsants (barbiturates, hydantoins, and carbamazepine) for seizure disorder	Allowed if stable dose for 12 months and free of seizures for 1 year
Anticonvulsants for other indications	Allowed if stable dose for at least 3 months and the Investigator confirms there have been no seizures within the past 12 months.
Tricyclic antidepressants	14 days
Monoamine oxidase inhibitors	14 days
Anti-tumor necrosis factor α (TNF α) antibodies (eg., infliximab and any other members of this class of drugs)	30 days or 5 half-lives, whichever is longer
Monoclonal antibodies	30 days or 5 half-lives, whichever is longer
Antipsychotic drugs (phenothiazines)	30 days
Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors and cimetidine	30 days
Inhaled herbal supplements	10 days
Theophylline	7 days

Note: For subjects who are being treated with retroviral therapy, including: entry inhibitors, nucleoside and nucleotide reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, or non-nucleoside reverse transcriptase inhibitors, the Investigator should consult with the Pearl Therapeutics Medical Monitor prior to Screening.

5.5 Other Restrictions, Illicit Drugs or Drugs of Abuse

5.5.1 Illicit Drugs

Illicit drugs or drugs of abuse will not be allowed from the start of Screening (Visit 1a) to the end of the Follow-up telephone call or to whenever the subject withdraws from the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented and the subject will be discontinued at the discretion of the investigator.

5.5.2 Dietary Restrictions

Subjects must not ingest xanthine-containing foods and beverages such as coffee, tea, chocolate, and cola, for at least 4 hours prior to each study visit after the Screening Visit and for the duration of each study visit. Decaffeinated beverages are acceptable.

5.6 Reasons and Procedures for Early Termination

Subjects may be withdrawn from the study at any time at their own request, upon request of the Investigator, or by Pearl Therapeutics, at any time or for any reason. If a subject is lost to follow up (ie., fails to return for study visits) reasonable efforts must be made to contact the subject and complete study termination procedures. All subjects who discontinue the study because of an AE will be followed up at suitable intervals in order to evaluate the course of the AE and to ensure the reversibility or stabilization of the abnormality. All subjects who prematurely discontinue the study after being randomized, regardless of the cause, should undergo only the assessments outlined in Section 8.9 on the day of discontinuation.

If a subject experiences any of the changes of concern listed below, a repeat assessment should be obtained, and, if confirmed, the Investigator or designee must make a determination as to the suitability of continuing the subject in the study.

The changes of concern include:

- Decrease in creatinine clearance to a value below 30 mL/min using Chronic Kidney Disease – Epidemiology Collaboration formula ***or*** a clinically relevant change from Baseline, as determined by the Investigator.
- Hepatic impairment, defined as abnormal liver enzyme/function test of AST, ALT or total bilirubin ≥1.5 times upper limit of normal on repeat testing.
- The Investigator or designee will need to determine whether the subject is having a clinical worsening of asthma (asthma exacerbation) and will also make a determination as to the suitability of continuing the subject in the specific treatment period.
  - If a subject requires use of rescue medication 4 or more times per day (ie., ≥8 puffs of Ventolin HFA) for 3 or more consecutive days.
- If a subject does not meet protocol-defined FEV_1 baseline stability criteria (Section 7.1.3) at the start of each treatment period, the subject will be discontinued.
- If a subject requires prescription of any prohibited medications as listed in Table 3, the subject should be discontinued from the study.
- If a female subject becomes pregnant during the course of the study, the subject will be discontinued and the pregnancy will be followed full-term through delivery or final outcome (see Section 7.2.9)

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

6.1 Subject Information

Clinical supplies will be packaged to support enrollment of the study.

Study personnel will have access to the Interactive Web Response System (IWRS) to allocate subjects to treatment sequence, to assign drug to subjects, 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 personal identification number (PIN). They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

6.2 Product Descriptions

Investigational materials will be provided by Pearl Therapeutics. Test products, dose, and mode of administration are summarized in Table 4.

Table 4. Product-Packaging Descriptions of Study Drug, Open-label Products and Placebo

Drug/Product Name & Dose	Product Strength	Dosage Form/Fill Count	Comments
Blinded Study Medication			
GP MDI (PT001) 28.8 µg ex-actuator	GP MDI 14.4 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations BID
GP MDI (PT001) 14.4 µg ex-actuator	GP MDI 7.2 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations BID
GP MDI (PT001) 7.2 µg ex-actuator	GP MDI 3.6 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations BID
GP MDI (PT001) 3.6 µg ex-actuator	GP MDI 1.8 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations BID
GP MDI (PT001) 1.9 µg ex-actuator	GP MDI 0.96 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations BID
Placebo			
Placebo MDI[a]	Formulation does not contain active ingredient	1 MDI 120 inhalations	Taken as 2 inhalations BID
Open-label Products			
Salmeterol xinafoate inhalation powder 50 µg	Serevent® Diskus® 50 µg per inhalation	1 DPI 60 inhalations	Taken as 1 inhalation, BID
Budesonide Inhalation Powder 360 µg[b]	Pulmicort® Flexhaler® 180 µg per inhalation	1 DPI 60 or 120 inhalations	Taken as 2 inhalations, BID
Budesonide Inhalation Powder 180 µg[b]	Pulmicort Flexhaler 90 µg per inhalation	1 DPI 60 or 120 inhalations	Taken as 2 inhalations, BID

Table 4. Product-Packaging Descriptions of Study Drug, Open-label Products and Placebo

Drug/Product Name & Dose	Product Strength	Dosage Form/Fill Count	Comments
Blinded Study Medication			
Albuterol Sulfate Inhalation Aerosol 90 µg ex-actuator[c]	US source: (Ventolin® HFA) Each actuation contains 108 µg corresponding to 90 µg albuterol base per actuation	1 MDI 60 or 200 actuations	Taken as directed Supplies are open-label

BID=twice daily; DPI=dry powder inhalation; ex-actuator=dose delivered from the actuator (ie., mouthpiece) of the MDI; GP MDI=Glycopyrronium Inhalation Aerosol; HFA=hydrofluoroalkane; MDI=Metered Dose Inhaler; US=United States

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

[a] Placebo MDI will be administered as a randomized treatment. All Placebo MDIs are created by Pearl Therapeutics in the image of the active test product.

[b] For subjects currently treated with ICS monotherapy or with any ICS combination drug at Screening, open-label Pulmicort Flexhaler DPI 180 µg or 360 µg will be provided by the Sponsor as controller therapy during the study.

[c] Rescue medication

For open-label Pulmicort Flexhaler (budesonide inhalation powder 180 µg and 360 µg), commercial DPIs will be provided. Manufacturer's instructions for study drug administration will be provided (see Appendix 4).

For open-label Ventolin HFA (albuterol sulfate inhalation aerosol 90 µg), commercial MDIs with dose counters will be provided. Manufacturer's instructions for study drug administration will be provided (see Appendix 5).

For open-label Serevent diskus (salmeterol xinafoate inhalation powder 50 µg), commercial DPIs with dose counters will be provided. Manufacturer's instructions for study drug administration will be provided (see Appendix 6).

6.3 Primary Packaging and Labeling Information

Investigational materials will be packaged by Pearl Therapeutics.

Blinded Supplies: Each MDI will be labeled with a 1-part label. The foil pouch will be labeled with a 1-part label. A 2-part label will be affixed to the carton holding the foil.

Open-label Supplies: Open-label Pulmicort Flexhaler and Ventolin HFA will be provided as individually labeled DPIs and MDIs, respectively. Each inhaler will contain 2 single investigational labels. Both Pulmicort Flexhaler and Ventolin will have a 2-part investigational label affixed to the carton.

Open-label Serevent Diskus will have a 2-part investigational label affixed to the commercial foil in which it is supplied. At the time of dispensing, the second panel of the 2-part foil label will be removed at the perforation and affixed to the Serevent Diskus inhaler. Serevent Diskus will have a 2-part investigational label affixed to the carton. All labels will be printed in black ink and may include the text provided in Table 5.

Table 5. Study Drug Label Text

- Packaging Lot Trace ID #
- Space for entry of screening #
- Component ID #
- Space for entry of randomization #
- 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)

ID=identification; #=number

6.4 Secondary Packaging and Labeling Information (Box)

Investigational drug supplies, and open-label Pulmicort Flexhaler and Ventolin HFA will be packaged in boxes as outlined in Table 6. Box configuration is subject to change as a result of packaging constraints.

Table 6. Description of Boxes

Drug Supplies	Box Contents
Blinded	1 MDI
Ventolin HFA	1 MDI
Pulmicort Flexhaler 180 µg	1 DPI
Pulmicort Flexhaler 360 µg	1 DPI
Serevent Diskus	1 DPI

DPI=dry powder inhaler; HFA=hydydrofluoralkane; MDI=metered dose inhaler

Each box will be labeled with a double-panel label printed with black ink and may include the text indicated in Table 7.

Table 7. Description of Box Labeling

- Packaging Lot ID #
- Space for entry of screening #
- Component ID #
- Space for entry of randomization #
- 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)

DPI=dry powder inhaler; ID=identification; MDI=metered dose inhaler; #=number

6.5 Unblinding Procedures

The IWRS should be used to unblind subjects and to unmask drug identity.
Pearl Therapeutics will not provide a disclosure envelope with the clinical supplies.
The Investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. Whenever possible, the Investigator must first discuss options with the Medical Monitor or appropriate study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the Investigator must notify Pearl Therapeutics as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

6.6 Storage Requirements

Blinded supplies: Clinical supplies should be kept in a secured location. Store between 20°and 25°C (68°to 77°F); excursions permitted to 15°C and 30°C (59°to 86°F). Do not refrigerate or freeze.

Pulmicort Flexhaler supplies: Store in a dry place at controlled room temperature 20° to 25°C (68° to 77°F) with the cover tightly in place. Keep out of the reach of children. Keep Pulmicort Flexhaler dry.

Ventolin HFA supplies: Store in a secured location at room temperature. Store between 15° and 25°C (59° and 77°F). Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use. SHAKE WELL BEFORE EACH SPRAY. 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.

Serevent Diskus supplies: Store in a dry place at controlled room temperature 20° to 25°C (68° to 77°F). Store in the unopened foil pouch and only open when ready for use. Keep out of the reach of children. Keep Serevent Diskus dry.

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. Documentation of temperature monitoring should be maintained.

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

Glycopyrronium and Placebo MDIs

Individual glycopyrronium and Placebo MDIs will be packaged in a foil pouch and contained in a treatment box. Both the treatment box and the foil overwrap will have a label with a component ID number. Sites should confirm that the identifier given by IWRS and the component ID number written on the label are the same. The box is labeled with a 2-part label. Write the subject number and treatment visit number on each of the 2-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. Site personnel will prime the inhaler device prior to giving to the subject by gently shaking the inhaler for 5 to 10 seconds and then spraying once into the air away from themselves and others. After approximately 30 seconds, the process should be repeated 3 more times.

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

Each dose will consist of 2 puffs from the MDI. Subjects will be dispensed the MDI and instructed to continue taking study medication BID approximately 12 hours apart, 2 puffs in the morning and 2 puffs in the evening, until the subject returns to the clinic. Refer to Appendix 3 for instructions on the administration of GP and Placebo MDIs.

Pulmicort Flexhaler (budesonide inhalation powder 180 µg and 360 µg)

Individual open-label Pulmicort Flexhaler DPIs labeled with a component ID number for IWRS assignment and tracking will be provided by Pearl Therapeutics. Sites will use IWRS to dispense Pulmicort Flexhaler to subjects throughout the study.

Refer to Appendix 4 for the manufacturer's instructions on the administration of Pulmicort Flexhaler.

Ventolin HFA (albuterol sulfate inhalation aerosol)

Individual open-label Ventolin HFA MDIs labeled with a component ID number for IWRS assignment and tracking will be provided by Pearl Therapeutics. Sites will use IWRS to dispense Ventolin HFA to subjects throughout the study. Ventolin HFA should be primed per manufacturer's instructions prior to dispensing to subject.

Refer to Appendix 5 for the manufacturer's instructions on the administration of Ventolin HFA. Study personnel will record the number on the dose counter at the time of dispensing (following priming) and upon return.

Serevent Diskus (Salmeterol xinafoate inhalation powder 50 µg)

Individual open-label Serevent Diskus DPIs labeled with a component ID number for IWRS assignment and tracking will be provided by Pearl Therapeutics. Sites will use IWRS to dispense Serevent Diskus to subjects.

Refer to Appendix 6 for the manufacturer's instructions on the administration of Serevent Diskus.

6.8 Drug Accountability/Return of Clinical Supplies

The Investigator(s) should emphasize to all study personnel and subjects that the study drugs are to be used only as directed by this protocol.

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated assistants have access. Storage conditions for the clinical supplies should be observed, monitored, and documented. Clinical supplies are to be dispensed only in accordance with the protocol. The Investigator or designated assistant should not open individual clinical boxes until all pre-dose assessments have been completed and the subject is eligible to be randomized/continue with the study. Any deviation from these instructions must be discussed with the Medical Monitor.

The Investigator is responsible for keeping accurate records of the clinical supplies received from Pearl Therapeutics, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the study. Study medication should be handled in accordance with Good Pharmacy Practices. The Medical Monitor should be contacted with any questions concerning handing of the investigational products.

At the end of the study, all clinical supplies including partial and empty containers must be returned as directed by Pearl Therapeutics. For each subject, all used study drug materials will be collected and stored together (e.g., in a plastic bag) and labeled with the subject number. Used subject supplies will be kept at room temperature in a secure and locked cabinet until returned to Pearl Therapeutics or designee.

Note: Used study drug will be stored separately from unused study drug. Sites should check with the Pearl Therapeutic representative as to the appropriate documentation needed for drug accountability.

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

7 STUDY PROCEDURES

It is recommended that whenever possible, all assessments during visits will be conducted in the following order: ACQ, vital signs, ECGs, clinical laboratory assessments, and spirometry.

7.1 Efficacy Assessments

7.1.1 Pulmonary Function Tests

Forced expiratory spirometry for derivation of FEV_1, FEF_{25-75}, FVC, and PEFR will be assessed using a spirometer that meets or exceeds minimum performance recommendations of the ATS/ERS criteria (see Appendix 1).

At Visits V1a, 1b, 2a and 2b, spirometry assessments will be conducted as described in Section 7.1.2.

At Visits 3 through 12, spirometry assessments will be conducted at 60 and 30 minutes prior to study drug administration, as well as at 15 and 30 minutes, and 1, 2, and 3 hours after dosing.

Refer to Section 5.1 and Section 5.2 for specific spirometry inclusion/exclusion criteria.

7.1.2 Characterization of Reversibility

Reversibility to Ventolin HFA (SABA) will be evaluated at Visits 1a and Visits 1b, 2a, and 2b (as needed) and tested as follows:

- Perform pre-bronchodilator PFTs prior to administration of Ventolin HFA (albuterol). **Note**: A single pre-dose bronchodilator PFT is collected at Visit 1a or 1b. At visit 2a or 2b, pre-bronchodilator PFTs will be performed within 60 minutes prior to administration of Ventolin HFA.
- Administer 4 puffs of Ventolin HFA.
- Perform post-bronchodilator PFT at 30 minutes after the administration of Ventolin HFA. If the criterion is not met, a repeat post-bronchodilator PFT may be performed at approximately 60 minutes post-dose to assess reversibility.
- Subjects who do not meet FEV_1 criteria at Visit 1a may, at the discretion of the Investigator, be retested for reversibility at Visit 1b. Subjects who fail to meet criteria at Visit 1b will be considered screen failures.
- Subjects who fail to meet FEV_1 criteria at Visit 2a will be considered screen failures unless they have received Pulmicort Flexhaler 360 µg BID and have a pre-dose FEV_1 above 90% predicted or do not meet the post-bronchodilator FEV_1 requirements, and based on the Investigator's judgment, have had their Pulmicort Flexhaler reduced to 180 µg BID. These subjects may be retested at Visit 2b.

7.1.3 FEV_1 Baseline Stability Criteria

FEV_1 baseline stability criteria are:

- At Visits 5, 7, 9, and 11, the average of the -60 min and -30 min FEV_1 values must be within 20% of the average of the -60 min and -30 min FEV_1 values from Visit 3. At these visits, if the pre-dose FEV_1 average is outside of the ±20% range, but the -30 min assessment is within ±20%, then another assessment may be conducted 30 minutes later. If the last 2 assessments meet the baseline stability requirements (ie., within ±20%), the initial 60 minute pre-dose assessment will not be used and the last 2 assessments will be used to establish the criteria for continued eligibility.
- Subjects must continue to meet the FEV_1 baseline eligibility criteria to be eligible for dosing at Visits 5, 7, 9 and 11. Subjects who do not meet the FEV_1 baseline stability criteria at these visits must be rescheduled as soon as is practical but within the protocol-specified washout window (7 to 14 days between treatment periods). Subjects who fail to meet stability criteria after 2 attempts within a Washout Period will be discontinued.

7.1.4 Standardization of Spirometry Collections

All PFTs, including FEV_1, FEF_{25-75}, FVC, and PEFR as defined in ATS/ERS guidelines (Miller, 2005), will be performed in accordance with ATS/ETS 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 standardized training. All technicians will be required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable pulmonary function testing (Miller, 2005) prior to performing testing on study subjects. After each test is performed, the spirometry software will provide immediate feedback to the technician indicating whether the effort met 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 to [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.

The volume accuracy of the spirometer is to be checked on each day that a subject is evaluated at the study site using a 3 L syringe across 3 flow ranges ie., at <2 L/sec, 4 to 6 L/sec, and >8 L/sec, with temperature and barometric pressure correction. The calibration syringe must meet ATS specifications and must not be used beyond the expiry date. Required accuracy is ±3%, ie., 3.09 L to 2.91 L (ATS/ERS). The results will be printed and maintained in a calibration log, which will be monitored for compliance during the monitoring visits (see Appendix 1).

7.1.5 Subject eDiary Data Collection

Subjects will be provided with an eDiary to be completed twice daily. The subject will record time of blinded study medication or open-label Serevent Diskus administration, morning and evening asthma symptoms, the use of rescue albuterol (Ventolin HFA), and the collection of daily peak flow rates using a Sponsor-provided portable peak flow meter.

Before issuing the eDiary to the subject, site personnel will be responsible for programming the eDiary and training the subject on the eDiary's proper use at Screening (Visit 1a). Subjects will be instructed to collect eDiary data during the Screening Period (between Visit 1a to Visit 3).

Site personnel will review the eDiary during the Screening Period to assess the subject's compliance and understanding of the use of the eDiary in maintaining a daily record of their study drug dosing, rescue medication use, asthma symptoms, and collection of daily peak flow rates.

At Visit 3 (Randomization), subjects must meet the compliance requirement of ≥70% subject completion of eDiary assessments in the last 7 days preceding that visit, in order to be randomized in the study. Subjects who fail to demonstrate proper eDiary compliance prior to Randomization (Visit 3) must be considered to be screen failures.

Those subjects who are randomized will receive an eDiary in which they will be asked to maintain twice-daily eDiary records (AM and PM) for the duration of the study, including treatment and Washout periods (between Visits 4 and 5, Visits 6 and 7, Visits 8 and 9, and Visits 10, 11, and 12). Subjects will continue to use the eDiary to maintain a daily record of their study drug dosing, rescue medication use (see Section 7.1.6), morning and evening asthma symptoms, and collection of daily peak expiratory flow rates (see Section 7.1.7).

At all visits (Visits 3 to 12), site personnel must review eDiary data prior to dosing study drug in the clinic (see Table 9).

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

The eDiary data report will be available to site personnel through the vendor's server, which should be reviewed by the study personnel at each visit. The review should verify that morning and evening eDiary entries have been recorded by the subject for compliance requirements. If missing entries are observed, the subject should be reinstructed on the importance of recording twice-daily entries. If the subject demonstrates persistent eDiary compliance issues, the subject should be evaluated, at the Investigator's discretion, for further study continuation.

7.1.6 Rescue Ventolin HFA Use

The subject will record the total number of "puffs" of rescue Ventolin HFA used on a daily basis, that being 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 that the subject requires 4 actuations, this should be recorded as 4 "puffs". Subjects requiring ≥8 puffs per day on 3 or more consecutive days with worsening symptoms should contact the site.

7.1.7 Peak Expiratory Flow Rate

Home Measurements

A portable peak flow meter will be provided by the Sponsor to all study subjects for measurement of PEFR at home.

Subjects will be issued and trained on peak flow meter use at the Screening Visit (Visit 1a) and instructed to collect peak flow meter data during the Screening Period (between Visit 1a and Visit 3) and record the data in their eDiaries. During the Screening Period, subjects will perform PEFR measurements at home in the morning and in the evening, immediately before and 30 minutes after dosing.

To use the peak flow meter, subjects will be instructed to forcefully exhale from total lung capacity 3 times into the peak flow meter and confirm the collection of PEFR measurements in the eDiary.

During the study treatment period (including washout periods) subjects will perform PEFR measurements at home in the morning and in the evening, immediately before and 30 minutes after dosing. At each study visit, the Investigator will review the PEFR readings and any findings will be discussed with the subject, and the clinical relevance will be determined. Subjects will bring their peak flow meter to the clinic at each visit.

In-Clinic Measurements

At each in-clinic treatment visit (Visits 3 to 12), subjects will measure PEFR immediately before and 30 minutes after dosing with study medication and record pre- and post-peak flow values and time of dosing in the subject's eDiary.

Note: The in-clinic 30 minute post-dose PEFR at each treatment visit (Visits 3 to 12) should be obtained after spirometry assessments, allowing enough time for the subject to recover from the PFT maneuvers.

7.1.8 Medication Compliance

Time of dosing with blinded investigational study medication or open-label Serevent Diskus will be recorded in the subject eDiary for each day of treatment. Investigational study medication compliance will be checked at all visits, and any issues that are identified will be noted in the appropriate study files.

7.1.9 Asthma Control Questionnaire

International guidelines for the treatment of asthma have identified that the primary clinical goal of asthma management is to optimize asthma control (minimization of symptoms,

activity limitation, bronchoconstriction, rescue β_2 -agonist use) and thus reduce the risk of life-threatening exacerbations and long-term morbidity. The ACQ-5 (Juniper, 1999) was developed and validated to meet these criteria. It measures both the adequacy of asthma control and change in asthma control, which occurs either spontaneously or as a result of treatment.

The ACQ-5 (see Appendix 7) will be completed at Visits 3 through 12, before any other study procedures are performed. It is to be completed in the clinic and requires subjects to recall their experiences during the previous week (7 days) prior to study site visits (starting from Visit 3).

7.2 Safety Assessments

Safety assessments include ECGs, vital sign measurements, clinical laboratory tests, and monitoring for AEs during the study period.

7.2.1 Medical/Surgical History and Physical Examination

Medical history will be collected at Screening (Visit 1a). A complete physical examination will be performed at Visit 1a (Screening) and Visit 12 or at the Premature Discontinuation Visit (Early Termination Visit), if applicable.

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 will be assessed in ordinary indoor clothing with shoes removed at Visit 1a (Screening) and Visit 12. Height will be recorded at Visit 1a (Screening) only.

7.2.2 Vital Sign Measurements

At all visits beginning at Screening and including the Premature Discontinuation Visit (if applicable), heart rate and systolic and diastolic blood pressure will be assessed. Assessments of heart rate and blood pressure will be obtained after the subject is supine or seated for 5 to 10 minutes.

At Visit 3 to Visit 12, vital signs will be obtained pre-dose within 1 hour of in-clinic dosing and at 30 minutes post-dose. Temperature will be obtained at pre-dose and 2 hours post-dose; no other temperature assessments will be required, unless clinically indicated.

If, in the opinion of the Investigator, a clinically significant change in a vital sign occurs, the measurement should be repeated at medically appropriate intervals, until the value returns to within an acceptable range**.**

7.2.3 12-Lead Electrocardiogram

A 12-lead ECG will be obtained at Visit 1a (Screening). At Visit 3, two ECGs will be obtained at 60 and 30 minutes before study drug administration and 30 min and 3 hours post-

dose (see Table 10). At Visits 4 to 12, an ECG recording will be obtained within 1 hour before study drug administration, and 30 min and 3 hours post-dose (see Table 10 and Table 11).

In the event of early termination, an ECG will also be obtained at the Premature Discontinuation Visit. Refer to Section 5.2 for specific ECG exclusion criteria.

7.2.4 Standardization of ECG Data Collection

To standardize ECG data collection, all sites will be provided with identical ECG equipment [redacted] with customized study-specific software. All study staff responsible for performing ECG collection will receive identical, detailed training at the Investigator meetings, as well as training sessions by phone at the site. Each site is required to demonstrate proficiency in the use of the equipment and the ability to perform technically-acceptable ECGs prior to performing testing on study subjects. After each test is performed, the ECG data will be transmitted electronically for centralized quality assurance review at [redacted] Feedback on the quality of the ECGs will be provided to the investigational site via a site qualification form.

Electrocardiogram parameters assessed will include: Heart rate, RR interval, PR interval, QRS axis, QRS interval, and QT/QTcF interval.

QT intervals and calculated QTcF intervals will be reviewed and checked for gross inaccuracies by the Investigator or designated ECG reviewer. If the calculated QTcF intervals are >500 msec, and have increased by ≥60 msec over baseline value, the Investigator will make a determination on the suitability of continuing the subject in the study.

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 Medical Monitor.

The decision to continue the treatment of any subject with prolonged QT or QTcF interval must be discussed and agreed upon by the Investigator and the Pearl Therapeutics Medical Monitor. All such subjects, including subjects 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 Medical Monitor must be contacted.

7.2.5 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.

Clinical laboratory tests (hematology [Complete Blood Count] and chemistry [Comprehensive Metabolic Panel]) will be obtained at Visit 1a (Screening) and Premature Discontinuation Visit (if applicable), and prior to dosing at Visits 3, 4, 6, 8, 10, and 12 (see Table 9). See Section 5.2 for specific criteria for clinical chemistry exclusion criteria. The clinical laboratory parameters that will be assessed are presented in Table 8.

Table 8. Clinical Laboratory Measures

Hematology	
Hemoglobin	Mean corpuscular hemoglobin
Hematocrit	Mean corpuscular hemoglobin concentration
White Blood Cell count with differential	Mean corpuscular volume
Red Blood Cell count	
Platelet Count	
Clinical Blood Chemistry	**Other Clinical Blood Chemistry**
Liver Function Tests	Albumin
Alanine aminotransferase	Blood urea nitrogen[a]
Aspartate aminotransferase	Calcium[a]
Alkaline phosphatase	Chloride[a]
Bilirubin, total	Cholesterol
Gamma-glutamyl transferase	Bicarbonate
	Creatinine[a]
	Glucose[a]
	Magnesium
	Potassium[a]
	Phosphate
	Protein, total
	Sodium[a]
	Triglycerides
Other Tests: Pregnancy test (women of child-bearing potential only): serum (human chorionic gonadotropin [hCG]) at Screening and Visit 12 only, and urine HCG at Visits 3 through 11, as detailed in Table 9. Creatinine clearance will be estimated by the CKD-EPI published formula.	

[a] Parameters included in the Basic Metabolic Panel

7.2.6 Adverse Events

7.2.6.1 Performing Adverse Events Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's eCRF and on the AE Reporting Form. In addition, certain AEs (as described in Section 7.2.6.2) are classified as "serious" (see Section 7.2.6.7) and must be reported to Pearl Therapeutics or its designee, no later than 24 hours after the Investigator recognizes/classifies the event as a serious adverse event (SAE).

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

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

Adverse events include, but are not limited to:

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

An AE does **not** include:

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

7.2.6.3 Pre-Randomization Adverse Events

Adverse events that occur between the time that the subject signs the ICF for the study and the time when that subject is randomized will be summarized as medical history and not as a treatment-emergent adverse event, unless the event meets the definition of an SAE, as defined in Section 7.2.6.7.

7.2.6.4 Severity

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

- Mild: Associated with no limitation of usual activities or only slight discomfort; generally not requiring alteration or cessation of study drug administration; and/or not needing therapeutic intervention.
- Moderate: Associated with limitation of usual activities or significant discomfort; generally requiring alteration or cessation of study drug administration; and/or requiring therapeutic intervention.
- Severe: Associated with inability of subject to carry out usual activities or very marked discomfort; considered to be life-threatening; resulting in significant disability or incapacity; and requiring therapeutic intervention.

7.2.6.5 Relationship

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

- Definitely: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; it disappears or decreases on cessation or reduction in study drug dose; and/or it reappears or worsens when the study drug is administered.
- Probably: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; and/or that could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments.
- Possibly: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug, but that could reasonably have been produced by a number of other factors including underlying disease, complications, concomitant drugs, or concurrent treatments.
- Not Related: A reaction for which sufficient data exist to indicate that the etiology is unrelated to the study drug.

7.2.6.6 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 (eg., elevated blood urea nitrogen and creatinine in the setting of an AE of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). In such cases, the laboratory abnormality itself (eg., elevated creatinine in a setting of renal failure) does not need to be recorded as an AE. However, isolated laboratory abnormalities should be reported as AEs if they are considered to be clinically significant by the Investigator.

Criteria for a "clinically significant" laboratory abnormality are:

- A laboratory abnormality that leads to a dose-limiting toxicity (eg., an abnormality that results in study drug dose reduction, suspension, or discontinuation)
- A laboratory abnormality that results in any therapeutic intervention (ie., concomitant medication or therapy)

- Other laboratory abnormality judged by the Investigator to be of any particular clinical concern (eg., significant fall in hemoglobin not requiring transfusion)

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

7.2.6.7 Serious Adverse Events

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

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

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

Hospitalization for a pre-existing condition, including elective procedures, which has not worsened, does not constitute an SAE.

An AE is considered "life-threatening' if, in the view of the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse reaction or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.2.6.8 Reporting Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for AE identification, documentation, grading, assignment of causality, and prompt notification of SAEs to Pearl Therapeutics' Medical Monitor or designee.

All SAEs must be reported to Pearl Therapeutics no later than 24 hours after the Investigator recognizes/classifies the event as an SAE. At a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report using the appropriate SAE Report Form. After the initial report, the Investigator must provide any additional information about an SAE to the Medical Monitor within 2 working days after he/she receives that information. This follow-up information will be a detailed written report that will include copies of hospital records, case reports, and autopsy reports, and other pertinent documents.

Post-study SAEs following the last dose of study drug must be reported to Pearl Therapeutics as described in Section 7.2.6.11.

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

7.2.6.9 Supplemental Investigations of SAEs

The Investigator and supporting personnel responsible for subject care should discuss with the Medical Monitor any need for supplemental investigations of SAEs. The results of these additional assessments 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.

7.2.6.10 Post-Study Follow-Up of Adverse Events

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

7.2.6.11 Notification of Post-Study Serious Adverse Events

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

7.2.6.12 IRB/IEC Notification of Serious Adverse Events

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

7.2.6.13 Health Authority Safety Reports

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

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

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

7.2.7 Adverse Events of Special Interest

Paradoxical bronchospasm and dry mouth will be considered Adverse Events of Special Interest (AESIs).

7.2.7.1 Paradoxical bronchospasm

Paradoxical bronchospasm may occur following the use of inhaled asthma medications. Monitoring for paradoxical bronchospasm will occur at every visit for the first 30 minutes post-dose. In this study, paradoxical bronchospasm is defined as a reduction in FEV_1 of ≥20% from the pre-dose value, with associated asthma symptoms of wheezing, shortness of breath and/or cough. All AEs and SAEs of paradoxical bronchospasm will be recorded as appropriate.

7.2.7.2 Dry Mouth

Subjects will be asked specifically about the presence of dry mouth at specified intervals (pre-dose and at 1 hour post-dose at every treatment visit (see Table 10 and Table 11, respectively). If dry mouth persists at 1 hour post-dose on Day 1 or Day 15, additional assessments will be conducted every hour until resolution of symptoms or completion of the test day. If present, the severity (mild, moderate, and severe) of dry mouth symptoms will be assessed. If dry mouth is not noted at 1 hour after study drug administration, further dry mouth assessments do not need to be conducted. All reports of dry mouth will be recorded as AEs.

7.2.8 Overdose

An overdose is defined as a dose greater than the highest dose level evaluated in this study that results in clinical signs and symptoms. In the event of an overdose of study medication, the Investigator should use clinical judgment in treating the overdose and contact the study Medical Monitor. The Investigator should refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drug(s) being used in this study.

7.2.9 Pregnancy

Any pregnancy that occurs from Screening until study completion must be reported to Pearl Therapeutics. To ensure subject safety, each pregnancy must be reported to Pearl Therapeutics within 14 days (2 weeks) of learning of its occurrence.

7.3 Termination of the Study

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

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

8 STUDY ACTIVITIES

A detailed schedule of procedures to be performed at each study visit is provided in Table 9. A detailed schedule for pre- and post-dose procedures to be performed on Day 1 and Day 15 of each treatment period are provided in Table 10 and Table 11, respectively.

Table 9. Schedule of Events

	Screening Period[a]			Treatment Period 1[a]		Treatment Period 2[a]		Treatment Period 3[a]		Treatment Period 4[a]		Treatment Period 5[a]		Follow-Up[a]
Treatment Day[a]	**Visit 1a[b] Up to Day -28**	**Visit 2a[c]**	**Visit 2b (as needed)**	**Rand. Visit 3 Day 1 1[a]**	**Visit 4 Day 15 15±2[a]**	**Visit 5 Day 1 1[a]**	**Visit 6 Day 15 15±2[a]**	**Visit 7 Day 1 1[a]**	**Visit 8 Day 15 15±2[a]**	**Visit 9 Day 1 1[a]**	**Visit 10 Day 15 15±2[a]**	**Visit 11 Day 1 1[a]**	**Visit 12 Day 15 or Final Visit[d] 15±2[a]**	**Telephone Follow-up (7-14 days after last Visit)**
Procedures														
Informed Consent	X													
Eligibility Criteria	X	X	X	X										
Verify Continued Eligibility					X	X	X	X	X	X	X	X	X	
Ventolin HFA Reversibility[e]	X	X	X											
Demographics, Medical, Surgical History	X													
Switch to Pulmicort Flexhaler 180 or 360 µg	X	X												
ACQ-5[f]				X	X	X	X	X	X	X	X	X	X	
Prior/Concomitant Medications[g]	X	X		X	X	X	X	X	X	X	X	X	X[h]	
Spirometry[i]	X	X		X	X	X	X	X	X	X	X	X	X	
Physical Examination[j]	X												X	
Vital Signs[k]	X	X		X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[l]	X			X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[m]	X			X		X		X		X		X	X	
Clinical Laboratory Testing[n]	X			X	X		X		X		X		X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inhalation Device Training	X			X	X	X	X	X	X	X	X	X		
Distribute/Collect Sponsor-provided Inhalers[g]	X			X	X	X	X	X	X	X	X	X	X	
Randomization				X										
Study Drug Administration[o]				X	X	X	X	X	X	X	X	X	X	
Dispense Peak Flow Meter[p]	X	X												
Collect PEFR in Clinic				X	X	X	X	X	X	X	X	X	X	
Dispense/Review Subject eDiary[p]	X			X	X	X	X	X	X	X	X	X	X	

Table 9. Schedule of Events (continued)

Treatment Day[a]	Screening Period[a]			Treatment Period 1[a]		Treatment Period 2[a]		Treatment Period 3[a]		Treatment Period 4[a]		Treatment Period 5[a]		Follow-Up[a]
	Visit 1a[b] Up to Day -28	Visit 2a[c]	Visit 2b[c] (as needed)	Rand. Visit 3 Day 1 1[a]	Visit 4 Day 15 15±2[a]	Visit 5 Day 1 1[a]	Visit 6 Day 15 15±2[a]	Visit 7 Day 1 1[a]	Visit 8 Day 15 15±2[a]	Visit 9 Day 1 1[a]	Visit 10 Day 15 15±2[a]	Visit 11 Day 1 1[a]	Visit 12 Day 15 or Final Visit[d] 15±2[a]	Telephone Follow-up (7-14 days after last Visit)
Procedures														
Study Drug Dispensing/ Collection	X[q]			X	X	X	X	X	X	X	X	X	X	
Paradoxical Bronchospasm[r]				X	X	X	X	X	X	X	X	X	X	
Dry Mouth Assessment[s]				X	X	X	X	X	X	X	X	X	X	
Return to Maintenance Asthma Medication													X[u]	

ACQ-5=Asthma Control Questionnaire 5; BID=twice daily; ECG=electrocardiogram; FEV_1=forced expiratory volume in 1 second; HFA=hydrofluoroalkane; ICS=inhaled corticosteroid; PEFR=peak expiratory flow rate; QID=4 times daily; Rand=Randomization

a Visit windows during each treatment period are relative to Day 1 of that treatment period. Washout Periods occur between Visits 4 and 5, Visits 6 and 7, Visits 8 and 9, and Visits 10 and 11 and are 7 to 14 days. Visit 1b must occur before Visit 2.

b Subjects who do not meet the FEV_1 criteria at Screening (Visit 1a) may, at the Investigator's discretion, be retested at Visit 1b. Subjects who are on non-ICS maintenance therapy at Visit 1a and who meet the spirometry entry criteria, will be allowed to proceed to the Randomization Visit (Visit 3).

c Those subjects who receive open-label Pulmicort Flexhaler 360 µg BID and have a pre-dose FEV_1 above 90% predicted or do not meet the post-bronchodilator FEV_1 requirements may, at the discretion of the Investigator or designee, have their open-label Pulmicort Flexhaler reduced to 180 µg BID. These subjects will continue the Screening Period for an additional 7 to 14 days from Visit 2a and return for repeat assessments at Visit 2b, using the same criteria for eligibility.

d If the subject discontinues the study early (early termination), the procedures that should be completed in the final visit are described in Section 8.9.

e See instructions for reversibility assessment in Section 7.1.2.

f See instructions for administering the ACQ-5 in Section 7.1.9 and Appendix 7.

g See listing of concomitant and prohibited medication in Section 5.4. At all visits beyond Screening, note time of last dose of short-acting bronchodilator and other asthma medications (if <6 hours, visit should be rescheduled).

h At the end of Visit 12, subject will be returned to pre-study or other appropriate inhaled maintenance asthma medication.

i Refer to Sections 7.1.1 and 7.1.4 for guidance related to spirometry assessments and criteria.

j Weight, assessed in ordinary indoor clothing with shoes removed at Visit 1a (Screening) and Visit 12. Height will be recorded at Visit 1a (Screening) only (Refer to Section 7.2.1).

k Refer to Section 7.2.2 for guidance on vital signs collection.

l On Day 1 of Treatment Period 1, two ECGs will be obtained at 60 and 30 minutes prior to dosing. Refer to Section 7.2.3 for guidance on ECG assessment.

m Serum pregnancy test (women of child-bearing potential only) will be performed at Screening and at Visit 12. On Day 1 of each treatment period (Visits 3, 5, 7, 9, 11), a urine pregnancy test will be performed.

n On Day 1, clinical laboratory assessments (hematology and chemistry) will be performed prior to administration of study drug. Refer to Section 7.2.5 for guidance on clinical laboratory testing.
o At the start of each treatment visit, subjects must withhold all asthma medications, including study drug and rescue medications (Ventolin HFA) for at least 6 hours prior to start of test day procedures.
p Refer to Sections 7.1.5 and 7.1.7 for guidance on subject eDiary and peak flow meter use, respectively.
q Sponsor-provided rescue and maintenance medication is dispensed only after a subject is determined to be eligible to proceed to Visit 2 (ie., only if a subject meets asthma definition following spirometry assessments at Screening). During the Screening Period, subjects previously treated with an ICS will be treated with Sponsor-provided open-label Pulmicort® Flexhaler® 180 or 360 µg BID, based on the equivalent dose of ICS at the time of Screening (Visit 1a). Subjects who require non-ICS maintenance therapy will be allowed to continue that therapy. All subjects will receive Sponsor-provided open-label rescue Ventolin® HFA Inhalation Aerosol (Ventolin HFA) as needed to control symptoms.
r See Section 7.2.7.1 for definition of paradoxical bronchospasm.
s See Section 7.2.7.2 for description of dry mouth assessments. If dry mouth persists at 1 hour post-dose, additional assessments will be conducted every hour until resolution of symptoms or completion of the test day.

Table 10. Visit Procedures on Day 1 of Each Treatment Period (Visits 3, 5, 7, 9, and 11)

Clinical Variable[a]	Pre-Dosing		Post-Dosing				
	-60 minutes	-30 minutes	15 minutes	30 minutes	1 hour	2 hours	3 hours
Paradoxical Bronchospasm Assessment[b]			X	X			
Dry Mouth Assessment[c]	X	X			X		
Vital Signs[d]	X			X			
12-Lead ECG[e]	X			X			X
Clinical Laboratory Testing[f]	X						
Spirometry (FEV_1, FEF_{25-75}, FVC, PEFR)	X	X	X	X	X	X	X
Dispense/Review Subject eDiary[g]		X					
Collect/Dispense Drug Supplies		X					

ECG=electrocardiogram; FEF_{25-75}=forced expiratory flow from 25-75%; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; HFA=hydrofluoroalkane; ICS = inhaled corticosteroid; PEFR=peak expiratory flow rate

a. Safety assessments (vital signs and ECG) should be started approximately 5 to 10 minutes ahead of the specified timepoint for spirometry assessment to ensure that spirometry for FEV_1, FVC, FEF_{25-75}, and PEFR determination will be conducted as close to the specified timepoints as possible (ie., FEV_1, FVC, FEF_{25-75}, and PEFR assessments need to be conducted within ±15 minutes of specified time prior to study drug administration; ±5 minutes of specified timepoint for the first 60 minutes after study drug administration; ±15 minutes of specified timepoint for assessments obtained thereafter).

b. Refer to Section 7.2.7.1 for definition of paradoxical bronchospasm

c. Refer to Section 7.2.7.2 for description of dry mouth assessments. If dry mouth persists at 1 hour post-dose on Day 1, additional assessments will be conducted every hour until resolution of symptoms or completion of the test day.

d. Temperature will be obtained pre-dose and 2 hours post-dose; no further temperature assessments required unless clinically indicated. Refer to Section 7 for further information on collection of vital signs.

e. On Day 1 of Treatment Period 1 (Visit 3) *ONLY*, 2 ECGs will be obtained 60 and 30 minutes prior to dosing. Refer to Section 7.2.3 for further guidance on ECGs.

f. Only on Day 1 of Treatment Period 1. Refer to Section 7.2.5 for further guidance on clinical laboratory testing.

g. Subjects must have a diagnosis of asthma confirmed at Visit 1a/b with bronchodilator reversibility (30 to 60 minutes after 4 puffs of salbutamol/albuterol) defined as an FEV_1 increase of at least 12% and at least 200 mL. Pre-bronchodilator FEV_1 must be ≥60% and <90% of predicted normal value at Screening (Visit 1a/b) and Visit 2.

h. Refer to Section 7.1.5 for guidance on subject eDiary use.

i. Sponsor-provided rescue and maintenance medication is dispensed only after a subject is determined to be eligible to proceed to Visit 2 (ie., only if a subject meets asthma definition following spirometry assessments at Screening). During the Screening Period, subjects previously treated with an ICS will be treated with Sponsor-provided open-label Pulmicort® Flexhaler® (Budesonide) 180 or 360 µg BID based on the equivalent dose of ICS at the time of Visit 1. Subjects who require non-ICS maintenance

Table 11. Visit Procedures on Day 15 of Each Treatment Period (Visits 4, 6, 8, 10, and 12)

Clinical Variable	Pre-Dosing		Post-Dosing				
	-60 minutes	-30 minutes	15 minutes	30 minutes	1 hour	2 hours	3 hours
Paradoxical Bronchospasm Assessment[a]			X	X			
Dry Mouth Assessment[b]	X	X			X		
Vital Signs[c,d]	X			X			
12-Lead ECG[e]	X			X			X
Clinical Laboratory Testing[f]	X						X
Spirometry (FEV_1, FEF_{25-75}, FVC, PEFR)	X	X	X	X	X	X	X
Dispense/Review Subject eDiary[g]		X					
Collect/Dispense Drug Supplies[h]		X					

ECG=electrocardiogram; FEF_{25-75}=forced expiratory flow from 25-75%; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; HFA=hydrofluoroalkane; ICS = inhaled corticosteroid; PEFR=peak expiratory flow rate

a. Refer to Section 7.2.7.1 for definition of paradoxical bronchospasm

b. Refer to Section 7.2.7.2 for description of dry mouth assessments. If dry mouth persists at 1 hour post-dose on Day 15, additional assessments will be conducted every hour until resolution of symptoms or completion of the test day.

c. Safety assessments (vital signs and ECG) should be started approximately 5 to 10 minutes ahead of the specified timepoint for spirometry assessment to ensure that spirometry for FEV_1, FVC, FEF_{25-75}, and PEFR determination will be conducted as close to the specified timepoints as possible (ie., FEV_1, FVC, FEF_{25-75}, and PEFR assessments need to be conducted within ±15 minutes of specified time prior to study drug administration; ±5 minutes of specified timepoint for the first 60 minutes after study drug administration; ±15 minutes of specified timepoint for assessments obtained thereafter).

d. Temperature will be obtained pre-dose and 2 hours post-dose; no further temperature assessments required unless clinically indicated. Refer to Section 7.2.2 for further information on collection of vital signs.

e. Refer to Section 7.2.3 for further guidance on ECGs.

f. Refer to Section 7.2.5 for further guidance on clinical laboratory testing.

g. Subjects must have a diagnosis of asthma confirmed at Visit 1a/b with bronchodilator reversibility (30 to 60 minutes after 4 puffs of salbutamol/albuterol) defined as an FEV_1 increase of at least 12% and at least 200 mL. Pre-bronchodilator FEV_1 must be ≥60% and <90% of predicted normal value at Screening (Visit 1a/b) and Visit 2.

h. Refer to Section 7.1.5 for guidance on subject eDiary use.

i. Sponsor-provided rescue and maintenance medication is dispensed only after a subject is determined to be eligible to proceed to Visit 2 (ie., only if a subject meets asthma definition following spirometry assessments at Screening). During the Screening Period, subjects previously treated with an ICS will be switched to Sponsor-provided open-label Pulmicort® Flexhaler® (Budesonide) 180 or 360 µg BID, based on the equivalent dose of ICS at the time of Visit 1a. Subjects who require non-ICS maintenance therapy will be allowed to continue that therapy. All subjects will also receive Sponsor-provided, open-label rescue Ventolin HFA Inhalation Aerosol (Ventolin HFA) as needed to control symptoms. For further information refer to Section 7.

8.1 Screening Visit (Visit 1a)

- Obtain informed consent.
- Register subject in IWRS to obtain subject screening number.
- Verify that subject meets inclusion/exclusion criteria.
- Obtain demographic data, including age, race, smoking history, and medical/surgical history.
- Obtain medication history, including asthma medications.
- Conduct a serum pregnancy test (β (beta)-hCG) for all female subjects unless it is documented in the medical history that the subject has been irreversibly surgically sterilized (hysterectomy, oophorectomy or bilateral tubal ligation) or are at least 2 years post-menopausal.
- Conduct a complete physical examination (ie., general appearance, skin, head, eyes, ears, nose, throat, neck [including thyroid], lymph nodes, chest, heart, abdomen, extremities, and nervous system).
- Obtain height, weight, and vital signs (heart rate and blood pressure after being supine or seated for 5 to 10 minutes, and oral or tympanic body temperature).
- Obtain a 12-lead ECG.
- Conduct spirometry assessments (see Section 7.1.1)
- Conduct reversibility testing to 4 puffs of Ventolin HFA (see Section 7.1.2).
  - Confirm subject is reversible (see Section 7.1.2 for Reversibility Criteria)
- Subjects previously treated with ICS will be switched to Pulmicort Flexhaler 180 µg or 360 µg BID, based on the equivalent dose of ICS at Screening.
- Obtain clinical laboratory samples (hematology and chemistry).
- Stop prohibited asthma medications and change concurrent asthma medications as specified in the protocol (see Section 5.4).
- Train subjects on use of Sponsor-provided inhalation devices.
- Dispense Sponsor-provided inhalers.
- Ventolin HFA for rescue medication will be provided by Sponsor to be used as needed to control symptoms.
- Dispense and train subjects on eDiary and peak flow meter use.
- Adverse events must be recorded during the Screening Period, that is, from the time of consent to the start of study treatment. Adverse events that occur between the time that the subject signs the ICF for the study and the time when that subject is randomized will be summarized as medical history and not as a study AE unless the event meets the definition of an SAE (see Section 7.2.6.2).
- Schedule next visit:
  - Visit 1b at Investigator discretion for subjects who do not meet the pre- and post-bronchodilator FEV_1 requirements

- Visit 2a for subjects who are switched to Pulmicort Flexhaler at least 14 days from Visit 1a.

- Visit 3 for non-ICS subjects who are eligible to proceed directly to the randomization visit.

8.2 Visit 1b (At Investigator Discretion)

- Assess continued eligibility criteria
- Repeat spirometry assessment to meet pre- and post-bronchodilator FEV_1 requirements using the same criteria for eligibility as Visit 1a (Section 7.1.1).
- Record any AEs that have occurred
  -

8.3 Visit 2a (For All Subjects Switched to Pulmicort Flexhaler)

- Assess continued eligibility criteria
- Record concomitant medications
- Record AEs, (if any).
- Repeat spirometry assessments to meet pre- and post-bronchodilator FEV_1 requirements using the same criteria for eligibility as Visit 1a.
- Conduct reversibility testing to 4 puffs of Ventolin HFA (see Section 7.1.2).
  - Confirm subject is reversible (see Section 7.1.2 for Reversibility Criteria)
- Obtain vital signs
- Schedule next visit:
  - Visit 2b for subjects who were switched from Pulmicort Flexhaler 360 to 180 µg, at least 7 days from Visit 2a.
  - Visit 3 for subjects who are eligible to proceed directly to the Randomization Visit

8.4 Visit 2b (At Investigator Discretion)

Subjects who receive open-label Pulmicort Flexhaler 360 µg BID and have a pre-dose FEV_1 above 90% predicted or do not meet the post-bronchodilator FEV_1 requirements may, at the discretion of the Investigator or designee, have their open-label Pulmicort Flexhaler reduced to 180 µg BID. These subjects will continue the Screening Period for an additional 7 to 14 days from Visit 2a.

- Assess continued eligibility criteria
- Record concomitant medications
- Record AEs, (if any).
- Repeat spirometry assessments to meet pre- and post-bronchodilator FEV_1 requirements using the same criteria for eligibility as Visit 1a.
- Conduct reversibility testing to 4 puffs of Ventolin HFA (see Section 7.1.2).
  - Confirm subject is reversible (see Section 7.1.2 for Reversibility Criteria)

- Obtain vital signs
- Schedule Visit 3 for subjects who are eligible to proceed directly to the randomization visit.

8.5 Randomization Visit (Visit 3; Treatment Period 1, Day 1)

- Review inclusion/exclusion criteria (see Section 5.1 and Section 5.2) and confirm subject's eligibility for Randomization.
- Obtain subject randomization number and treatment assignment information from IWRS, at which point the subject is to be considered randomized
- Review subject eDiary and peak flow values. If subject does not meet the eDiary compliance requirement, he/she will be considered a screen failure.
- Provide additional Sponsor-provided Pulmicort Flexhaler and Ventolin HFA as dispensed during the Screening Period, if necessary.
- Determine time of last dose of short-acting bronchodilators and other asthma medications (if <6 hours, Visit 3 must be rescheduled).
- Administer ACQ-5 (see Appendix 7).
- Review concomitant medications to ensure adherence to study-specified regimen.
- Record AEs, (if any).
- Perform all pre-dose assessments, including vital signs, ECGs, clinical laboratory testing, and urine pregnancy testing.
- Perform pre-dose spirometry.
- Assess pre-dose presence of dry mouth
- Distribute Sponsor-provided inhalers and re-train subjects on use, using Placebo MDIs.
- To allow for proper preparation of study drug, it is recommended that the seal around the treatment box is opened 15 to 30 minutes prior to dosing, and the instruction for the administration of study drug are followed.
  - Refer to Section 6.7 for detailed instructions for preparation of treatment for administration, including priming of the MDI prior to subject use.
- Dispense study drug. Subject will administer first dose of newly-assigned study drug at the clinic.
- Collect PEFR in clinic.
- Subjects* will record dosing time and PEFR in the eDiary.
- Perform post-dose assessments, including vital signs and spirometry.
- Assess subject for paradoxical bronchospasm at 15 and 30 minutes post-dosing
- Assess presence of dry mouth 1 hour post-dose
- Schedule Visit 4 within 14 ± 2 days, and ensure subject has adequate supply of study drug and rescue Ventolin HFA.
- Subjects will be instructed to bring the eDiary, peak flow meter, and all study medication to the next visit.

8.6 Visits 5, 7, 9, and 11 (Day 1 of Treatment Periods 2, 3, 4, and 5)

- Verify subject eligibility to continue.
- Review subject eDiary and peak flow values, and re-train subject if subject has not met eDiary compliance requirement (see Section 7.1.5).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the eCRF (if <6 hours, the visit must be rescheduled).
- Administer ACQ-5.
- Review concomitant medications to ensure adherence to study-specified regimen.
- Record AEs, (if any).
- Provide additional Sponsor-provided Pulmicort Flexhaler and Ventolin HFA, if necessary.
- Perform all pre-dose assessments, including vital signs and urine pregnancy testing (60 minutes prior to dosing).
- Perform pre-dose spirometry (60 and 30 minutes prior to dosing)
- Assess pre-dose presence of dry mouth
- Have subjects perform pre-dose eDiary collections including completion of symptom questions and pre-dose PEFR assessments.
- Obtain treatment assignment information from IWRS.
- To allow for proper preparation of study drug, it is recommended that the seal around the treatment box is opened 15 to 30 minutes prior to dosing, and the instruction for the administration of study drug are followed.
  - Refer to Section 6.7 for detailed instructions for preparation of treatment for administration, including priming of the MDI prior to subject use.
- Collect subject eDiary and peak flow meter.
- Subject will administer first dose of newly-assigned study drug at the clinic.
- Collect PEFR in clinic.
- Site personnel will record dosing time and PEFR in the eDiary.
- Perform post-dose assessments, including vital signs and spirometry.
- Assess subject for paradoxical bronchospasm at 15 and 30 minutes post-dosing
- Assess presence of dry mouth 1 hour post-dose
- Obtain new MDI (or Serevent DPI) and assignment information from IWRS.
- Schedule the next visit (Day 15 of the Treatment Period) within 14 ± 2days and ensure subject has adequate supply of study drug and rescue Ventolin HFA.
- Subjects will be instructed to bring the eDiary, peak flow meter and all study medication to the next visit.

8.7 Visit 4, 6, 8, and 10 (Day 15 of Treatment Periods 1, 2, 3, and 4)

- Verify subject eligibility to continue.
- Review subject eDiary and peak flow values, and retrain subject if subject has not met eDiary compliance requirement (see Section 7.1.5).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the eCRF (if <6 hours, the visit must be rescheduled).
- Record AEs, (if any).
- Administer ACQ-5.
- Review concomitant medications to ensure adherence to study-specified regimen.
- Collect study drug dispensed during the prior visit (Day 1 of the Treatment Period).
- Perform all pre-dose assessments, including vital signs, urine pregnancy testing, ECGs, clinical laboratory testing, and spirometry (60 minutes prior to dosing).
- Perform pre-dose spirometry (60 and 30 minutes prior to dosing)
- Assess pre-dose presence of dry mouth
- Have subjects perform pre-dose eDiary collections including completion of symptom questions and pre-dose PEFR assessments.
- To allow for proper preparation of study drug, it is recommended that the seal around the treatment box is opened 15 to 30 minutes prior to dosing, and the instruction for the administration of study drug are followed.
  - Refer to Section 6.7 for detailed instructions for preparation of treatment for administration, including priming of the MDI prior to subject use.
- Collect subject eDiary and peak flow meter.
- Subject will administer first dose of newly-assigned study drug at the clinic.
- Subject will collect PEFR in clinic.
- Site personnel will record dosing time and PEFR in the eDiary.
- Perform post-dose assessments, including vital signs, ECGs, clinical laboratory tests, and spirometry.
- Assess subject for paradoxical bronchospasm at 15 and 30 minutes post-dosing
- Assess presence of dry mouth 1 hour post-dose
- Schedule the next visit (Day 1 of the next Treatment Period) within 14 ± 2days and ensure subject has adequate supply of study drug and rescue Ventolin HFA.
- Subjects will be instructed to bring the eDiary, peak flow meter and all study medication to the next visit.

8.8 Visit 12 (Final Study Visit/Day 15 of Treatment Period 5)

- Verify subject eligibility to continue.
- Review subject eDiary and peak flow values.

- Determine time of last dose of short-acting bronchodilator and other asthma medications on the eCRF (if <6 hours, the visit must be rescheduled).
- Review concomitant medications to ensure adherence to study-specified regimen.
- Record AEs, (if any).
- Administer ACQ-5.
- Collect Sponsor-provided study medication including Ventolin HFA dispensed during the prior visit (Day 1 of Treatment Period 5).
- Conduct a complete physical examination (ie., general appearance, skin, head, eyes, ears, nose, throat, neck [including thyroid], lymph nodes, chest, heart, abdomen, extremities, and nervous system).
- Obtain weight.
- Perform all pre-dose assessments, including vital signs (including weight), physical examination, ECGs, clinical laboratory testing, serum pregnancy testing, and spirometry (60 minutes prior to dosing).
- Perform pre-dose spirometry (60 and 30 minutes prior to dosing)
- Assess pre-dose presence of dry mouth
- Have subjects perform pre-dose eDiary collections including completion of symptom questions and pre-dose PEFR assessments.
- Collect subject eDiary and peak flow meter.
- Obtain treatment assignment information from IWRS.
  - To allow for proper preparation of study drug, it is recommended that the seal around the treatment box is opened 15 to 30 minutes prior to dosing, and the instruction for the administration of study drug are followed. Refer to Section 6.7 for detailed instructions for preparation of treatment for administration, including priming of the MDI prior to subject use.
- Subject will administer in-clinic dosing from the newly –assigned MDI dispensed via IWRS.
- Subject will collect PEFR in clinic.Site personnel will record dosing time and PEFR in the eDiary.
- Perform post-dose assessments, including vital signs, ECGs, clinical laboratory tests, and spirometry.
- Assess subject for paradoxical bronchospasm at 15 and 30 minutes post-dosing
- Assess presence of dry mouth 1 hour post-dose
- Return the subject to pre-study or appropriate asthma maintenance medication.

8.9 Unscheduled Visits/Premature Discontinuation (Early Termination) Visits

Note: Premature discontinuation visits will be captured as unscheduled visits.

Visit 1b, 2a, and 2b are to be used only for repeat spirometry entry criteria; all other repeat assessments, if needed, will be captured as an unscheduled visit.

The following minimum procedures should be performed at the premature discontinuation visit:

- Review eDiary data and peak flow values.
- Record AEs, (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.
- Collect subject eDiary and peak flow meter.
- Collect all study drug.
- Inform subject about reporting all SAEs up to 14 days following the last dose of study drug.
- Return subject to pre-study or appropriate maintenance asthma medications.
- Capture the reason for subject discontinuation.
- Schedule a follow-up telephone call 7 to 14 days after the last study drug dosing. If the discontinuation visit is performed >7 days after the last study drug dosing, a follow-up telephone call will not be required.

8.10 Follow-Up Telephone Call

Subjects will be followed-up through a telephone call 7 to 14 days after the last study drug dosing. The following information will be requested:

- Review previously on-going asthma exacerbations and AEs, and record AEs (if any)
- Review concomitant medications

8.11 Completion of the Study

The Investigator will document the completion or the reason for early withdrawal from the study in the eCRF.

The following categories should be used to describe these events in the eCRF:

- Subject discretion (document reason)
- Investigator considers it to be in the best interest of the subject
- Adverse events(s)
- Administrative reasons (eg., early termination of the study)
- Subject lost-to-follow-up

- Lack of efficacy
- Major protocol deviation
- Death
- Completion of the study
- Protocol specified discontinuation criteria (see Section 5.6).
- Subjects who complete all visits but do not complete a follow-up telephone call will be regarded as study completers, and will be included in efficacy and safety analyses.

9 PLANNED STATISTICAL METHODS

9.1 Introduction

This study will be conducted as a 5-period, 7-treatment, incomplete block cross-over design evaluating the following 7 treatments in approximately 224 subjects:

- GP MDI 28.8 µg BID
- GP MDI 14.4 µg BID
- GP MDI 7.2 µg BID
- GP MDI 3.6 µg BID
- GP MDI 1.9 µg BID
- SAL 50 µg BID
- Placebo MDI BID

The primary objective of this study is to compare the efficacy of GP MDI to Placebo MDI and SAL on lung function, based on peak FEV_1.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

All efficacy assessments are relative to baseline and will be compared with Placebo MDI and SAL 50 µg, and where appropriate, the GP MDI dose levels will be compared. Since pre-dose values are known to be variable and an isolated timepoint may not accurately reflect the true baseline, the following baseline will be used for the statistical analyses of in-clinic assessments unless otherwise specified: the mean of available pre-dose values on the first day of each treatment cycle, ie., the mean of pre-dose values at Visits 2, 4, 6, 8, and 10, where the mean of the 60- and 30-minute pre-dose value for each Day 1 visit is obtained and then the average of all Day 1 visit means are averaged.

For eDiary-measured values, baseline is the average of the data obtained in the last week of the baseline period.

9.2.1.1 Primary Efficacy Endpoint

- Peak change from baseline in FEV_1 over 3 hours on Day 15

9.2.1.2 Secondary Efficacy Endpoints

- Change from baseline in morning pre-dose trough FEV_1 on Day 15
- FEV_1 AUC_{0-3} on Day 15
- Change from baseline in average daily pre-dose PEFR over 14 days
- Change from baseline in average daily post-dose PEFR over 14 days
- Change from baseline in average daily rescue medication use over 14 days
- Change from baseline in ACQ-5 score on Day 15

9.2.1.3 Other Efficacy Endpoints

- Forced vital capacity, PEFR, and FEF_{25-75} will be evaluated using AUC_{0-3} and peak change from baseline on Day 15

9.2.2 Safety Endpoints

The safety assessments include ECGs, vital sign measurements, clinical laboratory tests, and AEs during the study period.

9.3 Study Populations

The following analysis populations are defined in this study:

- The **Intent-To-Treat (ITT) Population** is defined as all subjects who are randomized to treatment. Treatment is assigned as randomized regardless of the treatment actually received.
- A **Modified ITT (mITT) Population** is a subset of the ITT Population including subjects who received treatment and have post-treatment efficacy data from at least 2 treatment periods. Data judged to be impacted by major protocol deviations will be determined prior to unblinding and excluded. In addition, home peak flow values obtained within 4 hours of Ventolin HFA dosing will be excluded. Statistical tabulations and analyses will be by randomized treatment, but data obtained after subjects receive an incorrect treatment will be excluded from the affected periods.
- The **Safety Population** is defined as all subjects who are randomized to treatment and receive at least 1 dose of the study treatment. Statistical analyses and tabulations will be by the treatment actually received.

Analyses will be performed as follows:

Demographics will be summarized for the ITT, mITT, and Non-randomized Populations. Extent of exposure will be summarized for the Safety Population. The Safety Population will be used to summarize safety.

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

9.4 Efficacy Analysis

9.4.1 Primary Efficacy Analysis

The peak change from Baseline in FEV_1 will be calculated using the largest FEV_1 value measured during the 3 hours post-dosing. Baseline will be calculated using the average of the pre-dose values from Day 1 of all treatment periods. The primary efficacy analysis will be based on mixed model with covariates of treatment, baseline FEV_1, period, ICS use subgroup, and treatment-by-subgroup interaction. The model will not include treatment sequence, unless that term is determined to be important ($p<0.10$). Intra-subject correlation across treatment periods will be modeled by including subject as a random effect. Estimated treatment differences and 95% CI's will be provided for all treatment comparisons based on the overall study population, and then separately within each of the 2 ICS use subgroups.

A 2-sided alpha level of 0.05 will be employed for comparisons of the GP MDI dose levels to Placebo MDI. Multiplicity will be controlled using a sequential approach separately within the overall population and within each ICS use subgroup (Refer to Section 9.6). Comparisons to SAL will be for non-inferiority using a margin of 100 mL, and will follow a similar sequential approach. Comparisons between GP MDI dose levels will also be made.

The primary analysis will be conducted using the mITT Population. Supportive analyses will be performed using the ITT Population. Assumptions underlying the primary analysis will be evaluated and additional analyses may be performed (see Section 9.8).

9.4.2 Secondary Efficacy Analysis

The secondary endpoints will be analyzed using a similar approach as that of the primary endpoint. Mixed models will be fit with a random subject effect for the correlation across periods. The fixed effects will include the relevant baseline, treatment, period, ICS use subgroup, and treatment-by-subgroup interaction. Sequence will not be included unless it is found to be significant in the model for the primary endpoint.

FEV_1 AUC_{0-3} is the area under the curve for the change from baseline in FEV_1 calculated using the trapezoidal rule. All observed data will be used with the trapezoidal rule to calculate AUC. To aid in interpretation, all AUC values will be normalized by dividing the AUC by the time from the first to the last non-missing value (typically 3 hours).

Daily pre-dose PEFR and daily post-dose PEFR will each be calculated as the average of the AM and PM measurements recorded for a given day. If either the AM or PM assessment is missing, only the single measurement will be used. Analyses of average daily pre-dose PEFR, average daily post-dose PEFR, and rescue Ventolin HFA usage will use the average of the non-missing daily values recorded in the subject diaries over each week and over the last week of treatment within each period. Baseline for these measures will be obtained using the non-missing values from the last 7 days prior to Randomization.

9.4.3 Other Efficacy Analysis

The other efficacy endpoints will be analyzed using a similar approach as the primary endpoint. Mixed models will be fit with a random subject effect for the correlation across periods. The fixed effects will include the relevant baseline, treatment, period, ICS use subgroup, and treatment-by-subgroup interaction. Sequence will not be included unless it is found to be significant in the model for the primary endpoint.

Area under the curve from time 0 to 3 for FVC, PEFR, and FEF_{25-75} will be calculated in a similar manner as that of FEV_1 AUC_{0-3}. Peak change from baseline for FVC, PEFR, and FEF_{25-75} will be calculated in a similar manner as that of peak change in FEV_1.

9.4.4 Safety Analysis

9.4.4.1 Adverse Events

Adverse events during each treatment regimen will be summarized by ICS use subgroup and by the number of subjects experiencing an event. They will be tabulated at the level of the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and the MedDRA System Organ Class. The version of MedDRA that is current at the time of database lock will be used for final reporting. Tabulations will be broken down by severity, AE's leading to discontinuation, and by relationship to study drug. No hypothesis tests will be performed. Since the washout period may include treatment with Pulmicort Flexhaler or maintenance non-steroidal therapy, AEs reported as starting during a Washout Period will be excluded from the main analyses of AEs. As a supportive analysis, AEs will be assigned to the last randomized treatment received, including those occurring during a Washout Period.

9.4.4.2 Adverse Events of Special Interest

Paradoxical bronchospasm and dry mouth will be considered AESIs, and will be tabulated separately from other AEs. Bronchospasm and dry mouth will be summarized by ICS use subgroup and by the number of subjects experiencing the event during scheduled assessment periods on a test day and during the particular treatment period. Tabulations for bronchospasm and dry mouth will differ from those for general AEs, since events of paradoxical bronchospasm/dry mouth with onset during a treatment period will be included while onset during a washout or follow-up period will be excluded. Bronchospasm/dry mouth events with onset outside a treatment period will be listed separately. No hypothesis tests will be performed.

9.4.4.3 Clinical Laboratory Measurements

Descriptive statistics (mean, median, standard deviation and range) for change from baseline for scheduled assessments will be tabulated for each laboratory parameter, treatment, and ICS use subgroup. For clinical laboratory measurements, baseline will be defined as the last available value prior to Randomization. Potentially clinically significant values will be identified and summarized.

9.4.4.4 Vital Signs

Descriptive statistics (mean, median, standard deviation and range) for change from baseline will be tabulated by vital sign parameter, treatment, and ICS use subgroup for each scheduled assessment time. For vital signs, baseline will be defined as the average of the values prior to dosing on the day of Randomization. In addition, potentially clinically significant values will be identified and summarized.

9.4.4.5 ECGs

Descriptive statistics (mean, median, standard deviation and range) for absolute values and change from baseline will be tabulated by ECG parameter, treatment, and ICS use subgroup for each scheduled assessment time. For ECG parameters, baseline values will be defined as the last value obtained prior to Randomization. In addition, potentially clinically significant values will be identified and summarized.

9.5 Randomization

Subjects will be randomly assigned to 1 of 24 treatment sequences using an IWRS. Each sequence will include exactly 5 of the 7 treatments included in this study in a randomized order. All subjects will receive GP MDI 7.2 µg and GP MDI 14.4 µg; three-quarters of the subjects will receive Placebo MDI and/or SAL 50 µg; and half of the subjects will receive GP MDI 2.0 µg, GP MDI 3.7 µg, and/or GP MDI 28.8 µg.

The 24 treatment sequences are shown below where: A = GP MDI 7.2 µg;
B = GP MDI 14.4 µg; C = Placebo MDI; D = Sal Diskus 50 µg; E = GP MDI 1.9 µg;
F = GP MDI 3.6 µg; G = GP MDI 28.8 µg:

ABCDE BDGAC FABED

EADCB GBCDA BFDAE

BDAEC ACBGD FCAGB

CEBAD ABDCG CGFBA

DCFBA FAECB DGEAB

AFBCD BEAFC GABDE

CADBF EBCAG BDAFG

DCABF CGEBA DBGFA

Randomization will be centralized and stratified by background therapy, either ICS or non-ICS (subjects not previously treated with ICS).

9.6 Experimental Design and Type I Error Control

The experimental design was chosen to be balanced with respect to period effects in the event that all subjects complete the study. The design was selected to focus on the GP MDI 7.2 µg and GP MDI 14.4 µg doses.

Type I error will be controlled for the primary endpoint by following a sequential approach in the overall population (ICS use subgroups combined). Due to larger sample size, GP MDI 14.4 µg will be compared to Placebo MDI first using a 2-sided alpha of 0.05. If the p-value is <0.05 for the comparison of GP MDI 14.4 µg to Placebo MDI, then the comparison of GP MDI 7.2 µg to Placebo MDI will be interpreted inferentially using a 2-sided alpha=0.05. If the comparison of GP MDI 7.2 µg versus Placebo MDI is statistically significant (p-value <0.05), testing will proceed to comparison of GP MDI 28.8 µg versus Placebo MDI. If this comparison is statistically significant (p-value <0.05), this inferential procedure of comparing progressively lower dose levels (3.6 µg then 1.9 µg) of GP MDI to Placebo MDI will be continued until an insignificant p-value is obtained (≥0.05) or until the comparison of GP MDI 1.9 µg versus Placebo MDI has been conducted.

For GP MDI dose levels shown to be superior to Placebo MDI, comparisons to SAL 50 µg will be for non-inferiority (1-sided, alpha=0.025) using a margin of 100 mL and will follow a similar sequential approach. However, superiority of SAL 50 µg relative to Placebo MDI must be obtained first at the 2-sided alpha level of 0.05.

The above described type I error control procedure will be repeated separately within each ICS use subgroup. However, the implementation within each subgroup will not be conditional on the outcomes in the overall population. Other than the specification of secondary endpoints, no further adjustments for Type I error will be made.

9.7 Sample Size Consideration

Power calculations are based on the properties of the primary endpoint, peak change in FEV_1 on Day 15. An estimate for the within-subject standard deviation (SD) is obtained from a Phase II study with tiotropium (Beeh, 2014). A within-subject SD of 210 mL and an intra-class correlation of 64% are assumed. It is further assumed that approximately224 subjects will be randomized and approximately180 subjects will complete the study and be included in the mITT Population. Under these assumptions, the power to demonstrate a difference of 75 or 100 mL for each comparison is provided in the table that follows:

Difference in Peak FEV_1	GP MDI 14.4 µg versus GP MDI 7.2 µg	GP MDI 14.4 or 7.2 µg versus Placebo	GP MDI 14.4 or 7.2 µg versus GP MDI 1.9, 3.6, or 28.8 µg	GP MDI 1.9, 3.6, or 28.8 µg versus Placebo	GP MDI 1.9, 3.6, or 28.8 µg versus GP MDI 1.9, 3.6, or 28.8 µg
Overall mITT Population					
75 mL	93%	90%	88%	84%	78%
100 mL	99%	99%	99%	97%	95%
Subgroups (ICS User or Non-ICS User)					
75 mL	67%	63%	59%	54%	49%
100 mL	89%	87%	83%	79%	73%

FEV_1=Forced expiratory volume in 1 second; GP=glycopyrronium; ICS=inhaled corticosteroid; MDI=metered-dose inhaler; mITT=modified intent-to-treat

9.8 Data Validation and Transformation

In general, spirometry measures follow a normal distribution. However, under certain circumstances, (eg., during an asthma exacerbation) extreme and atypical values can arise. Such values may disproportionately affect model-based estimates of the fixed effect and variance parameters. Prior to database lock and unblinding, the changes from baseline in spirometry measures will be examined as part of data quality management. This will include production of normal probability plots, kernel density estimates, and normal order outlier statistics. If a single or small number of extreme values are identified, such outliers may be removed from the analysis, if deemed implausible. Otherwise non-parametric methods or data transformations (eg., logarithmic or normal rank transformation will be considered. If outliers are removed, sensitivity analyses including those values will be reported.

9.9 Analysis Plan

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

9.10 Handling of Missing Data

Pre-dose spirometry values will use the average of the non-missing -60 min and -30 min values. Weekly averages for eDiary-based parameters will use all non-missing values.

9.11 Statistical Software

Data processing, statistical screening, descriptive reporting and analysis of the efficacy and safety data will be performed using [redacted] Graphs may also be produced using [redacted] (R Development Core Team, 2003).

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

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

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

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

- Guideline for 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 CFR dealing with clinical studies (21 CFR parts 50, 54, 56, and 312).
- Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects) http://www.wma.net/en/30publications/10policies/b3/index.html
- Any additional regulatory requirements.

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

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

10.3 Subject Information and Consent

The study will be conducted in accordance with applicable subject privacy requirements. The proposed ICF, which must be in compliance with applicable regulations, must be

reviewed and approved by the IRB/IEC and Pearl Therapeutics prior to initiation of the study.

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

10.4 Laboratory Accreditation

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

10.5 Confidentiality

10.5.1 Confidentiality of Data

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

10.5.2 Confidentiality of Subject/Patient Records

By signing this protocol, the Investigator agrees that Pearl Therapeutics (or representative), IRB/IEC, or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to Pearl Therapeutics. In addition, the Investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws (ie., Health Insurance Portability and Accountability Act), rules, and regulations.

10.6 Quality Control and Assurance

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

10.7 Data Management

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

10.8 Study Monitoring

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

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

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

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

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

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

10.9 Retention of Data

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

10.10 Financial Disclosure

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

10.11 Investigator's Final Report

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

10.12 Publication Policy

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

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

1. **Responsibility:** Each PI is responsible for the accuracy and completeness of all data from their site. Pearl Therapeutics (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.

2. **Authorship and Publication Committee:** Pearl Therapeutics, 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 Pearl Therapeutics for review, approval, and to ensure consistency with the policy in this protocol. Pearl Therapeutics will have the right to request appropriate modification to correct facts and to represent its opinions, or the opinions of the publication committee, if these differ with the proposed publication.
4. **Confidentiality:** Investigators will conduct all interactions with Pearl Therapeutics and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of non-clinical studies, or chemical formulae) may still need to remain confidential.
5. **Medical Journal Review:** Consistent with the intention of Pearl Therapeutics to publish the study in a fair and accurate manner, Pearl Therapeutics supports diligence in the publication review process of medical journals. Accordingly, upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, eg., protocol and amendments, data tabulations, *etc*. The journal and reviewers will need to make arrangements to maintain the confidentiality of such supplemental information, where relevant, and Pearl Therapeutics will make suitable arrangements to ensure that the identity of journal reviewers is kept confidential. Records will be maintained of reviewers and the respective documents and datasets that were reviewed by each of them.
6. **Reporting of Clinical Trials Results:** To provide transparency in the conduct and reporting of randomized clinical trials, Pearl reports clinical findings based on the guidance of The CONSORT (CONsolidated Standards of Reporting Trials) Statement [CONSORT, 2010] and a 25-item checklist which is intended to improve the reporting of a randomized controlled trial, and to facilitate reader understanding of the trial design, conduct, analysis and interpretation, and to support their ability to assess the validity of its results.
7. **Internet Clinical Trial Listing:** In addition, also consistent with the recommendations of the ICMJE, Pearl Therapeutics will make available appropriate information regarding the study via the internet. This will include registration and listing of the study on www.clinicaltrials.gov, the US National Institutes of Health listing of clinical trials, and other clinical trial listings as appropriate (eg., EudratCT;https://eudract.ema.europa.eu/). Per Astra Zeneca policy, Pearl Therapeutics posts clinical study protocols for public viewing when a manuscript is published in a medical journal. Prior to being made public, the protocol is reviewed by Astra Zeneca Intellectual Property.

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12 APPENDICES

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.

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

FEV_1, FVC, FEF_{25-75} 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 (ie., 37°C), ambient pressure saturated with water vapor, BTPS) with an accuracy of at least ±3% of reading or ±0.050 L, whichever is greater, with flows between 0 and 14 $L\text{-}s^{-1}$. The total resistance to airflow at 14.0 $L\text{-}s^{-1}$ must be <1.5 $cmH_2O\ L^{-1}s^{-1}$ (0.15 $kPa\ L^{-1}s^{-1}$). The total resistance must be measured with any tubing, valves, pre-filter, etc. included that may be inserted between the subject and the spirometer. Some devices may exhibit changes in resistance due to water vapor condensation, and accuracy requirements must be met under BTPS conditions for up to 8 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 rate (PEFR), is correlated with the pleural pressure during the maneuver, the flow–volume display is useful to assess the magnitude of effort during the initial portions of the maneuver. The ability to overlay a series of flow–volume curves registered at the point of maximal inhalation may be helpful in evaluating repeatability and detecting sub-maximal efforts. However, if the point of maximal inhalation varies between blows, then the interpretation of these results is difficult because the flows at identical measured volumes are being achieved at different absolute lung volumes. In contrast, display of the FVC maneuver as a volume–time graph provides more detail for the latter part of the maneuver. A volume–time tracing of sufficient size also allows independent measurement and calculation of parameters from the FVC maneuvers. In a display of multiple 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 ≥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 2 units of flow per 1 unit of volume

The time scale should be ≥20 mm-s^{-1}, and larger time scales are preferred (≥30 mm-s^{-1}) when manual measurements are made. When the volume–time plot is used in conjunction with a flow–volume curve (ie., 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.

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 (eg., 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 3 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, eg., ±3% of true. If a device fails its calibration check then new calibration procedure or equipment maintenance is required. Calibration checks must be undertaken daily, or more frequently, if specified by the manufacturer. The syringe used to check the volume calibration of spirometers must have an accuracy of ±15 mL or ±0.5% of the full scale (15 mL for a 3-L syringe), and the manufacturer must provide recommendations concerning appropriate intervals between syringe calibration checks. Users should be aware that a syringe with an adjustable or variable stop may be out of calibration if the stop is reset or accidentally moved. Calibration syringes should be periodically (eg., monthly) leak tested at more than 1 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 (eg., 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 1 of the following procedures: 1) consecutive injections of 1-L volume increments while comparing observed volume with the corresponding cumulative measured volume, eg., 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, eg., 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 3 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 3 relatively constant flows at a low flow, then 3 at a mid-range flow, and finally 3 at a high flow. The volumes achieved at each of these flows should each meet the accuracy requirement of ±3.5%.

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 (ie., 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 1 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

Body temperature, ambient pressure, saturated with water vapor correction

All spirometry values should be reported at BTPS by any method (measuring temperature and barometric pressure) proven effective by the manufacturer. For volume-type spirometers, the temperature inside the spirometer should be measured for each breathing maneuver. Regardless of the BTPS correction technique used, the ambient temperature must

always be recorded with an accuracy of ±1°C. In situations where the ambient air temperature is changing rapidly (>3°C in <30 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

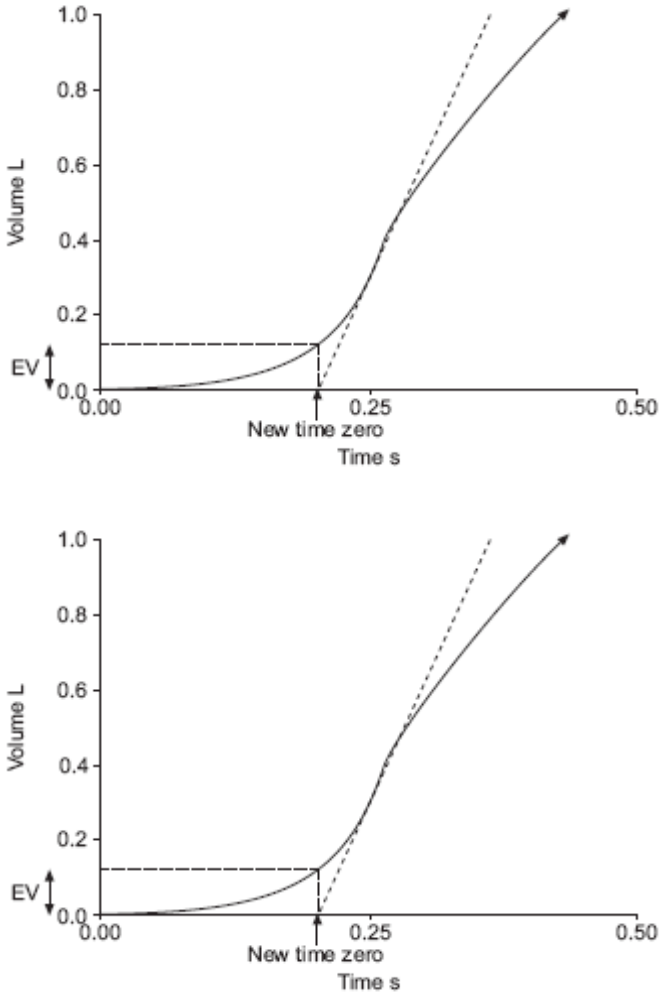
***Acceptable* Tests must meet the following 7 Criteria:**

1. 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)
1. No cough during the first second.
2. No Valsalva maneuver.
3. No leak.
4. No obstruction of mouthpiece.
5. No extra breaths.
6. Plateau achieved, ie., 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 rate (PEFR), 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 PEFR.

Between-Maneuver Reproducibility Criteria

After 3 acceptable spirograms have been obtained, apply the following tests

- The 2 largest values of FVC must be within 0.150 L of each other
- The 2 largest values of FEV_1 must be within 0.150 L of each other

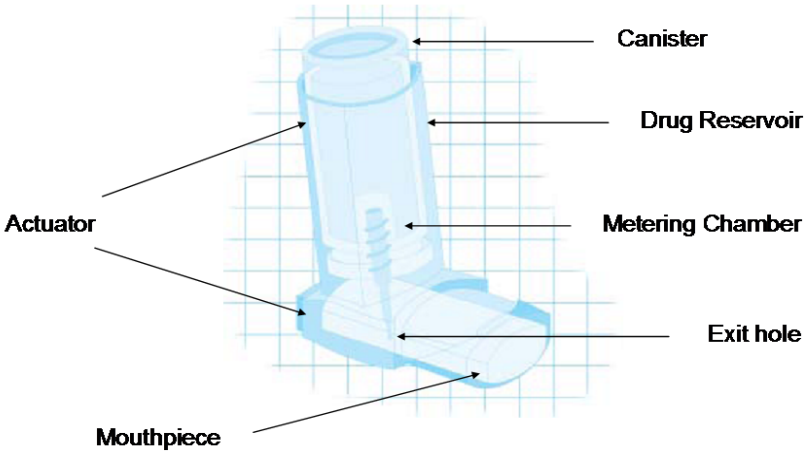
If these criteria are met, the spirometry testing for that time-point may conclude. The highest FEV_1 and the highest FVC obtained at each testing time-point (even if from different reproducible tracings) will be collected.

If acceptability criteria are not met, continue testing until they are met or the patient cannot/ should not continue (Maximum of 8 attempts).

Appendix 3 Subject Instructions for Use of GP MDI 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 3 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. Repeat steps 5 to 7, 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



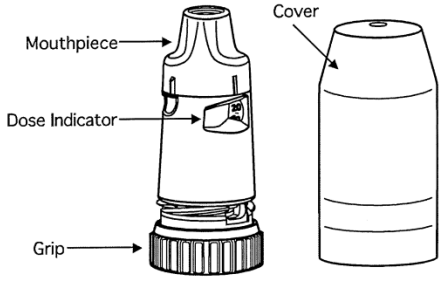
Appendix 4 Instructions for Use of Pulmicort Flexhaler *(budesonide inhalation powder)*

Patient Instructions for Use

How to use your PULMICORT FLEXHALER

Parts of your PULMICORT FLEXHALER

Fig 1



Priming PULMICORT FLEXHALER:

Before you use a new PULMICORT FLEXHALER for the first time, you must prime it.

To prime your PULMICORT FLEXHALER, follow the steps below:

1. Hold the inhaler by the brown grip so that the white cover points upward (upright position). With the other hand, turn the white cover and lift it off (see Figure 2).
2. Continue to hold your PULMICORT FLEXHALER upright as shown in Figure 1. Use your other hand to hold the inhaler in the middle. Do not hold the inhaler at the top of the mouthpiece.
3. Twist the brown grip as far as it will go in one direction and then fully back again in the other direction until it stops (it does not matter which way you turn it first). You will hear a "click" during one of the twisting movements (see Figures 3 and 4).
4. Repeat Step 3. Your PULMICORT FLEXHALER is now primed. You are ready to load your first dose.

You do not have to prime your PULMICORT FLEXHALER again after this even if you do not use it for a long period of time.

❶ Loading a dose

Fig 2

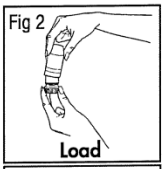


Fig 3

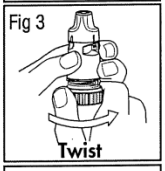


Fig 4

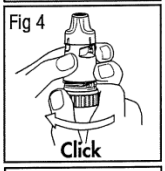
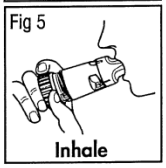


Fig 5



1. Hold your PULMICORT FLEXHALER upright as described above. With your other hand, twist the white cover and lift it off (see Figure 2).
2. Continue to hold your PULMICORT FLEXHALER upright to be sure that the right dose of medicine is loaded.
3. Use your other hand to hold the inhaler in the middle. Do not hold the mouthpiece when you load the inhaler.
4. Twist the brown grip fully in one direction as far as it will go. Twist it fully back again in the other direction as far as it will go (it does not matter which way you turn it first) [see Figure 3].
   - You will hear a "click" during one of the twisting movements (see Figure 4).
   - PULMICORT FLEXHALER will only give one dose at a time, no matter how often you click the brown grip, but the dose indicator will continue to move (advance). This means that if you continue to move the brown grip, it is possible for the indicator to show fewer doses or zero doses even if more doses are left in the inhaler.
   - **Do not shake the inhaler after loading it.**

❷ Inhaling a dose

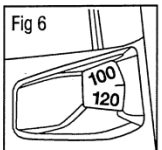
1. Turn your head away from the inhaler and breathe out (exhale). If you accidentally blow into your inhaler after loading a dose, follow the instructions for loading a new dose.
2. Place the mouthpiece in your mouth and close your lips around the mouthpiece. Breathe in (inhale) deeply and forcefully through the inhaler (see Figure 5).

3. You may not sense the presence of any medication entering your lungs when inhaling from PULMICORT FLEXHALER. This lack of sensation does not mean that you did not get the medication. You should not repeat your inhalations even if you did not feel the medication when inhaling.
4. Do not chew or bite on the mouthpiece.
5. Remove the inhaler from your mouth and exhale. **Do not blow or exhale into the mouthpiece.**
6. If more than one dose is prescribed repeat the steps above.
7. When you are finished taking your dose place the white cover back on the inhaler and twist shut.
8. **Rinse your mouth with water after each dose to decrease your risk of getting thrush. Do not swallow the water.**

Reading the Dose Indicator Window

- The label on the box or cover will tell you how many doses are in your PULMICORT FLEXHALER.
- Your PULMICORT FLEXHALER has a dose indicator window just below the mouthpiece. The dose indicator tells you about how many doses are left in the inhaler. Look at the middle of the window to find out about how many doses are left in your inhaler (see Figure 6).

Fig 6



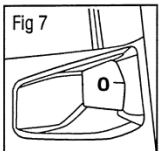
Dose Indicator

- The dose indicator is connected to the turning grip and moves (counts down) every time a dose is loaded. **It is not likely that you will see the dose indicator move with each dose.** You can usually see the indicator move each time you use about 5 doses.
- The dose indicator starts with either the number 60 or 120 when full, depending upon the strength of the inhaler. The indicator is marked in intervals of 10 doses. Markings are either with numbers or dashes (alternating), counting down to "0".

60 Dose Inhaler	120 Dose Inhaler	
20 – 40 – 60	80 – 100 – 120	Dose indicator starts at 60 or 120 depending on strength (90 mcg or 180 mcg) of the inhaler and counts down to 0.

- The dose indicator will tell you about how many doses are left in your PULMICORT FLEXHALER.
- **If you complete the instructions for loading the dose more than one time before you inhale the dose, you will only receive one dose.** The dose indicator will move a small amount but it is not likely that you will see the dose indicator move with each dose.
- **Your inhaler is empty when the number 0 on the red background reaches the middle of the dose indicator window. Throw away this inhaler. The inhaler may not give you the right amount of medicine, even though it may not feel completely empty and may seem like it continues to work (see Figure 7).**

Fig 7



Empty

- **Do not put your PULMICORT FLEXHALER in water (do not immerse it) to find out if it is empty. Check the dose indicator window to see how many doses are left.**
- Refill your PULMICORT FLEXHALER prescription before your medicine runs out. You will get a new inhaler each time you refill your prescription.

Cleaning your PULMICORT FLEXHALER

- Keep your PULMICORT FLEXHALER clean and dry at all times. Do not immerse it in water.
- Wipe the outside of the mouthpiece one time each week with a dry tissue.
- Do not use water or liquids when cleaning the mouthpiece.
- Do not try to remove the mouthpiece or twist it.

Do not use your PULMICORT FLEXHALER if it has been damaged or if the mouthpiece has become detached. Talk to your healthcare provider or pharmacist if you have any problems with your PULMICORT FLEXHALER.

PULMICORT FLEXHALER is a registered trademark of the [redacted]

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Appendix 5 Instructions for Use of` Ventolin HFA Inhaler

The Parts of Your VENTOLIN HFA Inhaler

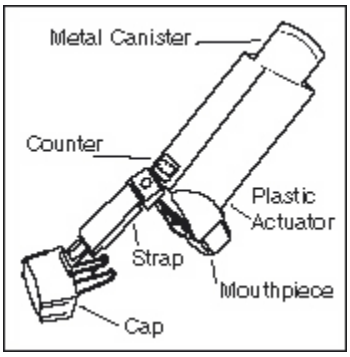

Figure 1

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.

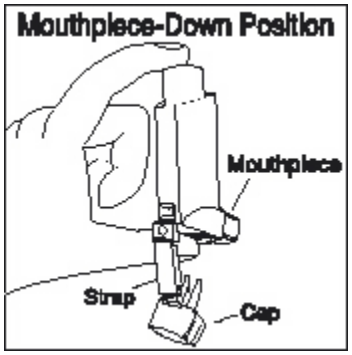

Figure 2

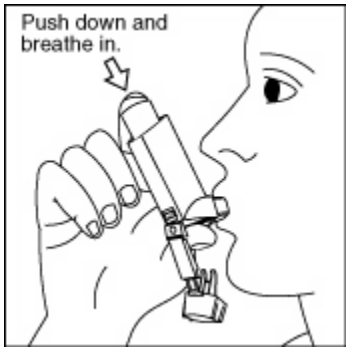

Figure 3

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

1. **When the counter reads 020**, you should refill your prescription or ask your doctor if you need another prescription for VENTOLIN HFA.
2. **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.
3. **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).

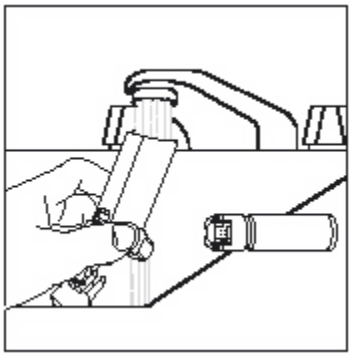

Figure 4

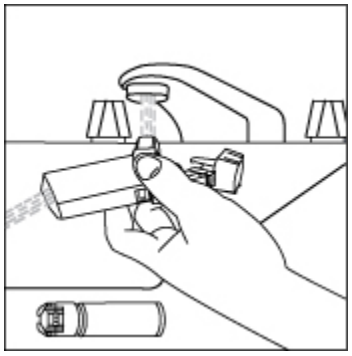

Figure 5

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).

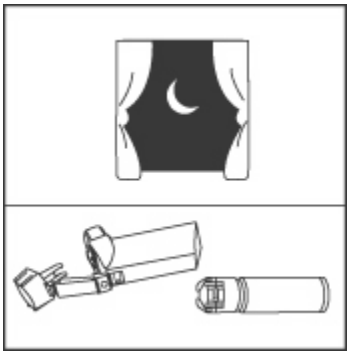

Figure 6

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.

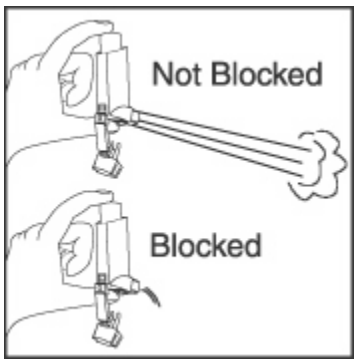

Figure 7

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 6 Instructions for Use of` Serevent Diskus Inhaler

For Oral Inhalation Only

Your Serevent Diskus inhaler

Figure A

Read this information before you start using your Serevent Diskus inhaler:

- Take Serevent Diskus out of the foil pouch just before you use it for the first time. Safely throw away the pouch. The DISKUS will be in the closed position.
- Write the date you opened the foil pouch in the first blank line on the label. **See Figure A.**
- Write the “use by” date in the second blank line on the label. **See Figure A.** That date is 6 weeks after the date you wrote in the first line.
- The counter should read **60**. If you have an institutional pack (with “INSTITUTIONAL PACK” on the foil pouch), the counter should read **28**.

How to use your Serevent Diskus inhaler

Follow these steps every time you use Serevent Diskus.

Step 1. Open your Serevent Diskus.

- Hold the DISKUS in your left hand and place the thumb of your right hand in the thumb grip. Push the thumb grip away from you as far as it will go until the mouthpiece shows and snaps into place. **See Figure B.**

Figure B

Step 2. Slide the lever until you hear it click.

- **Hold the Diskus in a level, flat position** with the mouthpiece towards you. Slide the lever away from the mouthpiece as far as it will go until it **clicks**. **See Figure C.**

Figure C

- The number on the counter will count down by 1. The DISKUS is now ready to use.

Follow the instructions below so you will not accidentally waste a dose:

- **Do not** close the DISKUS.
- **Do not** tilt the DISKUS.
- **Do not** move the lever on the DISKUS.

Step 3. Inhale your medicine.

- Before you breathe in your dose from the DISKUS, breathe out (exhale) as long as you can while you hold the DISKUS level and away from your mouth. **See Figure D.** Do not breathe into the mouthpiece.

Figure D

- Put the mouthpiece to your lips. **See Figure E.** Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.

Figure E

- Remove the DISKUS from your mouth and **hold your breath for about 10 seconds,** or for as long as is comfortable for you.
- **Breathe out slowly as long as you can. See Figure D.**
- The DISKUS delivers your dose of medicine as a very fine powder that you may or may not taste or feel. **Do not** take an extra dose from the DISKUS even if you do not taste or feel the medicine.

Step 4. Close the DISKUS.

- Place your thumb in the thumb grip and slide it back towards you as far as it will go. **See Figure F.** Make sure the DISKUS clicks shut and you cannot see the mouthpiece.
- The DISKUS is now ready for you to take your next scheduled dose in about 12 hours. **When you are ready to take your next dose, repeat Steps 1 through 4.**

Figure F

When should you get a refill?

The counter on top of the DISKUS shows you how many doses are left. After you have taken **55** doses (**23** doses from the institutional pack), the numbers **5** to **0** will show in red. **See Figure G**. These numbers warn you there are only a few doses left and are a reminder to get a refill.

Figure G

For correct use of the DISKUS, remember:

- Always use the DISKUS in a level, flat position.
- Make sure the lever firmly clicks into place.
- Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- **Do not** take an extra dose, even if you did not taste or feel the powder.
- **Do not** take the DISKUS apart.
- **Do not** wash the DISKUS.
- Always keep the DISKUS in a dry place.
- **Do not** use the DISKUS with a spacer device

Appendix 7 Asthma Control Questionnaire

(*The samples provided here is for illustrative purposes only*)

ASTHMA CONTROL QUESTIONNAIRE

(SYMPTOMS ONLY)

[redacted]

For further information:

[redacted]

[redacted]

SYMPTOMS ONLY MODIFIED [redacted]

NORTH AMERICAN ENGLISH

ASTHMA CONTROL QUESTIONNAIRE©

Page 1 of 1

Please answer questions 1 - 5

Circle the number of the response that best describes how you have been during the past week.

1.	On average, during the past week, how often were you **woken by your asthma** during the night?	0 Never 1 Hardly ever 2 A few times 3 Several times 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2.	On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3.	In general, during the past week, how **limited were you in your activities** because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited
4.	In general, during the past week, how much **shortness of breath** did you experience because of your asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal
5.	In general, during the past week, how much of the time did you **wheeze?**	0 Not at all 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time

SYMPTOMS ONLY MODIFIED [redacted]

NORTH AMERICAN ENGLISH

Appendix 8 Sponsor Signatory

Study Title: A Randomized, Double-Blind, Chronic-Dosing (14 days), 5-Period, 7-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-center, Dose-ranging Study to Assess the Efficacy and Safety of PT001 Relative to Placebo MDI and Open-Label Serevent® Diskus® in Adult Subjects With Intermittent Asthma or Mild to Moderate Persistent Asthma

Study Number: PT001101-01

Final Original Date: [redacted]

Signature: [redacted] Date: [redacted]

Name: [redacted]

Title: [redacted]

Pearl Therapeutics, Inc.

Appendix 9 Investigator's Agreement and Signature Page

Study Title:	A Randomized, Double-Blind, Chronic-Dosing (14 days), 5-Period, 7-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-center, Dose-ranging Study to Assess the Efficacy and Safety of PT001 Relative to Placebo MDI and Open-Label Serevent® Diskus® in Adult Subjects With Intermittent Asthma or Mild to Moderate Persistent Asthma
Study Number:	PT001101-01
Final Date:	[redacted]

I agree:

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

Signature: [redacted] Date [redacted]

Name: [redacted]

Affiliation: [redacted]