Clinical Trial Protocol: PT008001-00

Study Title: A Randomized, Double-Blind, Chronic Dosing (4 weeks), Four-Period, Five-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess the Efficacy and Safety of Four Doses of Budesonide Inhalation Aerosol (BD MDI, PT008) Relative to Placebo MDI in Adult Subjects With Mild to Moderate Persistent Asthma

Study Number: PT008001-00

Study Phase: IIb

Product Name: Budesonide Inhalation Aerosol; PT008

IND Number: 121629

Indication: Asthma

Investigators: Multicenter

Sponsor: Pearl Therapeutics, Inc.
[redacted]

Sponsor Contact: [redacted]

	Version Number	Date
Original Protocol	Version 1.0	[redacted]

SYNOPSIS

Sponsor:
Pearl Therapeutics

Names of Finished Products:
Budesonide Inhalation Aerosol; PT008

Name of Active Ingredients:
Budesonide

Study Title:
A Randomized, Double-Blind, Chronic Dosing (4 weeks), Four-Period, Five-Treatment, Incomplete Block, Cross-Over, Multicenter Study to Assess the Efficacy and Safety of Four Doses of Budesonide Inhalation Aerosol (BD MDI, PT008) Relative to Placebo MDI in Adult Subjects With Mild to Moderate Persistent Asthma

Study Number: PT008001-00

Study Phase: IIb

Study Objective(s):

Primary objective:
To demonstrate a lung function benefit of BD MDI compared with Placebo MDI in adult subjects with mild to moderate persistent asthma

Secondary Objective:
To characterize the dose response of BD MDI based on lung function in adult subjects with mild to moderate persistent asthma

Safety Objective:
To evaluate the safety and tolerability of BD MDI across all doses evaluated in the study

Study Design:

This is a randomized, double-blind, chronic dosing (28 days), four-period, five-treatment, incomplete block, cross-over, multicenter study to assess the efficacy and safety of four doses of BD MDI (320, 160, 80, and 40 µg ex-actuator, twice daily (BID)) and Placebo MDI (BID) in adult subjects with mild to moderate persistent asthma.

This multi-center study will be conducted at approximately 10 sites in the United States, contributing approximately 15 subjects per site. Across these sites, it is planned that approximately 150 adult subjects with mild to moderate persistent asthma who remain symptomatic despite treatment with Pulmicort® Flexhaler® 180 µg BID will be randomized into the study to provide approximately 120 subjects to complete the study. The entire study period is scheduled to take a maximum of 32 weeks for each subject.

Study Population:
Approximately 150 adult subjects with mild to moderate persistent asthma who remain symptomatic despite treatment with Pulmicort® Flexhaler® 180 µg BID, will be enrolled to provide approximately 120 subjects to complete the study (i.e., 4 treatment periods).

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

Product Name & Dose	Dosage Form	Product Strength	Comments
Budesonide Inhalation Aerosol 320 µg ex-actuator	MDI	160 µg per actuation	Taken as 2 inhalations
Budesonide Inhalation Aerosol 160 µg ex-actuator	MDI	80 µg per actuation	Taken as 2 inhalations
Budesonide Inhalation Aerosol 80 µg ex-actuator	MDI	40 µg per actuation	Taken as 2 inhalations
Budesonide Inhalation Aerosol 40 µg ex-actuator	MDI	20 µg per actuation	Taken as 2 inhalations
Albuterol Sulfate Inhalation Aerosol[§] 90 µg	MDI	Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece	US source: (Ventolin® HFA) *Supplies are open-label*
Budesonide Inhalation Powder[†] 180 µg	DPI	Taken as one inhalation. Each inhalation contains 180 µg of budesonide corresponding to 160 µg delivered from the mouthpiece	US source: (Pulmicort Flexhaler®) *Supplies are open-label*
Placebo	MDI	Formulation does not contain active ingredient	Taken as 2 inhalations from the MDI

[§] Rescue medication and reversibility testing.

[†] Asthma maintenance therapy during Screening and Washout Periods

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

All placebos are created by Pearl Therapeutics in the image of the active test product. The 320, 160, 80, and 40 µg ex-actuator delivery of BD MDI are equivalent to 370.0, 185.0, 92.4, and 46.2 µg ex-valve of BD MDI, respectively.

Duration of Treatment:
Each subject will receive 28 days (4 weeks) of study treatment with each of their assigned treatments for a total of 4 separate Treatment Periods. A Washout Period of at least 14 days (and up to 21 days) will occur between each Treatment Period. The entire study is scheduled to take a maximum of 32 weeks for each individual subject from the time of screening (See Table 10).

Efficacy Assessments:
Primary Efficacy Endpoint:

- Change from baseline in morning pre-dose trough forced expiratory volume in one second (FEV_1) at the end of the Treatment Period

Secondary Efficacy Endpoints:

- Change from baseline in mean morning pre-dose and mean evening pre-dose peak flow rate (PEFR) readings taken by the subject and recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in Asthma Control Questionnaire (ACQ) score at the end of the Treatment Period

Other Efficacy Endpoints:

- Change from baseline in morning pre-dose trough FEV_1 over the Treatment Period and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in mean morning and evening pre- and post-dose daily PEFR readings taken by subjects and recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Percentage of days without rescue Ventolin HFA use over the last week of the Treatment Period and over the entire Treatment Period
- Change from baseline in pre-dose trough forced vital capacity (FVC) at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough PEFR at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough forced expiratory flow 25-75% (FEF_{25-75}) at the end of each Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in the number of nighttime awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period, over each week of the Treatment Period, and over the entire Treatment Period
- Percentage of nights with awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period and over the entire Treatment Period

Safety Endpoints:

The safety assessments include ECGs, vital sign measurements, clinical laboratory tests, monitoring for paradoxical bronchospasm, physical examination findings, Adverse Events (AEs) and Serious Adverse Events (SAEs) during the study period.

Statistical Methods:

Sample Size Determination:

Power calculations are based on the properties of the primary endpoint, morning pre-dose trough $FEV_{1,}$ on the last day of each Treatment Period (end of treatment). An estimate of the total SD of 405 mL is taken from a 12-week trial comparing budesonide to ciclesonide (Boulet, 2006). Assuming that half of the variability comes from within subject and half between (i.e. intrasubject correlation=0.5), an estimate of the within subject standard deviation of 285 mL for morning pre-dose trough FEV_1 is obtained. Using this SD and assuming that 150 randomized provides approximately 120 completers, the power to demonstrate a 120 mL difference from Placebo MDI for BD MDI 320 μg or BD MDI 160 μg is approximately 90%. For BD MDI 80 μg and BD MDI 40 μg, the power to demonstrate a difference from Placebo MDI of 140 mL is approximately 80%.

Efficacy Analyses:

The primary efficacy analysis will compare the change from baseline at the end of treatment in morning pre-dose trough FEV_1 between BD MDI treatments and Placebo MDI using a repeated measures model with an unstructured model for the correlation across periods within subject. The model will include baseline FEV_1, response to albuterol, and period as covariates. Sequence will also be included if it explains significant variability. The primary population will be a modified Intent to Treat (mITT) Population. A two-sided alpha level of 0.05 will be employed. Multiplicity will be controlled using a sequential, dose-ordered approach.

Similar analyses will be conducted using the Intent to Treat (ITT) Population for the primary endpoint as well as for analyses of the secondary and other efficacy endpoints.

Safety analyses:

Safety analyses will be based on descriptive statistics for ECG, vital sign and laboratory measurements as appropriate, incidence of paradoxical bronchospasm, and on the number of subjects with AEs and SAEs.

Date of Original Approved Protocol: [redacted]

Prepared in: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ACQ	Asthma Control Questionnaire
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the curve
AV	Atrioventricular block
BD	Budesonide
BID	Bis in die, twice daily
BMP	Basic Metabolic Panel
BP	Blood Pressure
BPM	Beats per minute
BTPS	Body Temperature and Pressure Saturated
BUN	Blood urea nitrogen
$CaCl_2$	Calcium Chloride
CFR	Code of Federal Regulations
CMP	Comprehensive Metabolic Panel
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
CRO	Contract Research Organization
DBP	Diastolic blood pressure
DSPC	Distearoylphosphatidyl choline
DPI	Dry Powder Inhaler
e.g.	Exempli gratia, for example
ECG	Electrocardiogram
ex-actuator	dose delivered from the actuator (i.e., mouthpiece) of the MDI
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
HCG	Human chorionic gonadotropin
HR	Heart Rate
HFA	Hydrofluoroalkane
i.e.	Id est, that is
IBD	Incomplete Block Design
ICF	Informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IWRS	Interactive Web Response System
L	Liter
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
MAO	Monoamine oxidase inhibitor
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified ITT
mL	Milliliter
Msec (ms)	Millisecond

NHANES III	National Heart, Lung, and Blood Institute Third National Health and Nutrition Examination Survey
OTC	Over-the-counter
PEFR	Peak expiratory flow rate
PFT	Pulmonary function test
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PRN	Pro re nata, as needed
REML	Residual or restricted maximum likelihood
RFD	Rescue-free days
Rx	Treatment
QTcF	QT corrected using Fridericia's formula ($QT/(RR^{1/3})$)
SABA	Short-acting beta agonist
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SD	Standard deviation
SOP	Standard operating procedure
TNFα	Tumor necrosis factor α
TP	Treatment Period
US	United States

TRADEMARK INFORMATION

Trademarks Not Owned By Pearl Therapeutics

Advair

Atrovent

Combivent

Dulera

Pulmicort

Robinul

Robinul Forte

Symbicort

Ventolin HFA

1 INTRODUCTION

The World Health Organization (WHO) estimates that 235 million people currently suffer from asthma [WHO, 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 [Akinmabi, 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 (e.g. age 50, 60 or even later in life) [GINA, 2012]. Those individuals who develop asthma as adults are said to have adult onset asthma.

The current National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report-3, 2007 (NHLBI, 2007) recommends long-term treatment with inhaled corticosteroids (ICS) because of their superior effectiveness in managing the chronic airway inflammation that characterizes persistent asthma [NHLBI, 2007]. Additionally, the US Food and Drug Administration (FDA) issued a warning in February 2010 that long-acting beta agonists (LABAs) should never be used alone to treat asthma, and specifying that when they are used as part of a combination therapy, they should be administered only for the shortest duration possible and then discontinued and then patient should be maintained on a controller medication [FDA, 2010].

The NHLBI EPR-3 Guidelines recommend a stepwise approach to asthma treatment: inhaled corticosteroid (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, 2007].

Regular treatment with ICS improves symptoms, lung function , 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, 2012].

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 BD when used to treat chronic asthma, and a large range outcome measures have been used to assess its efficacy and safety.

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 (DSPC) and $CaCl_2$ that are cosuspended with crystalline active drug substances and formulated into suspension-based hydrofluoroalkane (HFA) metered dose inhalers (MDIs). The safety of porous particles is previously demonstrated in over 1000 patients with COPD.

Pearl Therapeutics is developing a broad range of MDI-based inhalation aerosols using its porous particle technology platform. These inhaled therapies include Glycopyrrolate (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) for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. GFF MDI is currently being evaluated in the PINNACLE 1 and PINNACLE 2 Phase III trials; and in a recently completed Phase I pharmacokinetic (PK) PK study with budesonide as a component in a fixed "triple" combination therapy with GP and FF.

1.1 Study Rationale

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

2 STUDY OBJECTIVES

2.1 Primary Objective

To demonstrate a lung function benefit of BD MDI compared with Placebo MDI in adult subjects with mild to moderate persistent asthma

2.2 Secondary Objective

To characterize the dose response of BD MDI based on lung function in adult subjects with mild to moderate persistent asthma

2.3 Safety Objective

To evaluate the safety and tolerability of BD MDI across all doses evaluated in the study

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoint

- Change from baseline in morning pre-dose trough forced expiratory volume in one second (FEV_1) at the end of the Treatment Period

3.1.2 Secondary Efficacy Endpoints

- Change from baseline in mean morning pre-dose and mean evening pre-dose peak flow rate (PEFR) readings taken by the subject and recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in Asthma Control Questionnaire (ACQ) score at the end of the Treatment Period

3.1.3 Other Efficacy Endpoints

- Change from baseline in morning pre-dose trough FEV_1 over each Treatment Period and at Day 15 and Day 29 of each Treatment Period
- Change from baseline in mean morning and evening pre- and post-dose daily PEFR readings taken by subjects and recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Percentage of days without rescue Ventolin HFA use over the last week of the Treatment Period and over the entire Treatment Period
- Change from baseline in pre-dose trough forced vital capacity (FVC) at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough PEFR at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough forced expiratory flow 25-75% (FEF_{25-75}) at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in the number of nighttime awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period, over the week of the Treatment Period, and over the entire Treatment Period
- Percentage of nights with awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period and over the entire Treatment Period

3.2 Safety Endpoints

The safety assessments include electrocardiograms (ECGs,) vital sign measurements, clinical laboratory tests, monitoring for paradoxical bronchospasm, physical examination findings, AEs and SAEs during the study period.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind, chronic dosing (4 weeks), four-period, five-treatment, incomplete block, cross-over, multi-center study to assess the efficacy and safety of four doses of BD MDI (320, 160, 80, and 40 µg BID) and Placebo MDI (BID) in adult subjects with mild to moderate persistent asthma.

This multi-center study will be conducted at approximately 10 sites in the United States, contributing approximately 15 subjects per site, in the US. Across these sites, it is planned that approximately 150 adult subjects with mild to moderate persistent asthma, who remain symptomatic despite treatment with Pulmicort Flexhaler 180 µg will be randomized into the study to provide approximately 120 subjects to complete the study. The entire study period is scheduled to take a maximum of 32 weeks for each individual subject (See Figure 1). The study is anticipated to run for approximately 12 months and should not exceed 18 months.

At the Screening Visit (Visit 1a), all subjects are to sign an informed consent form prior to the conduct of any screening assessments. The investigator or designee will obtain a medical history, physical examination, and any required documentation in order to determine eligibility for participation (inclusion/exclusion criteria). Reversibility of FEV_1 within 30 minutes following 4 puffs of Ventolin HFA will be assessed at Screening (Visit 1a) to determine eligibility to participate in the study. If the criterion is not met at 30 minutes, a repeat post-bronchodilator pulmonary function test (PFT) may be performed at 60 minutes to assess reversibility (See Section 7.1.1.1).

At the Investigators' discretion, subjects who do not meet the spirometry and/or reversibility entry criteria at Visit 1a can return for a repeat spirometry and/or reversibility assessment at an optional Screening visit (Visit 1b). Note: Visit 1b is to be used only for repeat spirometry entry criteria at any time between Visit 1a and Visit 2, all other repeat assessments, if needed, will be captured as an unscheduled visit. Repeat spirometry can be done anytime post Visit 1a and Visit 2, however, the subject must be in the 2 week run in period with Pulmicort Flexhaler 180 µg.

Providing the subject meets the eligibility criteria at Screening (Visit 1a or optional Visit1b), the investigator or designee will review current asthma medications and, if necessary, will adjust the prohibited asthma therapy to protocol-allowable asthma therapy as described in Section 5.4.

Subjects who meet all entry criteria but are using certain prohibited asthma medications (e.g., oral β_2-agonists, corticosteroids, corticosteroid/LABA fixed dose combination products, and leukotriene antagonists [e.g., zafirlukast, montelukast, zileuton]) will discontinue these medications for the duration of the trial.

During the Screening Period (between Visit 1 to Visit 3), all subjects will be prescribed open-label Pulmicort Flexhaler 180 µg BID provided by the sponsor and open-label rescue Ventolin HFA 108 µg MDI provided by the sponsor as needed to control symptoms.

Subjects will be issued and trained on an electronic diary (eDiary) and peak flow meter use at Visit 1 (Screening) and will be instructed to collect practice data during the Screening Period (between Visit 1 and Visit 3).

In order to standardize asthma maintenance medications and to determine disease severity, eligible subjects will undergo a run-in period of at least 14 days (2 weeks) but not greater than 28 days in duration, on sponsor provided open-label Pulmicort Flexhaler 180 µg BID and sponsor provided rescue Ventolin HFA MDI as needed to control symptoms, prior to returning to the clinic for Visit 2.

At Visit 2, reversibility to Ventolin HFA will be evaluated (See Section 7.1.1.1) and Visit 2 procedures completed (See Section 8.3). Subjects successfully meeting study entry criteria at Visit 2 will be scheduled for Visit 3 (Randomization Visit) at least 1 day from Visit 2, but no later than 28 days from Visit 1a (Screening).

At Visit 3 (Randomization Visit; Treatment Period 1, Day 1), subject eDiary compliance will be reviewed and all sponsor-provided Pulmicort Flexhaler and Ventolin HFA provided during the Screening Period will be discontinued and collected by site personnel for accountability. Eligible subjects will complete an Asthma Control Questionnaire (ACQ) (Juniper, 1999) (See Section 7.1.6 and Appendix 6) at Visit 3 prior to Randomization.

Subjects must have a minimum ACQ score of ≥1.5 and diary compliance of >70% in the last 7 days preceding Visit 3 and meet the FEV_1 baseline stability criteria (See Section 5.1) to be eligible for Randomization at Visit 3. Subjects who do not meet the ACQ minimum score, eDiary compliance or FEV_1 baseline stability criteria described above must be screen failed at Visit 3.

Subjects who continue to meet all entry inclusion/exclusion criteria at Visit 3 and that remain eligible for participation in the study will be randomized to one of the pre-defined treatment sequences.

Each sequence will include exactly 4 of the 5 treatment groups included in this study (placebo or BD MDI at one of the following doses: 320 µg, 160 µg, 80 µg, and 40 µg) BID. All pre-defined treatment sequences will include BD MDI 320 µg BID, BD MDI 160 µg BID and Placebo MDI BID as treatment options and half will include BD MDI 40 µg BID or BD MDI 80 µg BID in a randomized manner.

The subject, clinical site personnel and Pearl Therapeutics will be unaware of the treatment dose assigned (sequence) to a subject and it will not be possible to differentiate between study treatments as all blinded clinical supplies will be identical in image in all aspects. Randomization will be centralized, through the use of an IWRS (Interactive Web Response System). Study treatments will be administered twice daily. Each of the 4 treatments will be

administered for 28 ± 2 days with a Washout Period of at least 14 days (up to 21 days) during which subjects will administer Pulmicort Flexhaler 180 µg, BID and Ventolin HFA as needed in between Treatment Periods.

During Visit 3 (Treatment Period 1, Day 1), site staff must confirm the subject met all inclusion/exclusion criteria and ensure adequate washout (≥4 hours) of short acting bronchodilators. The study site staff will prime the MDI for subject use, the subjects will be dispensed study medication and will self-administer their first dose at the clinic under site personnel supervision prior to 10 AM.

Subjects will be required to remain at the clinic until completion of all protocol-defined visit assessments up to and including the last post-dose PEFR assessment (See Section 8.4). Subjects will then be discharged from the clinic and will continue to administer study medication and complete their eDiary for 14 days (2 weeks) and complete their eDiary 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 (2 weeks) of chronic Treatment 1 dosing at home and complete Visit 4 procedures (See Section 8.6). Subjects will then be discharged from the clinic and will continue to administer study medication and complete their eDiary for 14 days (2 weeks) at home until Visit 5 (Treatment Period 1, Day 29).

Subjects will return to the clinic following approximately 14 days (2 weeks) of chronic Treatment 1 dosing for Visit 5 (Treatment 1, Day 29) and complete the procedures for Visit 5 (See Section 8.7). On discharge, subjects will undergo a study medication Washout Period of at least 14 Days (2 Weeks) but no more than 21 Days (3 weeks) duration, on sponsor-provided open-label Pulmicort Flexhaler 180 µg BID and sponsor-provided rescue Ventolin HFA MDI as needed, to control symptoms, prior to initiating Treatment 2 in their assigned treatment sequence at Visit 6.

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

At Visits 6, 9 and 12 (Day 1 of Treatment Periods 2, 3 and 4, respectively), subjects will return to the clinic following their Washout Period and if eligible to continue, complete all Day 1 procedures for the Treatment Period (See Section 8.5). Pre-dose assessments will be performed and continued eligibility will be determined. Subjects must meet the FEV_1 baseline stability criteria (See Section 7.1.1.2) to be eligible for dosing at Visits 6, 9 and 12. Subjects who do not meet the FEV_1 baseline stability criteria at Visits 6, 9 and 12 must be rescheduled as soon as is practical, but within the protocol-specified washout window (14–21 days between Treatment Periods). Subjects who fail to meet stability criteria after 2 attempts within a Washout Period will be discontinued from the study.

Eligible subjects (e.g. subjects who meet FEV_1 baseline stability criteria and have withheld all asthma medications for 4 hours prior to the study visit) will be dispensed study drug relative to the IWRS and administer their first dose of study drug in the clinic under site

supervision. The post-dose PEFR will be performed and the subject discharged to continue daily study drug administration and eDiary completion at home until the next scheduled visit at 14± 2 days from Treatment Day 1 of the Treatment Period (See Section 8.5).

At Visits 7, 10, and 13 (Day 15 of Treatment Periods 2, 3 and 4, respectively), eligible subjects (e.g. subjects who have withheld all asthma medications for 4 hours prior to the study visit) will complete all pre-dose assessments and continued eligibility will be determined (See Section 8.6). Providing the subject does not meet rescue criteria (See Section 7.1.1.3), new study drug as assigned by IWRS will be dispensed, the subject will take their study medication under site supervision, and a post-dose PEFR will be obtained. The subject will be discharged to continue daily study drug administration and eDiary completion at home until the next scheduled visit at approximately 28±2 days from Treatment Day 1 of the Treatment Period.

At Visits 8 and 11 (Day 29 of Treatment Periods 2 and 3, respectively), eligible subjects (e.g. subjects who have withheld all asthma medications for 4 hours prior to the study visit) will complete all pre-dose assessments and continued eligibility will be determined (See Section 8.7). Subjects will administer their last dose of study drug from the MDI assigned at visit 7 and 10, respectively, and post-dose PEFR and vital signs will be obtained. The subject will be discharged to undergo a Washout Period of at least 14 Days (2 weeks) up to 21 Days (3 weeks) on sponsor-provided open-label Pulmicort Flexhaler 180 µg BID and Ventolin HFA as needed, for relief of asthma symptoms, prior to initiating Treatment Periods 3 and 4 at Visits 9 (Treatment Period 3, Day 1) and Visit 12 (Treatment Period 4, Day 1), respectively.

At Visit 14 (Day 29 of Treatment Period 4), eligible subjects (e.g. subjects who have withheld all asthma medications for 4 hours prior to the study visit) will complete all pre-dose assessments and continued eligibility determined (See Section 8.8). Subjects will administer their last dose of study drug from the MDI assigned at visit 13, and post-dose PEFR and vital signs will be obtained. Following completion of Visit 14 assessments, the subject will be discharged and returned to pre-study or appropriate inhaled asthma maintenance medication(s). Subjects completing Visit 14 (Day 29 of Treatment Period 4), or who require a Premature Discontinuation Visit, will be scheduled for a post-study follow-up telephone call (See Section 8.11) at least 7 days and up to 14 days from the date of last study dose.

General Guidance for Treatment Visits 3 through 14 (in clinic)

- 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 study medication and rescue medications (e.g. albuterol) for at least 4 hours, by confirming the last time of dosing for all asthma medication(s).

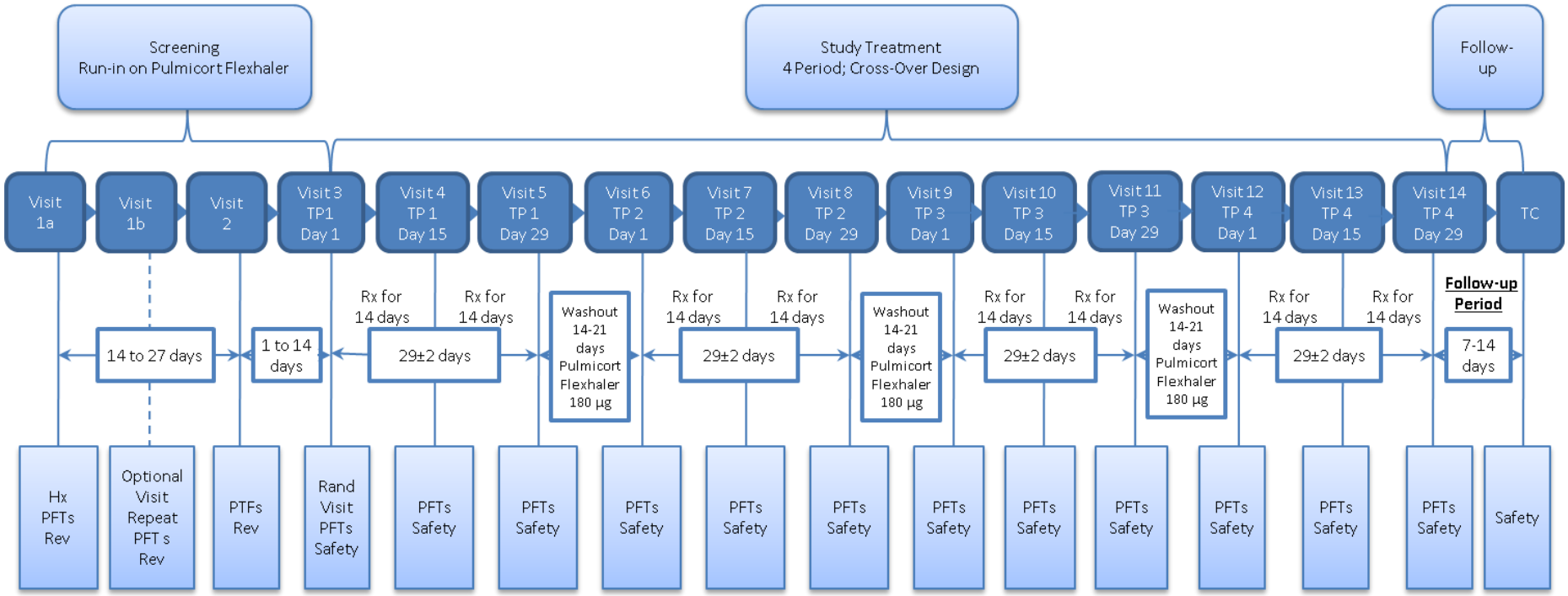
  Note: Subjects who inadvertently took rescue medication(s) within 4 hours of the start of study procedures must be rescheduled as soon as is practical but within the specified visit window. In addition, before the in-clinic dose is administered, the site must confirm the subject met all other protocol specified requirements (e.g. FEV_1 baseline stability). Subjects will remain in the clinic until 30 minutes post dose, for observation (safety).

- Subjects must not ingest caffeine-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 a dosing schedule at home consistent with their in clinic dosing time.
    - Subjects will be required to take their study medication twice a day in the morning between 06:00 and 10:00 AM (Breakfast time) and in the evening between 06:00 and 10:00 PM (Dinner time).
- In order to minimize diurnal variance, sites should make every effort to assess subjects at the same time throughout the study and to discuss the importance of dosing in a timely manner every 12 hours.
    - Subjects will be required to return to the clinic at approximately the same time as Visit 3 for all treatment visits (± 2 hours) but not to exceed 10:00 AM and will be required to remain at the clinic until completion of all protocol-defined Visit assessments.
    - Sites should make every effort to ensure that the in-clinic dosing time is before 10:00 AM and within 12 ± 2 hours of the prior at-home evening dosing time.
- Sites are encouraged to call the subject on the day before a scheduled visit to remind the subject of the following:
    - To take their last dose the evening before (12 ± 2 hours) prior to the scheduled visit.
    - To bring their study medications with them to the clinic, to withhold all Asthma medications (including ICS) for at least 4 hours prior to 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 will be recorded as the time of administration of the second puff of study medication.
- 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 test day. Site personnel may request the subject to surrender all non-study asthma medications prior to start of the visit before performing any study procedures and return to subject at 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 (i.e., Treatment Day 15 procedures must be done between Treatment Day 13 and Treatment Day 17, inclusive).

- Similarly, every effort must be made to ensure that subjects return to the clinic on Day 29 (4 Weeks) following the initiation of each treatment arm. To accommodate scheduling conflicts a window of 28 ± 2 days from Treatment Day 1 is permitted (i.e., Treatment Day 29 procedures must be done between Treatment Day 27 and Treatment Day 31, inclusive).
- **Note:** If Visit 5, 8 or 11 occurs at Day 31 or later, the site must contact the Sponsor for guidance prior to initiating the next Treatment Period.

A Study Flow Diagram is displayed in Figure 1 below.

Figure 1. Study Flow Diagram:



Hx = Medical History, Rand = Randomization, PFT = Pulmonary Function Test, Rx = Treatment, Rev = Reversibility, TC = Telephone Call, TP = Treatment Period

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

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

1. Give their signed written informed consent to participate.
2. Are ≥ 18 – 65 years of age at Visit 1.
3. Have a diagnosis of mild to moderate persistent asthma, diagnosed at least 6 months prior to screening visit according to NHLBI EPR 3, (NHLBI, 2007) as follows:
   - Asthma symptoms >2 days per week
   - Nighttime awakenings 3–4 times per month or greater due to asthma symptoms
   - Use of short-acting beta agonist (SABA) for symptom control (not for prevention of exercise-induced bronchospasm) > 2 days per week
   - Minor or greater interference with normal activities
   - FEV_1 ≥ 60 – ≤ 85% predicted
4. Asthma Medication History: Must be currently receiving treatment with a low to medium dose of an ICS (as defined in Table 1) OR a combination of controller medications as defined in Table 2, containing a low (total daily) dose ICS (as defined in Table 1) for at least 4 weeks preceding screening.
5. Pulmonary Function: Must have a pre-albuterol (Ventolin HFA) FEV_1 of ≥ 60% and ≤ 85% of predicted normal value at Screening (Visit 1a or 1b) and Visits 2 and 3.
6. Reversibility: At Screening (Visits 1a or 1b) and at Visit 2, the subject must have an increase in FEV_1 of ≥ 12% and ≥ 200mL over the pre-albuterol (Ventolin HFA) FEV_1 within 30 – 60 minutes after the inhalation of 4 puffs of Ventolin HFA. Historical documentation of reversibility will not be permitted (See Section 7.1.1.1).
7. FEV_1 Baseline Stability Criteria: At Visit 3, 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 2 (See Section 7.1.1.2).
8. Asthma Symptom Criteria: Have required Ventolin HFA use on at least two of the last seven days and have an Asthma Control Questionnaire (ACQ) total score ≥ 1.5 prior to Randomization (Visit 3) (See Appendix 6).
9. A female is eligible to enter and participate in the study if she is of:
   - Non-child bearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal); or
   - Child bearing potential, has a negative serum pregnancy test at screening, and agrees to one of the following acceptable contraceptive methods used consistently and

correctly (i.e., in accordance with the approved product label and the instructions of the physician for the duration of the study from Screening until 14 days after Visit 14)

- Complete abstinence from intercourse from screening until 14 days after Visit 14 or
- Implants of levonorgestrel inserted for at least 1 month prior to the study drug administration but not beyond the third successive year following insertion; or
- Injectable progestogen administered for at least 1 month prior to study drug administration and administered for 1 month following study completion; or
- oral contraceptive (combined or progestogen only) administered for at least one monthly cycle prior to study drug administration; or
- Double barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository); or
- An intrauterine device (IUD), inserted by a qualified physician, with published data showing that the highest expected failure rate is less than 1% per year; or estrogenic vaginal ring; or
- percutaneous contraceptive patches.

10. Findings of clinical lab tests conducted at Screening must be acceptable to the Investigator.

5.2 Exclusion Criteria

The following subjects will be excluded from the trial:

1. Life-Threatening Asthma: A subject must not have life-threatening asthma. Life-threatening asthma is defined for this protocol 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 screening (Visit 1).
2. Worsening of Asthma: A subject must not have experienced a worsening of asthma which involved an emergency department visit, hospitalization or use of oral/parenteral corticosteroids within 6 weeks of Screening (Visit 1).
3. Intermittent, Seasonal, or Exercise-Induced Asthma Alone: Subjects with only intermittent, seasonal or exercise-induced asthma are excluded from participation in this study.
4. Concurrent Respiratory Disease: A subject must not have current evidence or diagnosis of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), or other respiratory abnormalities other than asthma.
5. Concurrent Conditions/Diseases: A subject with historical or current evidence of any clinically significant, co-morbid 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. Pregnant women or nursing mothers.
7. Chronic Obstructive Pulmonary Disease (COPD): A current diagnosis of COPD.
8. Smoking History: Current smokers or subjects with a $\geq$ 10 pack year history of cigarettes, cigars, or pipe smoking. E-cigarettes and inhaled marijuana should be treated as tobacco products.
9. Subjects who have had a respiratory tract infection within 6 weeks prior to Visit 1. 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. 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.
11. Subjects with documented myocardial infarction within a year from screening visit 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 three months of screening visit are to be excluded.
12. Clinically significant abnormal ECG: A clinically significant abnormal ECG is defined as (but not limited to) any of the following:
    - Clinically significant conduction abnormalities (e.g., left bundle branch block, Wolff-Parkinson-White syndrome or evidence of second degree (Mobitz Type II) or third degree atrioventricular (AV) block).
    - Clinically significant arrhythmias (e.g., atrial fibrillation, ventricular tachycardia)
    - A mean corrected QT interval using Fridericia's correction factor (QTcF) value at screening > 450 ms for males and > 470 ms for females or an ECG that is not suitable for QT measurements (e.g., poorly defined termination of the T wave).
    - 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

13. Uncontrolled Hypertension: Subjects who, in the opinion of the investigator, have clinically significant uncontrolled hypertension.
14. Subjects with abnormal liver function tests defined as aspartate aminotransferase (AST), alanine aminotransferace (ALT), alkaline phosphatase or total bilirubin ≥ 1.5 times upper limit of normal on repeat testing.
15. 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 have been adequately worked up, are clinically controlled and the subject's participation in the study would not represent a safety concern, are eligible
16. Drug Allergy: Subjects who have a history of hypersensitivity to any component of the MDI.
17. Substance Abuse: Subjects with a known or suspected history of alcohol or drug abuse within the last 2-year period prior to Screening.
18. Medication Prior to Spirometry: Subjects who are medically unable to withhold their short-acting bronchodilators for the 4-hour period required prior to spirometry testing at each study visit will be excluded.
19. Prohibited Asthma Medications: Subjects taking the following medications within the specified time intervals prior to Screening (Visit 1) are to be excluded:
    - 3 months: depot corticosteroids, intra-articular corticosteroids.
    - 6 weeks: parenteral and oral corticosteroids administered for an asthma exacerbation Note: Subjects requiring chronic maintenance therapy with oral corticosteroids are excluded from participation in this study.
    - Initiation or discontinuation of ICS within 30 days of Visit 1.
    - 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.
    - Subjects treated chronically with antibiotics are excluded from the study.
20. Taking other prohibited medications as defined in Table 3.
    - Anti-tumor necrosis factor α (TNFα) antibodies (e.g., infliximab and any other members of this class of drugs)
    - Antipsychotic drugs (phenothiazines)
    - Systemic calcineurin inhibitors
    - Systemic antifungal agents

- Protease inhibitors and cimetidine
- Immunosuppressants (Methotrexate, Cyclosporins, etc.)
- Any oral, inhaled or systemic corticosteroids
- Use of any LABA as single agent (as indicated in FDA mandated black box warning for LABAs)

21. Spirometry Performance:
    - Acceptability Criteria: Subjects who cannot perform acceptable spirometry ,i.e. meet ATS/ERS acceptability criteria
    - Repeatability Criteria: Subjects who cannot perform technically acceptable spirometry with at least three acceptable flow-volume curves with two or more meeting ATS repeatability criteria for FEV_1 during at least one of the pre-bronchodilator assessments at Visit 2 (-60 minute or -30 minute) and at the post-bronchodilator assessment at Visit 2
    - FEV_1 Baseline Stability: See Section 7.1.1.2
22. Non-compliance: Subjects unable to comply with study procedures, including non-compliance with eDiary completion [i.e. less than 70% subject completion of eDiary assessment in the last 7 days preceding Visit 3 (Randomization Visit)].
23. 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.
24. 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.
25. 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.
26. 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 the Screening Visit (Visit 1). Only subjects continuing to meet entry inclusion/exclusion criteria at Visit 3 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 case report form (CRF)

page. Any additions, deletions, or changes in the dose of these medications while in the study should be entered on the CRF.

Any current ongoing medications, including OTC drugs and herbal supplements, will be allowed provided they are not prohibited by the protocol (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 CRF page with indication, total daily dose, and dates of drug administration.

Asthma Medications:

The definition of the doses of ICS considered "low" and "medium" is provided below in Table 1**.**

Table 1. Estimated Equipotent Daily Doses of Inhaled Glucocorticosteroids*

Drug	Low Dose (µg)	Medium Daily Dose (µg)	High Daily Dose (µg)
Beclomethasone dipropionate - CFC	200 - 500	> 500 - 1000	> 1000 - 2000
Beclomethasone dipropionate - HFA	100 - 250	> 250 - 500	> 500 - 1000
Budesonide	200 - 400	> 400 - 800	> 800 - 1600
Ciclesonide	80 - 160	>160 - 320	> 320 - 1280
Flunisolide	500 - 1000	> 1000 - 2000	> 2000
Fluticasone propionate	100 - 250	> 250 - 500	> 500 - 1000
Mometasone furoate	200	> 400 - 800	> 800
Triamcinolone acetonide	400 - 1000	> 1000 - 2000	> 2000

*comparisons based on efficacy data
Source: GINA (2012)

Table 2 provides the list of asthma controller medications permitted (low to medium dose) and prohibited (high dose) in this study.

Table 2. Asthma Controller Medications

Low dose ICS + Leukotriene modifiers
Low dose ICS + Theophylline products
Low dose ICS + Inhaled anticholinergics or combination products (e.g. Atrovent or Combivent)
Low dose ICS + Long-acting inhaled anticholinergics (i.e. Spiriva)
Long acting beta agonists or combination products containing low to medium dose ICS and a long acting beta agonist: **Permitted**: Advair/Seretide DISKUS 100/50 µg and 250/50 µg BID, Advair HFA 90/42 µg (administered as two puffs of 45/21µg) BID, Advair HFA 230/42 µg (administered as two puffs of 115/21µg) BID, Symbicort 160/9 µg (administered as two puffs of 80/4.5 µg) BID, Dulera 200/10 µg (administered as two puffs of 100/5µg) BID.
Long acting beta agonists or combination products containing high dose ICS and a long acting beta agonist: **Prohibited:** Advair/Seretide DISKUS 500/50 µg, Advair HFA 460/42 µg (administered as two puffs of 230/21µg) BID; Symbicort 320/9 µg (administered as two puffs of 160/4.5 µg) BID; Dulera 400/10 µg (administered as two puffs of 200/5µg) BID and Breo Ellipta 100/25 µg (administered as one inhalation) QD.

Source: GINA (2012)

Prohibited Medications:

The use of the medications listed in Table 3 below is not permitted during this study, if initiated the subject needs to be discontinued immediately. If the subject had previously been prescribed any of the prohibited medications below and was recently discontinued, the minimum Washout Period prior to screening is provided:

Table 3. Prohibited Medications

Prohibited Medications	Minimum cessation period prior to Visit 1 (Screening)
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, amiodarone 3 months
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 (e.g.infliximab and any other members of this class of drugs)	30 days or 5 half-lives whichever is longer
Monoclonal antibodies	30 days or 5 half-lives whichever is longer
Antipsychotic drugs (phenothiazines)	30 days
Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors and cimetidine	30 days

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

Illicit drugs or drugs of abuse will not be allowed from the start of Screening (Visit 1) to the end of the trial (Visit 14), or to whenever the subject discontinues the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented.

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

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

abnormality. All subjects who prematurely discontinue the study after being randomized, regardless of the cause, should undergo the assessments outlined in Section 8.10 on the date 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 needs to 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 CKD-EPI formula or a clinically relevant change from baseline as determined by the investigator.
- Hepatic impairment defined as abnormal liver function test of AST, ALT or total bilirubin ≥1.5 times upper limit of normal on repeat testing.
- The principal investigator (PI) or designee will need to determine whether the subject is having an asthma exacerbation and will also make a determination as to the suitability of continuing the subject in the specific treatment period.
    a. If a subject requires use of rescue medication 4 or more times per day (i.e. 8 puffs of Ventolin HFA) for three or more consecutive days.
    b. If a subject meets the protocol-defined rescue criteria (Section 7.1.1.3) during the Treatment Period.
- If a subject does not meet protocol-defined FEV_1 baseline stability criteria (Section 7.1.1.2) 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, they should be discontinued from the study.

If a subject becomes pregnant during the course of the study, the subject will be discontinued.

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

6.1 Subject Information

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

Study personnel will have access to an 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 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 as summarized in **Table 4** below.

Table 4. Product Descriptions

Product Name & Dose	Dosage Form	Product Strength	Comments
Budesonide Inhalation Aerosol 320 µg ex-actuator	MDI	160 µg per actuation	Taken as 2 inhalations
Budesonide Inhalation Aerosol 160 µg ex-actuator	MDI	80 µg per actuation	Taken as 2 inhalations
Budesonide Inhalation Aerosol 80 µg ex-actuator	MDI	40 µg per actuation	Taken as 2 inhalations
Budesonide Inhalation Aerosol 40 µg ex-actuator	MDI	20 µg per actuation	Taken as 2 inhalations
Albuterol Sulfate Inhalation Aerosol[§] 90 µg	MDI	Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece	US source: (Ventolin® HFA) *Supplies are open-label*
Budesonide Inhalation Powder[†] 180 µg	DPI	Taken as one inhalation. Each inhalation contains 180 µg of budesonide corresponding to 160 µg delivered from the mouthpiece	US source: (Pulmicort Flexhaler®) *Supplies are open-label*
Placebo	MDI	Formulation does not contain active ingredient	Placebo Taken as 2 inhalations from the MDI
[§] Rescue medication and reversibility testing. [†] Asthma maintenance therapy during Screening and Washout Periods Note: All study drugs will be administered by oral inhalation.			
All placebos are created by Pearl Therapeutics in the image of the active test product. The 320, 160, 80, and 40 µg ex-actuator delivery of BD MDI are equivalent to 370.0, 185.0, 92.4, and 46.2 µg ex-valve of BD MDI, respectively.			

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

For open-label Pulmicort Flexhaler (budesonide inhalation powder 180 µg), commercial dry powder inhalers (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).

6.3 Primary Packaging and Labeling Information

Investigational materials will be packaged by Pearl Therapeutics as summarized in Table 5 below.

Table 5. Packaging of Clinical Supplies

Product Name and Potency	Product Strength	Label Claim	Dosing Instructions
BD MDI 320 µg ex-actuator	BD MDI 160 µg per inhalations	1 MDI 120 inhalations	Take 2 inhalations as directed in the morning and evening.
BD MDI 160 µg ex-actuator	BD MDI 80 µg per inhalations	1 MDI 120 inhalations	Take 2 inhalations as directed in the morning and evening.
BD MDI 80 µg ex-actuator	BD MDI 40 µg per inhalations	1 MDI 120 inhalations	Take 2 inhalations as directed in the morning and evening.
BD MDI 40 µg ex-actuator	BD MDI 20 µg per inhalations	1 MDI 120 inhalations	Take 2 inhalations as directed in the morning and evening
Placebo MDI		1 MDI 120 inhalations	Take 2 inhalations as directed in the morning and evening
Pulmicort Flexhaler (budesonide inhalation powder 180 µg) †	US source: (Pulmicort Flexhaler®) Each inhalation contains 180 µg *Supplies are open label*	1 DPI 120 inhalations	Use only as directed.
Albuterol Sulfate inhalation aerosol§ 90 µg ex-actuator	US source: (Ventolin HFA) Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	1 MDI 200 actuations	Use only as directed.

§ Rescue medication and reversibility testing.
† Asthma maintenance therapy during screening and Washout Periods

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

Open-label Supplies: Open-label PulmicortFlexhaler and Ventolin HFA will be provided as individually labeled DPIs and MDIs, respectively. Each inhaler will contain a single investigational labell. For Pulmicort Flexhaler, a two-part label will be affixed to the carton. Ventolin MDIs will be packaged in foil pouches. Foil pouches will receive a one-part label. The two-part label will be affixed to the carton holding the foil.

Both single and two-part labels will be printed with black ink and may include the text provided in Table 6.

Table 6. 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)

6.4 Secondary Packaging and Labeling Information (Box)

Investigational drug supplies will be packaged in boxes as outlined below in Table 7. Open label Ventolin HFA supplies will be provided in boxes as also outlined below. Box configuration is subject to change as a result of packaging constraints.

Table 7. Description of Boxes

Drug Supplies	Box Contents
Blinded	1 MDI
Ventolin HFA	1 MDI
Pulmicort Flexhaler	1DPI

Each box will be labeled with a double panel label printed with black ink and may include the following text (See Table 8).

Table 8. Description of Box Labelling

• 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)

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.

Ventolin HFA supplies: Open-label supplies should also be kept 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.

Pulmicort Flexhaler supplies: Store in a dry place at controlled room temperature 20–25°C (68-77°F) with the cover tightly in place. Keep out of the reach of children. Keep Pulmicort Flexhaler 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 or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained.

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

BD and Placebo MDIs

Individual BD 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 foil overwrap is labeled with a two-part label. Write the subject number and treatment visit number on each of the two-part labels. The 'tear-off' part of the label is to be placed onto the IWRS confirmation report.

All MDIs must be primed before the first use. Priming involves releasing a certain number of sprays (4) into the air before the first use of the inhaler. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that it's ready to use. Site personnel will prime the inhaler device prior to giving to the subject by gently

shaking the inhaler for 5-10 seconds and then spraying once into the air away from themself and others. After approximately 30 seconds, the process should be repeated three more times.

The MDI must be primed in a separate room from the subject treatment area. Since the MDI is primed in a separate room before dosing, there is a possibility that there may be a delay between priming and dosing, and therefore to ensure consistency in the administration for all subjects, the MDIs are to be gently shaken (5-10 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 twice daily, 2 puffs in the morning and 2 puffs in the evening approximately 12 hours apart, until the subject returns to the clinic. See Appendix 3 for instructions on the administration of BD and Placebo MDIs.

Pulmicort Flexhaler (budesonide inhalation powder 180 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 during screening and Washout Periods. See Appendix 4 for the manufacturer's instructions on the administration of Pulmicort Flexhaler

Ventolin HFA (albuterol sulfate inhalation aerosol)

Individual open-label Ventolin HFA DPIs 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 during Screening and Washout Periods. Ventolin HFA should be primed per manufacturer's instructions prior to dispensing to subject. See 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.

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 this 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 placed in a plastic bag (Ziploc or similar type bag) and labeled with the subject number. Used subject supplies will be kept at room temperature in a secure and locked cabinet until returned to Pearl Therapeutics or designee.

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

7 STUDY PROCEDURES

All assessments during Visits 3 through 14 should be conducted in the following order: vital signs, ECGs, clinical laboratory assessments, and spirometry.

7.1 Efficacy Assessments

7.1.1 Pulmonary Function Tests

Forced expiratory spirometry for derivation of FEV_1, FVC, PEFR, and $FEF_{25–75\%}$ will be assessed using a spirometer that meets or exceeds minimum performance recommendations of the American Thoracic Society/European "Respiratory Society (ATS/ERS) criteria (See Appendix 1).

At each visit, spirometry will be conducted 60 minutes and 30 minutes prior to Ventolin HFA, Pulmicort Flexhaler, or randomized study drug administration. The average of these two assessments will be used to calculate the baseline and pre-dose values for each parameter.

At Visits 3, 6, 9, and 12 (Day 1 of each treatment period) subjects must meet the Baseline Stability Criteria (see Section 7.1.1.2) prior to dosing in order to continue in the study.

Refer to Section 5.1 and Section 5.2 for specific spirometry inclusion/exclusion criteria that result in discontinuation from the study.

7.1.1.1 Characterization of Reversibility

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

Reversibility testing to Ventolin HFA:

- Perform pre-bronchodilator PFTs -60 min and -30 min prior to administration of Ventolin HFA (albuterol).
- 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 at 30 minutes, a repeat post-bronchodilator PFT may be performed at 60 minutes to assess reversibility.

Subjects who do not meet reversibility criteria at Visit 1a may, at the discretion of the investigator, be retested for reversibility at Visit 1b. Subjects who fail to meet reversibility criteria at Visit 1b will be screen failed. Subjects who do not meet reversibility criteria at Visit 2 following at least 14 days on Pulmicort Flexhaler will be screen failed.

7.1.1.2 FEV_1 Baseline Stability Criteria

The baseline stability criteria are as follows:

At Visit 3, 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 2 (See Section 5.1 for baseline FEV_1 stability inclusion criterion). At Visit 3, 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 two assessments meet the baseline stability requirements (i.e., within ± 20%), the initial 60 minute pre-dose assessment will not be used and the last two assessments will be used to establish the eligibility criteria. Subjects who do not meet the FEV_1 baseline stability criteria at Visit 3 must be screen failed.

At Visits 6, 9, and 12, 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 two assessments meet the baseline stability requirements (i.e., within ±20%), the initial 60 minute pre-dose assessment will not be used and the last two assessments will be used to establish the eligibility criteria.

Subjects must meet the FEV_1 baseline stability criteria to be eligible for dosing at Visits 6, 9 and 12. Subjects who do not meet the FEV_1 baseline stability criteria at Visits 6, 9 and 12 must be rescheduled as soon as is practical but within the protocol-specified washout window (14–21 days between Treatment Periods). Subjects who fail to meet stability criteria after 2 attempts within a Washout Period will be discontinued.

7.1.1.3 Rescue Criteria for Randomized Subjects

Rescue criteria will be evaluated on Visits 4, 7, 10, and 13 (Day 15 of each Treatment Period), and during any unscheduled visits occurring during any Treatment Period. Subjects meeting rescue criteria will be advanced to the Washout Period and given treatment with Pulmicort Flexhaler 180 µg BID.

The Rescue Criteria are met if the average of the -60 min and -30 min FEV_1 are > 30% below 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 > 30% below the average of Visit 3 baseline FEV_1, but if the -30 min assessment is within 30%, then another assessment may be conducted 30 minutes later (at the Investigator's discretion). If the last two assessments meet the rescue criteria requirements (i.e., within ± 30%), the initial 60 minute pre-dose assessment will not be used and the last two assessments will be used to establish the eligibility criteria.

In lieu of FEV_1 criteria, if a Rescue Period is required based on worsening of asthma symptoms (e.g. cough, wheeze, nighttime awakenings, increased SABA use, etc.), and in the opinion of the Investigator, the subject may to be transitioned to a Washout Period. The Investigator should make every effort to collect trough PFTs prior to transitioning the subject to a Washout Period.

If a subject is advanced to a Washout Period and that period is completed, subjects may continue in the study to the next Treatment Period provided the Baseline Stability Criteria are met (See Section 7.1.1.2).

If the Rescue Criteria are met during the fourth and final Treatment Period, then the procedures for discontinuation should be followed and the subject will be considered to have successfully completed the treatment portion of the study.

See Section 8.9 for instructions on handling subjects who meet Rescue Criteria.

7.1.1.4 Standardization of Spirometry Collections

All pulmonary function tests, including FEV_1, FVC, PEFR and $FEF_{25–75\%}$ 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 at the investigator meetings. All technicians will be required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable pulmonary function tests (ATS criteria, Miller, 2005) prior to performing testing on study 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 ([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 i.e., at <2 L/sec, 4–6 L/sec and >8 L/sec with temperature and barometric pressure correction. The calibration syringe must meet ATS specifications and must not be used beyond the expiry date. Required accuracy is ± 3%, i.e., 3.09 L to 2.91 L (ATS/ERS). The results will be printed and maintained in a calibration log, which will be monitored for compliance during the monitoring visits (See Appendix 2).

7.1.2 Subject eDiary Data Collection

Subjects will be provided with an electronic diary (eDiary) to be completed twice daily to record time of study medication administration and Pulmicort Flexhaler, morning and evening asthma symptoms, the use of study medication, Pulmicort Flexhaler and rescue albuterol (Ventolin HFA), and 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 electronic diary and training the subject on the eDiary use.

Subjects will be issued and trained on an eDiary use at Screening Visit (Visit 1a or 1b) and instructed to collect eDiary data during the Screening Period (between Visit 1 to Visit 3).

Site personnel will review the eDiary during the Screening Period to assess the subject's compliance and understanding of how to use the eDiary to maintain a daily record of their time of dosing for Pulmicort Flexhaler, rescue medication use, morning and evening asthma symptoms and collection of daily peak flow rates using a sponsor-provided portable peak flow meter.

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

At Visits 3, 6, 9, and 12 (Day 1 of each Treatment Period), subjects will receive an eDiary in which they will be asked to maintain daily eDiary records (AM and PM) until the end of the Treatment Period.

eDiary data will be collected during the Washout Periods (between Visits 5 and 6, Visits 8 and 9, and Visits 11 and 12).

Note: At all treatment visits (Visits 3 – 14), subjects will record pre-dose and 30 minutes post-dose home peak flow values and the time of study medication dosing in their eDiary while in the clinic.

At Visits 3, 4, 5, 7, 8, 10, 11, 13 and 14, site personnel must review eDiary data prior to dosing study medication in the clinic (See Table 10).

The eDiary data report will be available to site personnel through the vendor's server. The eDiary data report 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. The subject should be reinstructed, as appropriate, on the importance of recording twice daily entries if missing entries are observed. If the subject demonstrates persistent eDiary compliance issues the subject should be evaluated, at the Investigator's discretion, for further study continuation.

7.1.3 Rescue Ventolin HFA Use

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

7.1.4 Home Peak Expiratory Flow Rate

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

Subjects will be issued and trained on peak flow meter use at Screening Visit (Visit 1a or 1b) and instructed to collect peak flow meter data during the Screening Period (between Visit 1 to Visit 3).

At Visits 3, 6, 9, and 12 (Day 1 of each Treatment period), subjects will be given a peak flow meter and be asked to record peak flow readings in their eDiary until the end of the Treatment Period.

Peak flow meter data will be collected during the Washout Periods (between Visits 5 and 6, Visits 8 and 9, and Visits 11 and 12).

The peak flow meter will be used by all subjects for home measurements of pre- and post-dose morning and evening assessments. At each study visit, the Investigator will review the PEFR readings and any findings will be discussed with the subject and clinical relevance determined. Subjects will bring their peak flow meter to the clinic at each visit.

At each treatment visit (Visits 3 – 14) subjects will measure, in clinic, PEFR immediately before and 30 minutes after dosing with study medication and must record pre and post peak flow values and time of dosing in their eDiary.

Note: The in-clinic 30 minute post-dose PEFR at each treatment visit (Visits 3 – 14) should be obtained after spirometry assessments allowing enough time for the subject to recover from the pulmonary function test maneuvers. The subject will be instructed to forcefully exhale from total lung capacity 3 times into the peak flow meter and confirm the collection of PEFR measurements on the eDiary card. These PEFR measurements will be performed from Day 1 to Day 29 of each Treatment Period at home and on in-clinic days.

Subjects will perform PEFR measurements at home in the morning and in the evening immediately before and 30 minutes after dosing during the screening and Treatment Periods.

7.1.5 Medication Compliance

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

7.1.6 Asthma Control Questionnaire (ACQ)

The Asthma Control Questionnaire (Juniper, 1999) was developed and validated to measure asthma control in adults (See Appendix 6). It is 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). 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 Asthma Control Questionnaire (ACQ) (Juniper, 1999) was developed 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.

ACQ will be completed at Visits 3 through 14 before any other study procedures are performed.

Subjects who do not meet an ACQ minimum score of ≥ 1.5 at Visit 3 will be screen failed. (See Section 5.1)

7.2 Safety Assessments

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

7.2.1 Medical/Surgical History and Physical Examination

Medical history will be collected at Screening and updated during Visits 1a to Visits 3 (Screening Period). A complete physical examination will be performed at Visit 1a (Screening) and Visit 14 or Premature Discontinuation (Early Termination) Visit.

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 14. Height will be recorded at Visit 1a (Screening) only.

Perform a Chest X-ray or CT scan if one has not been performed on the subject within the last 6 months at Visit 1a.

7.2.2 Vital Sign Measurements

Heart rate, systolic and diastolic blood pressure (‘vital signs’) will be assessed at all visits, (including Premature Discontinuation Visit). Assessments will be obtained after being supine or seated for 5 – 10 minutes. If in the opinion of the investigator a clinically significant vital sign change occurs, then the measurement should be repeated at medically appropriate intervals until the value returns to within an acceptable range**.**

A single set of vital signs will be obtained at Visits 1a (Screening) and Premature Discontinuation Visit (See Section 8.10).

At Visit 3 to Visit 14, 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 at all visits and will not be repeated at subsequent time points unless clinically indicated (See Table 10).

Refer to Section 5.2 for specific vital signs exclusion criteria.

7.2.3 12-Lead Electrocardiogram (ECG)

An ECG will be obtained at Visits 1a (Screening) and the Premature Discontinuation Visit.

At Visits 3, 5, 6, 8, 9, 11, 12, 14 (Day 1 and Day 29 of each Treatment Period), an ECG recording will be obtained pre-dose within 1 hour of in-clinic dosing (See Table 10).

Refer to Section 5.2 for specific ECG exclusion criteria.

7.2.3.1 Standardization of ECG Data Collection

To standardize ECG 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 site phone training sessions. 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 ([redacted] Feedback on the quality of the ECGs will be provided to the investigational site via a site qualification form.

The ECG parameters that will be assessed include heart rate, RR interval, PR interval, QRS axis, QRS interval, and QT/QTcF (Fridericia's Formula) interval.

QT intervals and calculated QTcF (Fridericia's Formula) intervals will be reviewed and checked for gross inaccuracies by the investigator or designated ECG reviewer. If the calculated QTcF intervals are greater than 500 msec, and have increased by 60 msec or more over baseline value, the investigator will make a determination on the suitability of continuing the subject in the study. Refer to Section 5.2 for specific criteria for QTcF that prompt subjects to be excluded from the study. If QTcF interval prolongation exceeding the limits allowable for inclusion in the study occurs and is verified during treatment, the subject's medical background should be examined closely for risk factors that may have contributed to the event, including genotyping for hereditary long QT syndromes, if appropriate.

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.

7.2.4 Clinical Laboratory Tests

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

Clinical laboratory tests [hematology (Complete Blood Count) and chemistry (Comprehensive Metabolic Panel)] will be obtained at Visit 1a (Screening) and Premature Discontinuation Visit, and prior to dosing at Visits 3, 5, 8, 11, and 14 (See Table 10).

Serum pregnancy testing will be performed in women of child-bearing potential.at Visit 1a (Screening) Visit 14, and Premature Discontinuation Visit. Urine HCG testing will occur at Visits 3, 6, 9 and 12.

Refer to Section 5.2 for specific criteria for clinical chemistry exclusion criteria.

The following clinical laboratory parameters that will be assessed are noted in Table 9.

Table 9. Clinical Laboratory Measures

Hematology	
Hemoglobin	Mean corpuscular hemoglobin (MCH)
Hematocrit	Mean corpuscular hemoglobin concentration (MCHC)
White Blood Cell count with differential	Mean corpuscular volume (MCV)
Red Blood Cell count	
Platelet Count	

Clinical Blood Chemistry	
Liver Enzyme and Other Function Tests	**Other Clinical Blood Chemistry**
Alanine aminotransferase (ALT)	Albumin
Aspartate aminotransferase (AST)	Blood urea nitrogen (BUN)[a]
Alkaline phosphatase	Calcium[a]
Bilirubin, total	Chloride[a]
Gamma-glutamyl transferase	Cholesterol
	Bicarbonate
	Creatinine[a]
	Glucose[a]
	Magnesium
	Potassium[a]
	Phosphate
	Protein, total
	Sodium[a]
	Triglycerides

Other Tests:

Pregnancy test (women of child-bearing potential only): serum [human chorionic gonadotropin (HCG)] at Screening and Final Visit only and Urine HCG at appropriate visits for this study as detailed in Table 10.

Creatinine clearance will be estimated by the CKD-EPI published formula.

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

7.2.5 Adverse Events

7.2.5.1 Performing Adverse Events Assessments

The investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's case report form and on the AE Reporting Form. If the AE is "alarming", the investigator must report the AE immediately to Pearl Therapeutics. In addition, certain AEs (as described in Section7.2.5.2) are classified as "serious" and must be reported no later than 24 hours after the investigator recognizes/classifies the event as a serious adverse event to Pearl Therapeutics or its designee.

In the case of serious adverse events, after discussing the details of the AE, the investigator and the Medical Monitor may discontinue the subject from the study prematurely.

7.2.5.2 Adverse Event Definitions

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

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

Adverse events include, but are not limited to:

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

An AE does **not** include:

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

7.2.5.3 Pre-Randomization Adverse Events

Adverse events that occur between the time the subject signs the informed consent form 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 7.2.5.7.

7.2.5.4 Severity

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

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

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

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

7.2.5.5 Relationship

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

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

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

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

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

7.2.5.6 Clinical Laboratory Adverse Events

Many laboratory abnormalities observed during the course of a study will be included under a reported AE describing a clinical syndrome (e.g., elevated BUN and creatinine in the setting of an adverse event of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). In such cases, the laboratory abnormality itself (e.g., elevated creatinine in a setting of renal failure) does not need to be recorded as an AE. However, isolated laboratory abnormalities should be reported as AEs if they are considered to be clinically significant by the investigator.

Criteria for a "clinically significant" laboratory abnormality are:

- A laboratory abnormality that leads to a dose-limiting toxicity (e.g., an abnormality that results in study drug dose reduction, suspension or discontinuation)

- A laboratory abnormality that results in any therapeutic intervention (i.e., concomitant medication or therapy)

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

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

7.2.5.7 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 adverse event

- 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 patient or 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 adverse event 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.

7.2.5.8 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 a serious adverse event. At a minimum, a description of the event and the investigator's judgment of causality must be provided at the time of the initial report using the appropriate form (e.g., SAE Report Form). After the initial report, as necessary, the investigator must provide any additional information on a SAE to the Medical Monitor within two working days after he/she receives that information. This follow-up information will be a detailed written report that will include copies of hospital records, case reports, and autopsy reports, and other pertinent documents.

Post-study SAEs following the last dose of study drug must be reported to Pearl Therapeutics as described in Section7.2.5.10.

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

7.2.5.9 Supplemental Investigations of SAEs

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

7.2.5.10 Post-Study Follow-Up of Adverse Events

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

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

7.2.5.11 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 following the last dose of study drug, it must be reported to Pearl Therapeutics, whether or not the event is attributable to study drug. All SAEs must be reported to Pearl Therapeutics no later than 24 hours after the investigator recognizes/classifies the event as a serious adverse event.

7.2.5.12 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 informed consent form or other measures based on its review of an SAE report.

7.2.5.13 Health Authority Safety Reports

Pearl Therapeutics or its representatives will submit a safety report to the FDA and/or any other appropriate regulatory agencies, for any 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.

7.2.6 AEs of Interest

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 PEFR of $\geq$30% from the pre-dose value, with associated asthma symptoms of wheezing, shortness of breath and/or cough. All AEs and SAEs will be recorded as appropriate.

7.2.7 Overdose

An overdose is defined as a dose greater than the high 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, adverse events, and other significant data pertaining to the study drug(s) being used in this study.

7.2.8 Pregnancy

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

7.3 Termination of the Study

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

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

8 STUDY ACTIVITIES

Detailed schedules for pre- and post-dose procedures to be performed on each study visit are provided. A time and events schedule is provided below in Table 10.

Table 10. Schedule of Events

Procedures	Screening[a]			Treatment Period 1[a]			Treatment Period 2[a]			Treatment Period 3[a]			Treatment Period 4[a]			Telephone Follow-Up
	Visit 1a	Visit 1b (as needed)	Visit 2	Visit 3 Rand. TP 1 Day 1	Visit 4 TP 1 Day 15	Visit 5 TP1 Day 29	Visit 6 TP 2 Day 1	Visit 7 TP 2 Day 15	Visit 8 TP 2 Day 29	Visit 9 TP 3 Day 1	Visit 10 TP 3 Day 15	Visit 11 TP 3 Day 29	Visit 12 TP 4 Day 1	Visit 13 TP 4 Day 15	Visit 14 TP 4 Day 29 Or Final Visit[q]	Telephone Follow-up
Treatment Day[a]	**Up to -28**	**Up to -27**	**-14 to -1**	**1[a]**	**15±2[a]**	**29±2[a]**	**1[a]**	**15±2[a]**	**29±2[a]**	**1[a]**	**15±2[a]**	**29±2[a]**	**1[a]**	**15±2[a]**	**29±2[a]**	**7-14[a]**
Informed Consent	X															
Eligibility Criteria	X	X	X	X												
Verify Cont. Eligibility					X	X	X	X	X	X	X	X	X	X	X	
Ventolin HFA Reversibility[b]	X	X	X													
Demographics, Medical, Surgical History	X	X	X	X												
Switch to Pulmicort Flexhaler 180 µg BID[c]	X					X			X			X				
ACQ[d]				X	X	X	X	X	X	X	X	X	X	X	X	
Prior/Concomitant Medications[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Spirometry[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination[g]	X														X	
Vital Signs[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[i]	X			X		X	X		X	X		X	X		X	
Pregnancy Test[j]	X			X			X			X			X		X	
Clinical Laboratory Testing[k]	X			X		X			X			X			X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inhalation Device Training[l]	X			X			X			X			X			
Study Drug Administration[l]				X	X	X	X	X	X	X	X	X	X	X	X	

Procedures	Screening[a]			Treatment Period 1[a]			Treatment Period 2[a]			Treatment Period 3[a]			Treatment Period 4[a]			Telephone Follow-Up
	Visit 1a	Visit 1b (as needed)	Visit 2	Visit 3 Rand. TP 1 Day 1	Visit 4 TP 1 Day 15	Visit 5 TP1 Day 29	Visit 6 TP 2 Day 1	Visit 7 TP 2 Day 15	Visit 8 TP 2 Day 29	Visit 9 TP 3 Day 1	Visit 10 TP 3 Day 15	Visit 11 TP 3 Day 29	Visit 12 TP 4 Day 1	Visit 13 TP 4 Day 15	Visit 14 TP 4 Day 29 Or Final Visit[q]	Telephone Follow-up
Treatment Day[a]	**Up to -28**	**Up to -27**	**-14 to -1**	**1[a]**	**15±2[a]**	**29±2[a]**	**1[a]**	**15±2[a]**	**29±2[a]**	**1[a]**	**15±2[a]**	**29±2[a]**	**1[a]**	**15±2[a]**	**29±2[a]**	**7-14[a]**
Dispense Peak Flow Meter[m]	X	X														
Dispense Subject Diary[m]	X	X														
Collect PEFR in Clinic[n]				X	X	X	X	X	X	X	X	X	X	X	X	
Review Subject Diary[m]			X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Dispensing/ Collection	X			X	X	X	X	X	X	X	X	X	X	X	X	
Paradoxical Bronchospasm[o]				X	X	X	X	X	X	X	X	X	X	X	X	
Return to Maintenance Asthma Medications[p]															X	

ACQ=asthma control questionnaire; BID=twice-daily; ECG=electrocardiogram; PEFR= peak expiratory flow rate; TP=Treatment Period

a. Visit windows during each Treatment Period are relative to Day 1 of that Treatment Period. Washout Periods occur between Visits 5 and 6, Visits 8 and 9, and Visits 11 and 12 are 14-21 days. If Visit 5, 8 or 11 occurs at Day 31 or later, the site must contact sponsor for guidance prior to initiating next treatment period. Visit 1b must occur before Visit 2.
b. See instructions for reversibility assessment in Section 7.1.1.1.
c. At Screening, stop prohibited asthma medications and change asthma medications as specified in Section 5.4 (i.e., Sponsor-provided Pulmicort Flexhaler and Ventolin HFA).
d. See instructions for administering the ACQ in Section 7.1.6 and Appendix 6.
e. See listing of prohibited and concomitant medication in Section 5.4. At all visits beyond Screening, note time of last dose of short-acting bronchodilator and other asthma medications (if <4 hours, visit should be rescheduled).
f. See Section 7.1.1 for guidance related to Spirometry assessments and criteria.
g. Weight, assessed in ordinary indoor clothing with shoes removed at Visit 1a (Screening) and Visit 14. Height will be recorded at Visit 1a (Screening) only. (See Section 7.2.1).
h. See Section 7.2.2 for guidance on vital signs collection.
i. See Section 7.2.3 for guidance on ECG assessment.
j. See Section 7.2.4 for guidance on the administration of pregnancy test (women of child- bearing potential only).
k. See Section 7.2.4 for guidance on clinical laboratory testing.
l. At the start of each treatment visit, subject must withhold all asthma medications, including study medication and rescue medications (Ventolin HFA) for at least 4 hours prior to start of test day procedures. If appropriate, re-train subject on use of inhalation device.
m. See Section 7.1.2 for guidance on the eDiary use, and Section 7.1.4 for guidance on peak flow meter use.
n. See Section 7.1.4 for further information on the collection of PEFR.

Procedures	Screening[a]			Treatment Period 1[a]			Treatment Period 2[a]			Treatment Period 3[a]			Treatment Period 4[a]			Telephone Follow-Up
	Visit 1a	Visit 1b (as needed)	Visit 2	Visit 3 Rand. TP 1 Day 1	Visit 4 TP 1 Day 15	Visit 5 TP1 Day 29	Visit 6 TP 2 Day 1	Visit 7 TP 2 Day 15	Visit 8 TP 2 Day 29	Visit 9 TP 3 Day 1	Visit 10 TP 3 Day 15	Visit 11 TP 3 Day 29	Visit 12 TP 4 Day 1	Visit 13 TP 4 Day 15	Visit 14 TP 4 Day 29 Or Final Visit[q]	Telephone Follow-up
Treatment Day[a]	Up to -28	Up to -27	-14 to -1	1[a]	15±2 [a]	29±2 [a]	1[a]	15±2 [a]	29±2 [a]	1[a]	15±2 [a]	29±2 [a]	1[a]	15±2 [a]	29±2 [a]	7-14 [a]

o. See Section 7.2.6 for definition of paradoxical bronchospasm.

p. At the end of the Visit 14, return subject to pre-study or other appropriate inhaled maintenance asthma medications.

q. If a subject discontinues the study prematurely (early termination) the procedures that should be completed at the Final Visit are described in Section 8.10.

8.1 Screening Visit (Visits 1a, 1b)

- Obtain informed consent.
- Register subject in IWRS to obtain subject screening number.
- Obtain demographic data, including age, race, smoking history, medical/surgical history, and asthma medication history.
- Verify that subject meets inclusion/exclusion criteria.
- Obtain medication history, including asthma medications.
- Conduct a serum pregnancy test for all female subjects unless it is documented in the medical history that the subject has been irreversibly surgically sterilized (hysterectomy, oophorectomy or bilateral tubal ligation) or they are at least 2 years post-menopausal.
- Conduct a complete physical examination (general appearance, skin, head, eyes, ears, nose, throat, neck [including thyroid], lymph nodes, chest, heart, abdomen, extremities, and nervous system).
- Obtain height, weight, and vital signs (heart rate and blood pressure after being supine or seated for 5 – 10 minutes, and oral or tympanic 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 7.1.1.1).
    - Confirm subject's ability to use MDI correctly (provide coaching as needed).
    - Repeat spirometry assessments 30 minutes following 4 puffs Ventolin HFA
    - Confirm subject is reversible (See Section 5.1 for Reversibility Criteria)
- Obtain clinical laboratory samples (hematology and chemistry).
- Complete Chest X-ray or CT scan if not performed within the last 6 months.
- Schedule next visit:
    - Visit 1b at Investigator discretion for subjects who fail reversibility criteria at Visit 1a (at least 1 day prior to Visit 2).

- Visit 2 for subjects who meet eligibility criteria to continue, at least 14 days but no more than 27 days from Visit 1a.

- Stop prohibited asthma medications and change concurrent asthma medications as specified in the protocol (See Section 5.4).

- Subjects who meet entry criteria will have their inhaled asthma medication switched to Pulmicort Flexhaler 180 µg BID and Ventolin HFA for rescue medication.

- 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 the subject signs the informed consent form for the study and the time when that subject is randomized will be summarized as medical history and not as a study adverse event unless the event meets the definition of an SAE (See Section7.2.5.7).

8.2 Visit 1b (At Investigator Discretion)

- Assess continued eligibility criteria

- Record concomitant medications

- Repeat spirometry assessment and reversibility to Ventolin HFA (See Section 5.1 and Section 7.1.1.1).

- Record any AEs that have occurred

- Schedule Visit 2 for subjects who meet eligibility criteria to continue, at least 14 days but no more than 27 days from Visit 1a.

8.3 Visit 2 (Reversibility Testing Following Pulmicort Flexhaler Run-in)

- Review subject eDiary and retrain subject if subject has not met eDiary compliance requirement (See Section 5.2).

- Determine time of last SABA use (if < 4 hours, Visit 2 should be delayed or rescheduled).

- Review inclusion/exclusion criteria and confirm subject eligibility to continue.

- If not previously reviewed, review clinical laboratory testing results from Visit 1a and record any clinically significant findings.

- Record adverse events, if any.

- Review all prior medications and adherence to asthma regimen,

- Obtain pre-bronchodilator vital signs.
- Perform reversibility testing to Ventolin HFA (See Section 5.1 and Section 7.1.1.1).
- Schedule Visit 3 (Randomization Visit) for subjects who meet eligibility criteria to continue. Note: Visit 3 can be scheduled at minimum, 1 day after Visit 2, and no later than 28 days after Visit 1a (Screening).

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

- Review subject eDiary and peak flow values. Screen fail subject if subject has not met eDiary compliance requirement (See Section 5.2).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the CRF (if <4 hours, Visit 3 must be rescheduled).
- Assess ACQ (See Appendix 6)
- Record adverse events (if any).
- Review concomitant medications to ensure adherence to study specified regimen.
- Collect sponsor-provided Pulmicort Flexhaler and Ventolin HFA dispensed during the Screening Period.
- Complete all pre-dose assessments, including vital signs, ECGs, clinical laboratory testing, urine pregnancy testing and spirometry.
- Review inclusion/exclusion criteria, including baseline stability criteria (See Section 7.1.1.2) and confirm subject eligibility for Randomization
- Re-dispense subject eDiary and peak flow meter prior to dosing for subject recording of in-clinic PEFR and dosing time.
- Have subject perform and record pre-dose PEFR.
- Obtain subject randomization number and 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 15–30 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 first dose of newly assigned study drug at the clinic.
    - The subject is to be considered randomized as soon as the site personnel have received the subject treatment assignment from the IWRS.
- Have subject record dosing time in the eDiary.
- Have subject collect and record PEFR in eDiary at 30 minutes post-dosing.
- Perform vital signs at 30 minutes post-dosing and assess subject for paradoxical bronchospasm.
- Subjects will be instructed to bring the eDiary, peak flow meter and all study medication to the next visit.
- Schedule Visit 4 within 14 ± 2days, and ensure subject has adequate supply of study drug and rescue Ventolin HFA.

8.5 Visits 6, 9, 12 (Day 1 of Treatment Periods 2, 3 and 4)

- Review subject eDiary and peak flow values, and retrain subject if subject has not met eDiary compliance requirement (See Section 5.2).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the CRF (if <4 hours, the visit must be rescheduled).
- Assess ACQ.
- Record adverse events (if any).
- Review concomitant medications to ensure adherence to study specified regimen.
- Collect sponsor-provided Pulmicort Flexhaler and Ventolin HFA dispensed for use during the Washout Period.
- Complete all pre-dose assessments, including vital signs, ECGs, urine pregnancy testing, spirometry (60 and 30 minutes prior to dosing).
- Confirm subject eligibility to continue, including baseline stability criteria (See Section 7.1.1.2).
- Have subject perform and record pre-dose PEFR.
- 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 15–30 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 first dose of newly assigned study drug at the clinic.
- Have subject record dosing time in the eDiary.
- Have subject collect and record PEFR in eDiary at 30 minutes post-dosing.
- Perform vital signs at 30 minutes post-dosing and assess subject for paradoxical bronchospasm.
- Subjects will be instructed to bring the eDiary, peak flow meter and all study medication to the next visit.
- 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.

8.6 Visit 4, 7, 10 and 13 (Day 15 of Treatment Periods 1, 2, 3 and 4)

- Review subject eDiary and peak flow values, and retrain subject if subject has not met eDiary compliance requirement (See Section 5.2).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the CRF (if <4 hours, the visit must be rescheduled).
- Assess ACQ.
- Record adverse events (if any).
- Review concomitant medications to ensure adherence to study specified regimen.
- Collect blinded study drug dispensed during the prior visit (Day 1 of the Treatment Period).
- Complete all pre-dose assessments, including vital signs and spirometry (60 and 30 minutes prior to dosing).
- Review subject eligibility to continue.
- Have subject perform and record pre-dose PEFR.

- To allow for proper preparation of study drug, it is recommended that the seal around the treatment box is opened 15–30 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 first dose of newly assigned study drug at the clinic.
- Have subject record dosing time in the eDiary.
- Have subject collect and record PEFR in eDiary at 30 minutes post-dosing.
- Perform vital signs at 30 minutes post-dosing and assess subject for paradoxical bronchospasm.
- Obtain new MDI and assignment information from IWRS.
- Subjects will be instructed to bring the eDiary, peak flow meter and all study medication to the next visit.
- Schedule the next visit (Day 29 of the Treatment Period) within 29 ± 2 days from Day 1 of the Treatment Period, and ensure subject has adequate supply of study drug and rescue Ventolin HFA.

8.7 Visit 5, 8 and 11 (Day 29 of Treatment Period 1, 2 and 3)

- Review subject eDiary and peak flow values, and retrain subject if subject has not met eDiary compliance requirement (See Section 5.2).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the CRF (if <4 hours, the visit must be rescheduled).
- Assess ACQ.
- Record adverse events (if any).
- Review concomitant medications to ensure adherence to study specified regimen.
- Collect sponsor-provided study medication including Ventolin HFA dispensed during the prior visit (Day 15 of the Treatment Period).
- Complete all pre-dose assessments, including vital signs, ECGs, clinical laboratory testing, and spirometry (60 and 30 minutes prior to dosing).
- Review subject eligibility to continue.

- Have subject perform and record pre-dose PEFR.
- Subject will administer in-clinic dosing from MDI dispensed at previous visit (Day 15 of Treatment Period).
- Have subject record dosing time in the eDiary.
- Have subject collect and record PEFR in eDiary at 30 minutes post-dosing.
- Perform vital signs at 30 minutes post-dosing and assess subject for paradoxical bronchospasm (See Section 7.2.6).
- Obtain from IWRS the Pulmicort Flexhaler 180 µg and Ventolin HFA assignment for use during the Washout Period. Subjects will be instructed to bring the Pulmicort Flexhaler and Ventolin HFA to the next visit, and continue to complete their PEFRs and their eDiary at home during the Washout Period.
- Schedule the next visit (Day 1 of the Treatment Period) within 14–21 days from Day 29 of the previous Treatment Period.

8.8 Visit 14 (Final Study Visit, Day 29 of Treatment Period 4)

- Review subject eDiary and peak flow values (See Section 5.2).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the CRF (if <4 hours, the visit must be rescheduled).
- Assess ACQ.
- Record adverse events (if any).
- Review concomitant medications to ensure adherence to study specified regimen.
- Collect sponsor-provided study medication including Ventolin HFA dispensed during the prior visit (Day 15 of Treatment Period 4).
- Complete all pre-dose assessments, including vital signs (including weight), physical examination, ECGs, clinical laboratory testing, serum pregnancy testing, and spirometry (60 and 30 minutes prior to dosing).
- Review subject eligibility to continue.
- Have subject perform and record pre-dose PEFR.

- Subject will administer in-clinic dosing from MDI dispensed at previous visit (Day 15 of Treatment Period).
- Have subject record dosing time in the eDiary.
- Have subject collect and record PEFR in eDiary at 30 minutes post-dosing.
- Perform vital signs at 30 minutes post-dosing and assess subject for paradoxical bronchospasm (See Section 7.2.6).
- Collect subject eDiary and peak flow meter.
- Return the subject to pre-study or appropriate asthma maintenance medication.
- Schedule a follow-up telephone call 7–14 days from Visit 14.

8.9 Management of Randomized Subjects Who Meet Rescue Criteria

- If rescue criteria are met at a scheduled visit during Treatment Periods 1, 2 and 3 (See Section 7.1.1.3), the Investigator at their discretion, may complete the remaining scheduled visit procedures (i.e. clinical laboratory testing, vital signs, etc.) and transition the subject to rescue period as follows:
  - Obtain from IWRS the Pulmicort Flexhaler 180 µg and Ventolin HFA assignment for use during the Rescue Period. Subjects will be instructed to bring the Pulmicort Flexhaler and Ventolin HFA to the next visit, and continue to complete their PEFRs and their eDiary at home during the Washout Period.
  - Schedule the next visit (Day 1 of the next Treatment Period) within 14–21 days from the day the Washout Period was initiated.
  - After the Washout Period, subjects may continue in the study to the next Treatment Period provided the Baseline Stability Criteria are met (See Section 7.1.1.2).
- Except during Treatment Period 4, if an unscheduled visit is required to manage worsening of asthma symptoms, and in the opinion of the Investigator, the subject may be transitioned to the Washout Period, the procedures outlined in Section 8.8 (Day 29) may be conducted at the Investigator's discretion during the unscheduled visit, prior to Washout Period transition described below.
  - Obtain from IWRS the Pulmicort Flexhaler 180 µg and Ventolin HFA assignment for use during the Rescue Period. Subjects will be instructed to bring the Pulmicort Flexhaler and Ventolin HFA to the next visit, and continue to complete their PEFRs and their eDiary at home during the Washout Period.

- Schedule the next visit (Day 1 of the next Treatment Period) within 14–21 days from day the Washout Period was initiated.

- After the Washout Period, subjects may continue in the study to the next Treatment Period provided the Baseline Stability Criteria are met (See Section 7.1.1.2).

- If the Rescue is required during the fourth and final Treatment Period, then the procedures for discontinuation should be followed and the subject will be considered to have successfully completed the treatment portion of the study.

8.10 Unscheduled Visits/Premature Discontinuation (Early Termination) Visits

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

Premature discontinuations visits will be captured as unscheduled visits. The following minimum procedures should be completed at the premature discontinuation visit:

- Review eDiary data and peak flow values.
- Record adverse events (if any).
- Review concomitant medications
- Conduct a physical examination, including vital signs.
- Perform ECG and collect blood samples for hematology and chemistry.
- Collect a blood sample for pregnancy test for women of child bearing potential.
- 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 subject discontinuation reason.
- Schedule a follow-up telephone call 7-14 days post last study drug dosing. If the discontinuation visit is performed > 7 days post last study drug dosing a follow-up telephone call will not be required.

8.11 Follow-Up Telephone Call

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

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

8.12 Completion of the Study

The investigator will document the completion or the reason for early withdrawal by a subject 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 (e.g., 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 did 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 4-period, 5-treatment, incomplete block cross-over design evaluating the following 5 treatments in approximately 150 subjects:

- BD MDI 320 µg
- BD MDI 160 µg
- BD MDI 80 µg
- BD MDI 40 µg
- Placebo MDI

The primary objective of this study will be to demonstrate a lung function benefit of BD MDI BID compared with Placebo MDI in adult subjects with mild to moderate persistent asthma.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

Baseline will use the average of the -60 and -30 min pre-dose values on Day 1 of each treatment period for clinical measured variables and is defined as the average of the non-missing Day 1 pre-dose means (averages of 60 and 30 minute pre-dose assessments) for each subject. For diary-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

- Change from baseline in morning pre-dose trough FEV_1 at the end of the Treatment Period

9.2.1.2 Secondary Efficacy Endpoints

- Change from baseline in mean morning pre-dose and mean evening pre-dose peak flow rate (PEFR) readings taken by the subject and recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in Asthma Control Questionnaire (ACQ) score at the end of the Treatment Period

9.2.1.3 Other Efficacy Endpoints

- Change from baseline in morning pre-dose trough FEV_1 over the Treatment Period and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in mean morning and evening pre- and post-dose daily PEFR readings taken by subjects and recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Percentage of days without rescue Ventolin HFA use over each week of the Treatment Period and over the entire Treatment Period
- Change from baseline in pre-dose trough forced vital capacity (FVC) at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough PEFR at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough forced expiratory flow 25-75% ($FEF_{25-75\%}$) at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in the number of nighttime awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period, over each week of the Treatment Period, and over the entire Treatment Period
- Percentage of nights with awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period and over the entire Treatment Period

9.2.2 Safety Endpoints

The safety assessments include ECGs, vital sign measurements, clinical laboratory tests, monitoring for paradoxical bronchospasm, physical examination findings, AEs and SAEs during the study period.

9.3 Analysis

9.3.1 Primary Efficacy Analysis

The primary efficacy analysis will compare the changes from baseline at the end of the treatment periods in morning pre-dose trough FEV_1 between BD MDI treatments and Placebo MDI using a repeated measures model with an unstructured model for the correlation across periods within subject. The model will include baseline FEV_1, response to albuterol, and period as covariates. Sequence will also be included if it explains significant variability ($p<0.10$). Estimated treatment differences and 95% CI's will be provided for all treatment comparisons. Multiplicity will be controlled for the BD MDI to Placebo MDI comparison using a sequential approach (See Section 9.5). A two-sided alpha level of 0.05

will be employed. In the event that the unstructured correlation model fails to converge, an Autoregressive Order 1 [AR(1)] model will be used and subject will be added to the model as a random effect.

The primary analysis will use be the modified Intent-to-Treat (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 9.7).

9.3.2 Secondary Efficacy Analysis

The secondary endpoints will be analyzed using a similar model as the primary endpoint. Repeated measures models with an unstructured model for the correlation across periods within subject will be fit. The model will include the relevant baseline and period as covariates. Sequence will also be included if it explains significant variability ($p<0.10$).

Analyses of morning and evening PEFR and rescue Ventolin HFA usage will use the average of the non-missing 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.

9.3.3 Other Efficacy Analysis

The other efficacy endpoints will be analyzed using a similar model as the primary endpoint. Repeated measures models with an unstructured model for the correlation with subject both across periods and within periods where appropriate will be fit. The model will include the relevant baseline and period as covariates. Sequence will not be included unless it was found to be important and included in the model for the primary endpoint. For analyses that use more than one measure per period, scheduled Treatment Day or Treatment Week will be added to the model as categorical covariates and their interaction with treatment will be included as well.

Additional comparisons will be made for pre-dose trough FEV_1 values between the Day 15 values and the values at the end of the baseline and Washout Periods in order to compare the efficacy of BD MDI to Pulmicort Flexhaler 180 µg. In order to perform these comparisons, a separate model will be fit where the baseline defined previously in Section 9.2.1 will be considered to represent the effect of Pulmicort. These data will be treated as coming from period 0. The model will therefore not include baseline or period since these would be confounded with Pulmicort treatment.

9.3.4 Safety Analysis

9.3.4.1 Adverse Events

Adverse events during each treatment regime will be summarized by the number of subjects experiencing an event. They will be tabulated at the level of the MedDRA preferred term, and the MedDRA System Organ Class. The version of MedDRA current at the time the first subject is randomized will be used throughout the study. Tabulations will be broken down by

severity, seriousness, AE's leading to discontinuation, and by relationship to study drug. No hypothesis tests will be performed. Since the washout period includes treatment with Pulmicort Flexhaler, 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.

9.3.4.2 Paradoxical Bronchospasm

Paradoxical Bronchospasm will be considered an adverse event of special interest, and will be tabulated separately. Bronchospasm will be summarized by the number of subjects experiencing the event, during scheduled assessment periods on a test day and during the particular treatment period. We note that tabulations for bronchospasms differ from those for general adverse events, since the tabulation involves tabulating the incidence of paradoxical bronchospasm with onset during a treatment period. Bronchospasm with onset outside a treatment period will be listed separately. No hypothesis tests will be performed, but an appropriate confidence interval may be provided.

9.3.4.3 Clinical Laboratory Measurements

Summary statistics (mean, median, standard deviation and range) of change from baseline for scheduled pre-dose assessments will be tabulated for each laboratory parameter and treatment. 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.

9.3.4.4 Vital Signs

Summary statistics (mean, median, standard deviation and range) of change from baseline will be tabulated by vital sign parameter and treatment 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.

9.3.4.5 ECGs

Summary statistics (mean, median, standard deviation and range) for absolute values and change from baseline will be tabulated by ECG parameter and treatment 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.

9.4 Randomization

Subjects will be randomly assigned to a treatment sequence using an IWRS. Each sequence will include exactly 4 of the 5 treatment groups included in this study. All subjects will receive BD MDI 320, 160 μg and Placebo MDI in a randomized manner, but only half will receive 40 or 80 μg.

The 8 treatment sequences are shown below where A is Placebo MDI, B is BD MDI 320 µg, C is BD MDI 160 µg, D is BD MDI 80 µg, and E is BD MDI 40 µg:

ABCD
ABCE
BDAC
BEAC
CADB
CAEB
DCBA
ECBA

Randomization will be centralized and center will not be used as a stratification factor.

9.5 Experimental Design and Type I Error Control

The experimental design was chosen to be balanced with respect to period and first order carry-over should all subjects complete. The design was selected to limit exposure to 12 weeks of BD MDI treatment at any dose and to focus on the higher doses.

Type I error will be controlled for the primary endpoint by following a sequential approach. First BD MDI 320 µg will be compared to Placebo MDI using a two-sided alpha of 0.05. If the p-value is <0.05 for the comparison of BD MDI 320 µg to Placebo MDI, then the comparison of BD MDI 160 µg to Placebo MDI will be interpreted inferentially using a two-sided alpha=0.05. If the p-value is <0.05 for the comparison of BD MDI 160 µg to Placebo MDI, then the comparison of BD MDI 80 µg to Placebo MDI will be interpreted inferentially using a two-sided alpha of 0.05. Finally, if the p-value is <0.05 for the comparison of BD MDI 80 µg to Placebo MDI, then the comparison of BD MDI 40 µg to Placebo MDI will be interpreted inferentially using a two-sided alpha of 0.05.

Other than the specification of secondary endpoints, no further adjustments for Type I error will be made.

9.6 Sample Size Consideration

Power calculations are based on the properties of the primary endpoint, morning pre-dose trough $FEV_{1,}$ on the last day of each treatment period (end of treatment). An estimate of the total SD of 405mL is taken from a 12-week trial comparing budesonide to ciclesonide (Boulet 2006). Assuming that half of the variability comes from within subject and half between (i.e. intrasubject correlation=0.5), an estimate of the within subject standard deviation of 285mL for morning pre-dose trough FEV_1 is obtained. Using this SD and assuming that 150 randomized provides approximately 120 completers, the power to demonstrate a 120mL difference from Placebo MDI for BD MDI 320 µg or BD MDI 160 µg is approximately 90%. For BD MDI 80 µg and BD MDI 40 µg, the power to demonstrate a difference from Placebo MDI of 140 mL is approximately 80%.

9.7 Data Validation and Transformation

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

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

9.8 Analysis Plan

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

9.9 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 ITT Population including subjects who received treatment and have post-treatment efficacy data from at least two treatment periods. Data judged to be impacted by major protocol deviations will be determined prior to unblinding and excluded. 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 one 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.

9.10 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] (Version 9.2 or higher). 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 (IRB) or Independent Ethics Committee (IEC) 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 (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR parts 50, 54, 56, and 312).

Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects) [http://www.wma.net/en/10home/index.html].

Any additional regulatory requirements.

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

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

10.3 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 (i.e. Health Insurance Portability and Accountability Act), rules and regulations.

10.6 Quality Control and Assurance

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

10.7 Data Management

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

10.8 Study Monitoring

In accordance with applicable regulations, GCP, and Pearl Therapeutics procedures, clinical monitors will contact the site prior to 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 principal investigator or sub-investigators named on the Form FDA 1572 will need to complete a financial disclosure form prior to study initiation, at any time during the study execution if new information needs to be disclosed, and for 1 year after study completion. Investigators should make the IRB/IEC aware of any financial interests that the investigator has in the investigational product.

10.11 Investigator's Final Report

Shortly after completion of the investigator's participation in the study, the investigator will submit a written report to Pearl 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 principal investigator is responsible for the accuracy and completeness of all data from their site. Pearl Therapeutics (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.
2. **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 nonclinical 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, e.g., protocol and amendments, data tabulations, *etc*. The journal and reviewers will need to make arrangements to maintain the confidentiality of such supplemental information, where relevant, and 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. **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.

11 REFERENCE LIST

Akinbami L. United States Centers for Disease Control. Asthma Prevalence, Health Care Use and Mortality: United States 2003-2005. http://www.cdc.gov/nchs/products/pubs/pubd/hestats/ashtma03-05/asthma03-05.htm.

Clissold SP, Heel RC. Budesonide. A preliminary review of its pharmacodynamic properties and therapeutic efficacy in asthma and rhinitis. *Drugs.* 1984;28(6):485-518.

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Updated 2012. http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf

Hochaus G. New developments in corticosteroids. *Proc Am Thorac Soc*. 2004;1(3):269-274.

Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14:902-907.

Miller M, Hankinson J, Brusasco V, et al. American Thoracic Society/European Respiratory Society. ATS/ERS Task Force: Standardization of Lung Function Testing: Number 2 in Series. European Respiratory Journal 2005;26(2):319-338.

National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of asthma. Full Report. 2007.

R Development Core Team.R: A language and environment for statistical computing.2003. A Foundation for Statistical Computing, Vienna, Austria.

United States Food and Drug Administration. FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm

WebMD. Drugs and Medications. Budesonide oral. http://www.webmd.com/drugs/drug-22008-budesonide+oral.aspx

World Health Organization. Asthma Fact Sheet. November 2013. http://www.who.int/mediacentre/factsheets/fs307/en/index.html

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 (i.e., 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 eight successive FVC maneuvers performed in a 10-minute period without inspiration from the instrument.

Display

For optimal quality control, both flow–volume and volume–time displays are useful, and test operators should visually inspect the performance of each maneuver for quality assurance before proceeding with another maneuver. This inspection requires tracings to meet the minimum size and resolution requirements set forth in this standard. Displays of flow versus volume provide more detail for the initial portion (first 1 s) of the FVC maneuver. Since this portion of the maneuver, particularly the peak expiratory flow 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 two units of flow per one unit of volume

The time scale should be ≥20 mm-s^{-1}, and larger time scales are preferred (≥30 mm-s^{-1}) when manual measurements are made. When the volume–time plot is used in conjunction with a flow–volume curve (i.e., both display methods are provided for interpretations and no hand measurements are performed), the time scale requirement is reduced to 10 mm-s^{-1} from the usually required minimum of 20 mm-s^{-1} (Table 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 (e.g., industrial surveys), calibration checks and quality-control procedures must be repeated before further testing begins.

Key aspects of equipment quality control are summarized in Table A1-2.

Table A1-2. Summary of Equipment Quality Control

Test	Minimal Interval	Action
Volume	Daily	Calibration check with a 3 L syringe
Leak	Daily	2 cm H_2O (0.3 kPa) constant pressure for 1 minute
Volume Linearity	Quarterly	1 L increments with a calibrating syringe measured over the entire volume range
Flow Linearity	Weekly	Test at least three different flow ranges
Time	Quarterly	Mechanical recorder check with stop watch
Software	New versions	Log installation date and perform test using "known" subject

Calibration is the procedure for establishing the relationship between sensor-determined values of flow or volume and the actual flow or volume. A calibration check is different from calibration and is the procedure used to validate that the device is within calibration limits, e.g., ± 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 (e.g., monthly) leak tested at more than one volume up to their maximum; this can be done by attempting to empty them with the outlet corked. A dropped or damaged syringe should be considered out of calibration until it is checked.

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

Quality Control for Volume-Measuring Devices

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

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

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

Volume-type spirometer systems must be evaluated for leaks every day. The importance of undertaking this daily test cannot be overstressed. Leaks can be detected by applying a constant positive pressure of ≥3.0 cmH2O (0.3 kPa) with the spirometer outlet occluded (preferably at or including the mouthpiece). Any observed volume loss of .30 mL after 1 minute indicates a leak and needs to be corrected.

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

Quality Control for Flow-Measuring Devices

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

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

Equipment

For measurements of VC and IC, the spirometer or flow meter must comply with the requirements for FVC (as described previously) and be capable of accumulating volume for ≥30 s. Expiratory maneuvers or, ideally, both inspiratory and expiratory maneuvers should

be included in the display of VC maneuver. Regardless of whether the inspiratory or expiratory maneuver is used for deriving measurements, a display of the entire recorded VC maneuver must be provided. The maximal expiratory volume must be assessed to determine whether the subject has obtained a plateau in the expiratory effort. For display of the slow VC, the time scale may be reduced to 5 mm-s^{-1}.

TECHNICAL CONSIDERATIONS

Minimal recommendations for spirometry systems

Accurate results require accurate equipment. Spirometer equipment recommendations apply to all spirometers and are minimal requirements. In some circumstances, it may be appropriate to exceed these requirements (i.e., in some research/surveillance applications). Instrumentation recommendations should be followed to provide accurate spirometric data and information that is comparable from laboratory to laboratory and from one time period to another. The accuracy of a spirometry system depends on characteristics of the entire system, from the volume or flow transducer and the use of an in-line filter, to the recorder, display or processor. Changes in any aspect of the equipment or errors at any step in the process can affect the accuracy of the results. For example, if the BTPS correction factor is wrong, an accurately measured FVC will be incorrectly reported. Spirometers are not required to measure all of the indices in Table A1-1, but must meet the recommendations for those that are measured. Accuracy and repeatability recommendations apply over the entire volume range of the instrument.

Table A1-3. Range and Accuracy Recommendations Specified for Forced Expiratory Maneuvers

Test	Range/Accuracy (BTPS)	Flow Range ($L\text{-}s^{-1}$)	Time (s)	Resistance and Back Pressure	Test Signal
VC	0.5–8 L, ± 3% of reading or ± 0.050 L, whichever is greater	0-14	30		3-L Calibration syringe
FVC	0.5–8 L, ± 3% of reading or ±0.050 L, whichever is greater	0-14	15	<1.5 cm H_2O L^{-1} s^{-1} (0.15 kPa $L^{-1}s^{-1}$)	24 ATS waveforms, 3-L Cal Syringe
FEV_1	0.5–8 L, ± 3% of reading or ± 0.050 L, whichever is greater	0-14	1	<1.5 cm H_2O L^{-1} s^{-1} (0.15 kPa $L^{-1}s^{-1}$)	24 ATS waveforms
Time Zero	The time point from which all FEV_t measurements are taken.			Back extrapolation	

FEVt: forced expiratory volume in t seconds

BTPS correction

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

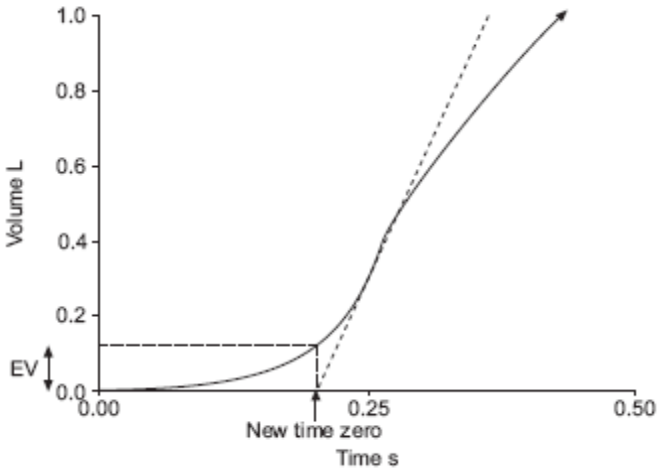
***Acceptable* Tests must meet the following 7 Criteria:**

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 below)
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, i.e., the volume-time curve shows no change in volume (<0.025 L) for ≥ 1s, and the patient has tried to exhale for at least 6 seconds.

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

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

Figure A2-1. Example of a Usable Spirogram



The expanded version of the early part of a subject's volume-time spirogram, illustrating back extrapolation through the steepest part of the curve, where flow is peak expiratory flow 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 three acceptable spirograms have been obtained, apply the following tests

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

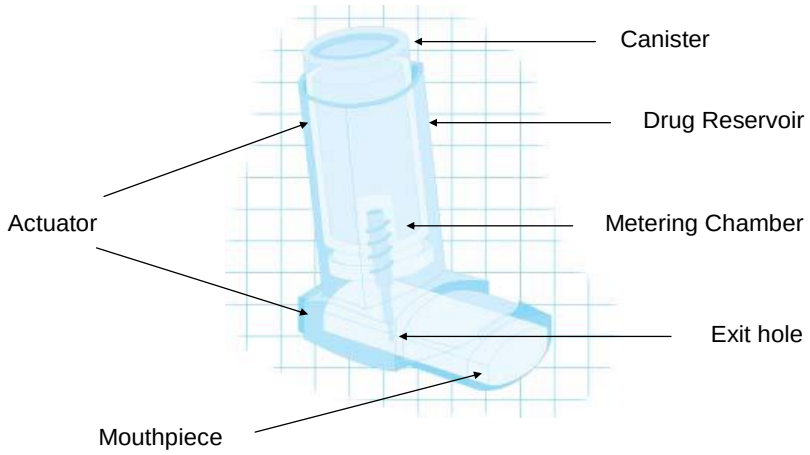
If these criteria are met, the spirometry testing for that time-point may conclude. The highest FEV_1 and the highest FVC obtained at each testing time-point (even if from different reproducible tracings), will be collected.

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 BD 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 three more times.
5. Gently shake the inhaler for 5 to 10 seconds before each spray.
6. Breathe out fully through your mouth, expelling as much air from your lungs as possible. Tilt your head back slightly, place the mouthpiece into your mouth, holding the inhaler with the mouthpiece down, and closing your lips around it. To allow the medication to enter your lungs, keep your tongue flat on the floor of your mouth.
7. While breathing in deeply and slowly through your mouth, fully depress the top of the metal canister with your index finger. Immediately after the spray is delivered, release your finger from the canister. When you have breathed in fully, remove the inhaler from your mouth and close your mouth.
8. Hold your breath as long as possible, up to 10 seconds, and then breathe normally.
9. 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



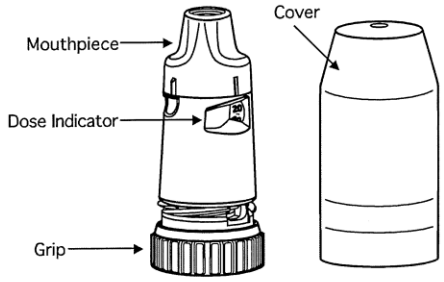
Appendix 4 Instructions for Use of Pulmicort Flexhaler*(budesonide inhalation powder)*

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

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.**

Fig 2

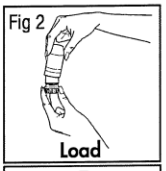


Fig 3

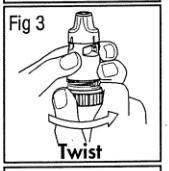


Fig 4

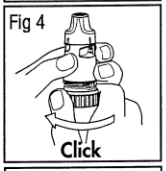
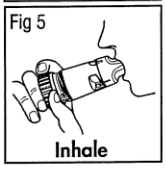


Fig 5



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).

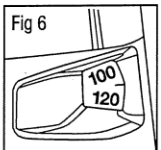
Patient Information 12

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



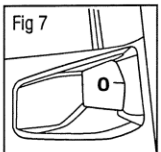
Dose Indicator

- 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

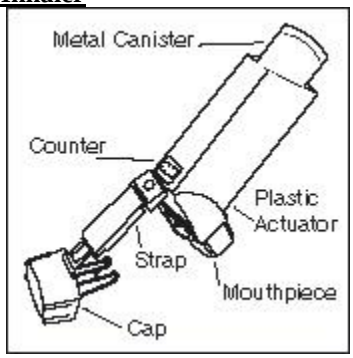


Figure 1

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.

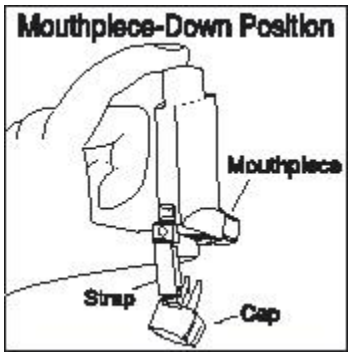


Figure 2

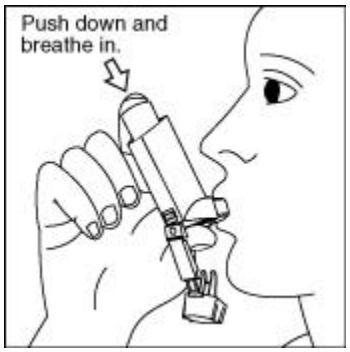


Figure 3

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).

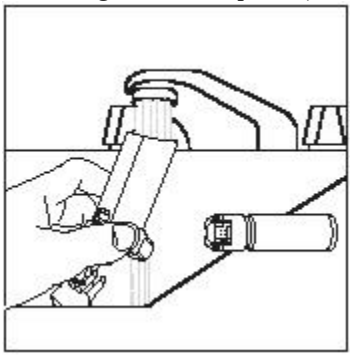


Figure 4

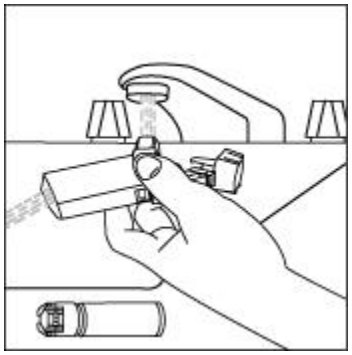


Figure 5

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).

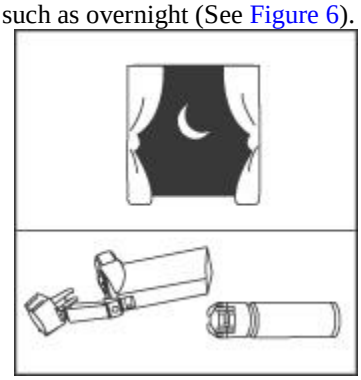


Figure 6

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.

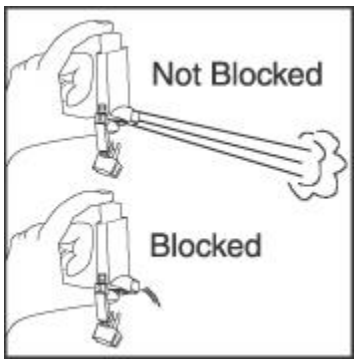


Figure 7

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 Asthma Control Questionnaire

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

ASTHMA CONTROL QUESTIONNAIRE

(SYMPTOMS ONLY)

UK ENGLISH VERSION

[redacted]

For further information:

[redacted]

[redacted]

[redacted]

SYMPTOMS ONLY MODIFIED [redacted] UK 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 time did you **wheeze?**
   - 0 Never
   - 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] UK ENGLISH

Appendix 7 Sponsor Signatory

Study Title: A Randomized, Double-Blind, Chronic Dosing (4 weeks), Four-Period, Five-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess the Efficacy and Safety of Four Doses of Budesonide Inhalation Aerosol (BD MDI, PT008) Relative to Placebo MDI in Adult Subjects With Mild to Moderate Persistent Asthma

Study Number: PT008001-00

Final Date: [redacted]

Signature: [redacted] Date: [redacted]

Name: [redacted]

Title: [redacted]

Appendix 8 Investigator's Agreement and Signature Page

Study Title: A Randomized, Double-Blind, Chronic Dosing (4 weeks), Four-Period, Five-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess the Efficacy and Safety of Four Doses of Budesonide Inhalation Aerosol (BD MDI, PT008) Relative to Placebo MDI in Adult Subjects With Mild to Moderate Persistent Asthma

Study Number: PT008001-00

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 Therapeutic with any necessary information regarding ownership interest and financial ties; to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and agree that Pearl Therapeutics may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- I agree to report all information or data in accordance with the protocol and any other study conduct procedures provided by Pearl Therapeutics
- That since the information in this protocol and IB is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision or conduct of the study is prohibited.
- To accurately transfer all required data from each subject's source document to the 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:_____ Date:_____

Name:_____

Affiliation: _____

Pearl

NOTE TO FILE

Study Title	A Randomized, Double-Blind, Chronic Dosing (4 weeks), Four-Period, Five-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess the Efficacy and Safety of Four Doses of Budesonide Inhalation Aerosol (BD MDI, PT008) Relative to Placebo MDI in Adult Subjects With Mild to Moderate Persistent Asthma
Protocol Number	PT008001-00
Pearl Therapeutics Representative Initiating Change to the Record	[redacted]
Date	[redacted]
Reason for Change	Incorporate administrative and editorial changes for consistency

- On Tuesday, [redacted] the PT008001 protocol was circulated for a final approval and sign-off. During his review prior to the sign-off, [redacted] noticed three proposed changes that required incorporation.

Description of Changes:

- **Page 42. Section 7.1.1.1;** [redacted] **Comment/Query:** The following text should not have been deleted: "*Subjects who do not meet reversibility criteria at Visit 2 following at least 14 days on Pulmicort Flexhaler will be screen failed.*"
  - ***Action:*** The text was restored and confirmed to also align with Inclusion Criteria #6.

- **Page 47. Section 7.2.1;** [redacted] **Comment/Query:** If a subject is an early discontinuation – are we performing a full physical on them? If not, please explain why not? If we are – please add appropriate text at end of the sentence. How does this occur in the case of early termination?
  - ***Reply/action:***
    - A physical is being performed on subjects requiring early termination.
    - To clarify this, *"(Early Termination)"* was added to the header of Section 8.10.
    - The text *"Or Final Visit"* was added to the Visit 14 header cell, and a footnote was added beneath the table to state: *"If a subject discontinues the study prematurely (early termination) the procedures that should be completed at the Final Visit are described in Section 8.10"*.
    - In Section 7.2.1 text was revised in the first paragraph to clarify Premature Discontinuation and Early Termination as follows: *"Medical history will be collected at Screening and updated during Visits 1a to Visits 3 (Screening Period). A complete physical examination will be performed at Visit 1a (Screening) and Visit 14 or Premature Discontinuation (Early Termination) Visit."*

- **Page 63. Section 8.4;** [redacted] **Comment/Query:** Is the following text still appropriate? *"To allow for proper preparation of study drug, it is recommended that the seal around the treatment box is opened 15–30 minutes prior to dosing, and the instruction for the administration of study drug are followed."* Are study treatments still in treatment boxes or are these bulk packaged?
  - ***Reply/Action:*** [redacted] has confirmed that individual treatment kits are being used. The statement is correct. No further action necessary.

- On [redacted] a change was requested by [redacted] to revise text as follows:
  - **Page 70. Section 8.12**; Our notes indicated that [redacted] would like the language on the study completion form updated to reflect "Major Protocol Deviation". The final protocol still includes "Major Protocol Violation" in the categories for Early Withdrawal (Section 8.12).
    - ***Reply/Action:*** The section was revised to read Major Protocol Deviation in accordance with the request.

Further actions: After incorporation of these changes, for version integrity the file was renamed to reflect the date of [redacted]

Authorized Signature:

[redacted]

[redacted]

Date

[redacted]

Date

Clinical Trial Protocol: PT008001-01

Study Title:	A Randomized, Double-Blind, Chronic Dosing (4 weeks), Four-Period, Five-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess the Efficacy and Safety of Four Doses of Budesonide Inhalation Aerosol (BD MDI, PT008) Relative to Placebo MDI in Adult Subjects With Mild to Moderate Persistent Asthma
Study Number:	PT008001-01
Study Phase:	IIb
Product Name:	Budesonide Inhalation Aerosol; PT008
IND Number:	121629
Indication:	Asthma
Investigators:	Multicenter
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]

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

SUMMARY OF CHANGES

ORIGINAL PROTOCOL (Version 1.0) dated [redacted]
to
AMENDMENT 1 (Version 2.0) dated [redacted]

This protocol is amended to Version 2.0, as follows:

- To facilitate enrollment, the number of sites was increased from 10 to ***25*** sites. Contribution of subjects was adjusted from 10 to ***6*** subjects per site. This change is reflected in the Synopsis and Section 4.1.
- The Table of Investigational Product-Packaging Descriptions of Study Drug, Open-label Products and Placebo Description was updated to combine information. This change is reflected in the Synopsis and Section 6.2.
- The statistical analysis models for the primary and secondary analyses were updated for consistency with statistical models for other efficacy endpoints, specifically; repeated measures ***mixed*** model, ***random subject effect*** and ***fixed effects***. This is reflected in the Synopsis and in Sections 9.3.1, 9.3.2, and 9.3.3.
- The following text was added for clarification at Screening Visit (Visit 1a): ***pre-bronchodilator pulmonary function tests (PFTs) will be assessed prior to administration of Ventolin HFA (albuterol). Post-bronchodilator testing may be performed to assess reversibility***. This change is reflected in Section 4.1 and Section 7.1.2.
- eDiary compliance was corrected to read **greater or equal to** 70% as follows: Subjects must have a minimum ACQ score of ≥ 1.5 and eDiary compliance of **≥ *70%*** in the last 7 days preceding Visit 3 and meet the FEV_1 baseline stability criteria to be eligible for Randomization at Visit 3. This change is reflected in Section 4.1.
- Inclusion Criteria #3 (see bullet below) was removed as this information is reflected in Inclusion Criteria #5.
    - ~~$FEV_1 \geq 60 \leq 85\%$ predicted~~
- Exclusion Criteria #22 was corrected to reflect non-compliance of eDiary as <***70%***. Section 5.2.
- The sentence above Table 1, Estimated Equipotent Daily Doses of Inhaled Glucocorticosteroids, adds another dose and should read: The definition of the doses of ICS considered "low", "medium", and ***"high"*** is provided below in Table 1. This change is reflected in Section 5.4.
- In Table 3, Prohibited Medications, ***amiodarone 3 months*** was deleted under Immunosuppressants. Table 3
- Clarification of Rescue Ventolin HFA was provided as follows: Subjects requiring ***equal to or more than*** 8 puffs per day on 3 or more consecutive days with worsening symptoms should contact the site. Change is reflected in Section 7.1.7.

- The terms *dry mouth* and *tremor* were deleted in overall Safety Assessments (Section 7.2).
- Clarification of x-ray requirement in Medical/Surgical History and Physical Examination paragraph as follows: ***At Visit 1a, obtain a chest x-ray only if the subject has not had a chest x-ray or computed tomography (CT) scan of the chest/lungs within the last 6 months.*** (Section 7.2.1).
- Schedule of Events Table was modified as original Table was numbered incorrectly. (Table 9)
- Bullet points in Section 8.4 (Randomization Visit) through Section 8.8 (Visit 14) were modified to clarify eDiary collection. (Sections 8.4 - 8.8) : They now read:
  - ***Have subjects perform pre-dose eDiary collections including completion of symptom questions and pre-dose PEFR assessments.***
  - ***Have subject perform post-dose eDiary collections including PEFR at 30 minutes post-dosing.***

Note: Other minor protocol inconsistencies, typographical errors, general editorial or formatting changes which may have been made throughout this document do not compromise subject safety or the intent of the original design of the study.

SYNOPSIS

Pearl Therapeutics, Inc. (Pearl) [redacted]
Names of Finished Products: Budesonide Inhalation Aerosol; PT008
Name of Active Ingredients: Budesonide
Study Title: A Randomized, Double-Blind, Chronic Dosing (4 weeks), Four-Period, Five-Treatment, Incomplete Block, Cross-Over, Multicenter Study to Assess the Efficacy and Safety of Four Doses of Budesonide Inhalation Aerosol (BD MDI, PT008) Relative to Placebo MDI in Adult Subjects With Mild to Moderate Persistent Asthma
Study Number: PT008001-01
Study Phase: IIb
Study Objective(s): **Primary Objective:** To demonstrate a lung function benefit of BD MDI compared with Placebo MDI in adult subjects with mild to moderate persistent asthma. **Secondary Objective:** To characterize the dose response of BD MDI based on lung function in adult subjects with mild to moderate persistent asthma.
Safety Objective: To evaluate the safety and tolerability of BD MDI across all doses evaluated in the study.
Study Design: This is a randomized, double-blind, chronic dosing (4 weeks), four-period, five-treatment, incomplete block, cross-over, multicenter study to assess the efficacy and safety of four doses of BD MDI (320, 160, 80, and 40 µg ex-actuator, twice daily [BID]) and Placebo MDI (BID) in adult subjects with mild to moderate persistent asthma. It is planned to conduct this multi-center study at approximately 25 sites in the United States, with each site contributing approximately 6 subjects. Across these sites, it is planned that approximately 150 adult subjects with mild to moderate persistent asthma who remain symptomatic despite treatment with Pulmicort Flexhaler® 180 µg BID will be randomized into the study to provide approximately 120 completers. The entire study

period is scheduled to take a maximum of 32 weeks for each subject.

Study Population:
Approximately 150 adult subjects with mild to moderate persistent asthma who remain symptomatic despite treatment with Pulmicort Flexhaler (budesonide inhalation powder) 180 µg BID, will be enrolled to provide approximately 120 completers (eg., 4 treatment periods).

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

Drug/Product Name & Dose	Product Strength	Dosage Form/Fill Count	Comments
Study Drug			
Budesonide Inhalation Aerosol 320 µg ex-actuator	160 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Budesonide Inhalation Aerosol 160 µg ex-actuator	80 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Budesonide Inhalation Aerosol 80 µg ex-actuator	40 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Budesonide Inhalation Aerosol 40 µg ex-actuator	20 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Open-label Products			
Albuterol Sulfate Inhalation Aerosol[§] 90 µg (Ventolin HFA)	Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece	1 MDI 200 actuations	US source: (Ventolin® HFA) *Supplies are open-label*
Budesonide Inhalation Powder[†] 180 µg (Pulmicort Flexhaler)	Taken as one inhalation. Each inhalation contains 180 µg of budesonide corresponding to 160 µg delivered from the mouthpiece	1 DPI 120 actuations	US source: (Pulmicort Flexhaler®) *Supplies are open-label*
Placebo			
Placebo	Formulation does not contain active ingredient	1 MDI 120 inhalations	Taken as 2 inhalations from the MDI

[§] Rescue medication and reversibility testing.

[†] Asthma maintenance therapy during Screening and Washout Periods

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

All placebos are created by Pearl Therapeutics in the image of the active test product. The 320, 160, 80, and 40 µg ex-actuator delivery of BD MDI are equivalent to 370.0, 185.0, 92.4, and 46.2 µg ex-valve of BD MDI, respectively.

Duration of Treatment:
Each subject will receive 4 weeks (28 days) of study treatment with each of their assigned treatments for a total of 4 separate Treatment Periods. A Washout Period of at least 14 days (and up to 21 days) will occur between each Treatment Period. The entire study is scheduled to take a maximum of 32 weeks for each individual subject from the time of screening (see Figure 1).

Efficacy Assessments:

Primary Efficacy Endpoint:

- Change from baseline in morning pre-dose trough forced expiratory volume in one second (FEV_1) at the end of the Treatment Period

- Secondary Efficacy Endpoints:
- Change from baseline in mean morning pre-dose and mean evening pre-dose peak flow rate (PEFR) readings taken by the subject and recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in Asthma Control Questionnaire (ACQ) score at the end of the Treatment Period

Other Efficacy Endpoints:

- Change from baseline in morning pre-dose trough FEV_1 over the Treatment Period and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in mean morning and evening pre- and post-dose daily PEFR readings taken by subjects and recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Percentage of days without rescue Ventolin HFA use over the last week of the Treatment Period and over the entire Treatment Period
- Change from baseline in pre-dose trough forced vital capacity (FVC) at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough PEFR at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough forced expiratory flow 25-75% (FEF_{25-75}) at the end of each Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in the number of nighttime awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period, over each week of the Treatment Period, and over the entire Treatment Period
- Percentage of nights with awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period and over the entire Treatment Period

Safety Endpoints:

The safety assessments include electrocardiograms (ECGs,) vital sign measurements, clinical laboratory tests, monitoring for paradoxical bronchospasm, physical examination findings, AEs and SAEs during the study period.

Statistical Methods:

Sample Size Determination:

Power calculations are based on the properties of the primary endpoint, morning pre-dose trough $FEV_{1,}$ on the last day of each Treatment Period (end of treatment). An estimate of the total standard deviation (SD) of 405 mL is taken from a 12-week trial comparing budesonide to ciclesonide (Boulet, 2006). Assuming that half of the variability comes from within subject and half between (ie., intrasubject correlation=0.5), an estimate of the within subject standard deviation of 285 mL for morning pre-dose trough FEV_1 is obtained. Using this SD and assuming that 150 randomized subjects will provide approximately 120 completers, the power to demonstrate a 120 mL difference from Placebo MDI for BD MDI 320 μg or BD MDI 160 μg is approximately 90%. For BD MDI 80 μg and BD MDI 40 μg, the power to demonstrate a difference from Placebo MDI of 140 mL is approximately 80%.

Efficacy Analyses:

The primary efficacy analysis will compare the change from baseline at the end of the treatment periods in morning pre-dose trough FEV_1 between BD MDI treatments and Placebo MDI using a repeated measures mixed model with a random subject effect for the correlation across periods. The fixed effects will include baseline FEV_1, response to albuterol, and period. Sequence will also be included if it explains significant variability. The primary population will be a *modified* Intent to Treat (mITT) Population. A two-sided alpha level of 0.05 will be employed. Multiplicity will be controlled using a sequential, dose-ordered approach.

Similar analyses will be conducted using the Intent to Treat (ITT) Population for the primary endpoint as well as for analyses of the secondary and other efficacy endpoints.

Safety Analyses:

Safety analyses will be based on descriptive statistics for ECG, vital sign and laboratory measurements as appropriate, incidence of paradoxical bronchospasm, and on the number of subjects with AEs and SAEs.

Date of Original Approved Protocol: [redacted]

Date of Amendment 1: [redacted]

TABLE OF CONTENTS

List of In-Text Tables

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ACQ	Asthma Control Questionnaire
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the curve
AV	Atrioventricular block
BD	Budesonide
BID	Bis in die, twice daily
BMP	Basic Metabolic Panel
BP	Blood Pressure
BPM	Beats per minute
BTPS	Body Temperature and Pressure Saturated
BUN	Blood urea nitrogen
$CaCl_2$	Calcium Chloride
CFR	Code of Federal Regulations
CMP	Comprehensive Metabolic Panel
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
CRO	Contract Research Organization
CT	Computed tomography
DBP	Diastolic blood pressure
DSPC	Distearoylphosphatidyl choline
DPI	Dry Powder Inhaler
eg	*Exempli gratia*, for example
ECG	Electrocardiogram
ex-actuator	dose delivered from the actuator (ie., mouthpiece) of the MDI
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
hCG	Human chorionic gonadotropin
HR	Heart Rate
HFA	Hydrofluoroalkane
ie	*Id est*, that is
IBD	Incomplete Block Design
ICF	Informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IWRS	Interactive Web Response System
L	Liter
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
MAO	Monoamine oxidase inhibitor
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified ITT
mL	Milliliter

Msec (ms)	Millisecond
NHANES III	National Heart, Lung, and Blood Institute Third National Health and Nutrition Examination Survey
OTC	Over-the-counter
PEFR	Peak expiratory flow rate
PFT	Pulmonary function test
PI	Principal Investigator
PIN	Personal identification number
PK	Pharmacokinetic
PP	Per Protocol
PRN	Pro re nata, as needed
PT	Preferred term
REML	Residual or restricted maximum likelihood
RFD	Rescue-free days
Rx	Treatment
QTcF	QT corrected using Fridericia's formula ($QT/(RR^{1/3})$)
SABA	Short-acting beta agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
TNFα	Tumor necrosis factor α
TP	Treatment Period
µg	Microgram
US/USA	United States

TRADEMARK INFORMATION

Trademarks Not Owned By Pearl Therapeutics

Advair

Atrovent

Breo

Combivent

Diskus

Dulera

Ellipta

Pulmicort Flexhaler

Robinul

Robinul Forte

Seretide

Symbicort

Ventolin HFA

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 (eg., age 50, 60 or even later in life) [GINA, 2012]. Those individuals who develop asthma as adults are said to have adult onset asthma.

The current National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report-3, 2007 [NHBLI, 2007]recommends long-term treatment with inhaled corticosteroids (ICS) because of their superior effectiveness in managing the chronic airway inflammation that characterizes persistent asthma [February 2010 that long-acting beta agonists (LABAs) should never be used alone to treat asthma, and specifying that when they are used as part of a combination therapy, they should be administered only for the shortest duration possible and then discontinued and then patient should be maintained on a controller medication [FDA, 2007].

The NHLBI EPR-3 Guidelines recommend a stepwise approach to asthma treatment: inhaled corticosteroid (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 [NHBLI, 2007].

Regular treatment with ICS improves symptoms, lung function , 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, 2012

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 BD when used to treat chronic asthma, and a large range outcome measures have been used to assess its efficacy and safety.

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 (DSPC) and calcium chloride ($CaCl_2$) that are cosuspended

with crystalline active drug substances and formulated into suspension-based hydrofluoroalkane (HFA) metered dose inhalers (MDIs). The safety of porous particles is previously demonstrated in over 1000 patients with COPD.

Pearl Therapeutics is developing a broad range of MDI-based inhalation aerosols using its porous particle technology platform. These inhaled therapies include Glycopyrrolate (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) for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. GFF MDI is currently being evaluated in the PINNACLE 1 and PINNACLE 2 Phase III trials; and in a recently completed Phase I pharmacokinetic (PK) study with budesonide as a component in a fixed "triple" combination therapy with GP and FF.

1.1 Study Rationale

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

2 STUDY OBJECTIVES

2.1 Primary Objective

To demonstrate lung function benefit of BD MDI compared with Placebo MDI in adult subjects with mild to moderate persistent asthma

2.2 Secondary Objective

To characterize the dose response of BD MDI based on lung function in adult subjects with mild to moderate persistent asthma

2.3 Safety Objective

To evaluate the safety and tolerability of BD MDI across all doses evaluated in the study.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoint

- Change from baseline in morning pre-dose trough forced expiratory volume in one second (FEV_1) at the end of the Treatment Period

3.1.2 Secondary Efficacy Endpoints

- Change from baseline in mean morning pre-dose and mean evening pre-dose peak flow rate (PEFR) readings taken by the subject and recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in Asthma Control Questionnaire (ACQ) score at the end of the Treatment Period

3.1.3 Other Efficacy Endpoints

- Change from baseline in morning pre-dose trough FEV_1 over each Treatment Period and at Day 15 and Day 29 of each Treatment Period
- Change from baseline in mean morning and evening pre- and post-dose daily PEFR readings taken by subjects and recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Percentage of days without rescue Ventolin HFA use over the last week of the Treatment Period and over the entire Treatment Period
- Change from baseline in pre-dose trough forced vital capacity (FVC) at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough PEFR at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough forced expiratory flow 25-75% (FEF_{25-75}) at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in the number of nighttime awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period, over the week of the Treatment Period, and over the entire Treatment Period

- Percentage of nights with awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period and over the entire Treatment Period.

3.2 Safety Endpoints

The safety assessments include electrocardiograms (ECGs,) vital sign measurements, clinical laboratory tests, monitoring for paradoxical bronchospasm, physical examination findings, AEs and SAEs during the study period.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind, chronic dosing (4 weeks) four-period, five-treatment, incomplete block, cross-over, multi-center study to assess the efficacy and safety of four doses of BD MDI (320, 160, 80, and 40 µg BID) and Placebo MDI (BID) in adult subjects with mild to moderate persistent asthma.

This multi-center study will be conducted at approximately 25 sites in the United States (US), contributing approximately 6 subjects per site. Across these sites, it is planned that approximately 150 adult subjects with mild to moderate persistent asthma, who remain symptomatic despite treatment with Pulmicort Flexhaler® 180 µg will be randomized into the study to provide approximately 120 subjects to complete the study. The entire study period is scheduled to take a maximum of 32 weeks for each individual subject (see Figure 1). The study is anticipated to run for approximately 12 months and should not exceed 18 months.

At the Screening Visit (Visit 1a), all subjects are to sign an informed consent form (ICF) prior to the conduct of any screening assessments. The Investigator or designee will obtain a medical history, physical examination, and all required documentation in order to determine eligibility for participation (inclusion/exclusion criteria). Pre-bronchodilator pulmonary function tests (PFTs) will be assessed prior to administration of Ventolin HFA (albuterol). Post-bronchodilator testing may be performed to assess reversibility (see Section 7.1.2).

At the Investigators' discretion, subjects who do not meet the spirometry and/or reversibility entry criteria at Visit 1a can return for a repeat spirometry and/or reversibility assessment at an optional Screening visit (Visit 1b). **Note**: Visit 1b is to be used only for repeat spirometry entry criteria at any time between Visit 1a and Visit 2. All other repeat assessments, if needed, will be captured as an unscheduled visit. Repeat spirometry can be done anytime post Visit 1a and Visit 2, however, the subject must be in the 2-week run in period with Pulmicort Flexhaler 180 µg.

Providing the subject meets all eligibility criteria at Screening (Visit 1a or optional Visit 1b), the Investigator or designee will review current asthma medications and, if necessary, will adjust the prohibited asthma therapy to protocol-allowable asthma therapy as described in Section 5.4.

Subjects who meet all entry criteria but are using certain prohibited asthma medications (eg., oral β_2-agonists, corticosteroids, corticosteroid/LABA fixed dose combination products, and leukotriene antagonists [eg., zafirlukast, montelukast, zileuton]) will discontinue these medications for the duration of the trial.

During the Screening Period (between Visit 1 to Visit 3), all subjects will be prescribed open-label Pulmicort Flexhaler 180 µg BID provided by the Sponsor and open-label rescue Ventolin HFA 108 µg MDI provided by the Sponsor, as needed, to control symptoms.

Subjects will be issued and trained in the use of an electronic diary (eDiary) and peak flow meter at Visit 1 (Screening). Subjects will be instructed to collect practice data during the Screening Period (between Visit 1 and Visit 3).

In order to standardize asthma maintenance medications and to determine disease severity, eligible subjects will undergo a run-in period of at least 14 days (2 weeks) but not greater than 28 days in duration, using Sponsor-provided open-label Pulmicort Flexhaler 180 µg BID and Sponsor-provided rescue Ventolin HFA MDI, as needed, to control symptoms prior to returning to the clinic for Visit 2.

At Visit 2, reversibility to Ventolin HFA will be evaluated (see Section 7.1.2) and Visit 2 procedures completed (see Section 8.3). Subjects who successfully meet study entry criteria at Visit 2 will be scheduled for Visit 3 (Randomization Visit) at least 1 day from Visit 2, but no later than 28 days from Visit 1a (Screening).

At Visit 3 (Randomization Visit; Treatment Period 1, Day 1), subject eDiary compliance will be reviewed and all sponsor-provided Pulmicort Flexhaler and Ventolin HFA provided during the Screening Period will be discontinued and collected by site personnel for accountability. Eligible subjects will complete an Asthma Control Questionnaire (ACQ) (Juniper, 1999) (see Section 7.1.10 and Appendix 6) at Visit 3 prior to Randomization.

Subjects must have a minimum ACQ score of ≥1.5 and eDiary compliance of ≥70% in the last 7 days preceding Visit 3 and meet the FEV_1 baseline stability criteria (see Section 5.1) to be eligible for Randomization at Visit 3. Subjects who do not meet the ACQ minimum score, eDiary compliance and/or FEV_1 baseline stability criteria described above must be screen failed at Visit 3.

Subjects who continue to meet all entry inclusion/exclusion criteria at Visit 3 and those who remain eligible for participation in the study will be randomized to one of the pre-defined treatment sequences. Each sequence will include exactly 4 of the 5 treatments included in this study. All subjects will receive BD MDI 320, BD MDI 160 µg, and Placebo MDI in a randomized order, but only half of the subjects will be randomized to receive BD MDI 40 µg or BD MDI 80 µg.

The subject, clinical site personnel, and Pearl Therapeutics will be unaware of the treatment dose sequence assigned to each subject, and it will not be possible to differentiate between study treatments as all blinded clinical supplies will be identical in image in all aspects.

Randomization will be centralized, through the use of an IWRS (Interactive Web Response System). Study treatments will be administered twice daily. Each of the 4 treatments will be administered for 28 ±2 days with a Washout Period of at least 14 days (up to 21 days) during which subjects will administer Pulmicort Flexhaler 180 µg, BID and Ventolin HFA, as needed, in between Treatment Periods.

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 (≥4 hours) of short acting bronchodilators. 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 last post-dose PEFR assessment (see Section 8.4). Subjects will then be discharged from the clinic and will continue to administer study medication and complete their eDiary entries at home for 14 days (2 weeks) 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 (2 weeks) of chronic Treatment 1 dosing at home and complete Visit 4 procedures (see Section 8.6). Subjects will then be discharged from the clinic and will continue to administer study medication and complete their eDiary entries for 14 days (2 weeks) at home until Visit 5 (Treatment Period 1, Day 29).

Subjects will return to the clinic following approximately 14 days (2 weeks) of chronic Treatment 1 dosing for Visit 5 (Treatment 1, Day 29) and complete the procedures for Visit 5 (see Section 8.7). On discharge, subjects will undergo a study medication Washout Period of at least 14 Days (2 weeks) but no more than 21 Days (3 weeks) duration, using Sponsor-provided open-label Pulmicort Flexhaler 180 µg BID and Sponsor-provided rescue Ventolin HFA MDI, as needed, to control symptoms, prior to initiating Treatment 2 in their assigned treatment sequence at Visit 6.

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

At Visits 6, 9 and 12 (Day 1 of Treatment Periods 2, 3 and 4, respectively), subjects will return to the clinic following their Washout Period and if eligible to continue, complete all Day 1 procedures for the Treatment Period (see Section 8.5). Pre-dose assessments will be performed and continued eligibility will be determined. Subjects must meet the FEV_1 baseline stability criteria (see Section 5.1) to be eligible for dosing at Visits 6, 9 and 12. Subjects who do not meet the FEV_1 baseline stability criteria at Visits 6, 9 and 12 must be rescheduled as soon as is practical, but within the protocol-specified washout window (14-21 days between Treatment Periods). Subjects who fail to meet stability criteria after two attempts within a Washout Period will be discontinued from the study.

Eligible subjects (eg., subjects who meet FEV_1 baseline stability criteria and have withheld all asthma medications for 4 hours prior to the study visit) will be dispensed study drug relative to the IWRS and administer their first dose of study drug in the clinic under site supervision. The post-dose PEFR will be performed and the subject discharged to continue daily study drug administration and eDiary completion at home until the next scheduled visit at 14 $\pm$2 days from Treatment Day 1 of the Treatment Period (see Section 8.5).

At Visits 7, 10, and 13 (Day 15 of Treatment Periods 2, 3 and 4, respectively), eligible subjects (eg., subjects who have withheld all asthma medications for 4 hours prior to the study visit) will complete all pre-dose assessments and continued eligibility will be

determined (see Section 8.6). Providing the subject does not meet rescue criteria (see Section 7.1.4), new study drug as assigned by IWRS will be dispensed, the subject will take their study medication under site supervision, and a post-dose PEFR will be obtained. The subject will be discharged to continue daily study drug administration and eDiary completion at home until the next scheduled visit at approximately 28±2 days from Treatment Day 1 of the Treatment Period.

At Visits 8 and 11 (Day 29 of Treatment Periods 2 and 3, respectively), eligible subjects (eg., subjects who have withheld all asthma medications for 4 hours prior to the study visit) will complete all pre-dose assessments and continued eligibility will be determined (see Section 8.7). Subjects will administer their last dose of study drug from the MDI assigned at Visits 7 and 10, respectively, and post-dose PEFR and vital signs will be obtained. The subject will be discharged to undergo a Washout Period of at least 14 Days (2 weeks) up to 21 Days (3 weeks) on Sponsor-provided open-label Pulmicort Flexhaler 180 µg BID and Ventolin HFA, as needed, for relief of asthma symptoms, prior to initiating Treatment Periods 3 and 4 at Visit 9 (Treatment Period 3, Day 1) and Visit 12 (Treatment Period 4, Day 1), respectively.

At Visit 14 (Day 29 of Treatment Period 4), eligible subjects (eg., subjects who have withheld all asthma medications for 4 hours prior to the study visit) will complete all pre-dose assessments and continued eligibility determined (see Section 8.8). Subjects will administer their last dose of study drug from the MDI assigned at Visit 13, and post-dose PEFR and vital signs will be obtained. Following completion of Visit 14 assessments, the subject will be discharged and returned to pre-study or appropriate inhaled asthma maintenance medication(s). Subjects completing Visit 14 (Day 29 of Treatment Period 4), or who require a Premature Discontinuation Visit, will be scheduled for a post-study follow-up telephone call (see Section 8.11) at least 7 days and up to 14 days from the date of last study dose.

General Guidance for Treatment During In-clinic Visits 3 through 14

- 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 study medication and rescue medications (eg., Ventolin HFA [albuterol]) for at least 4 hours, by confirming the last time of dosing for all asthma medication(s).

  Note: Subjects who inadvertently took rescue medication(s) within 4 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 30 minutes post dose, for observation (safety).

- Subjects must not ingest caffeine-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 a dosing schedule at home consistent with their in clinic dosing time.
    - Subjects will be required to take their study medication twice a day: 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.

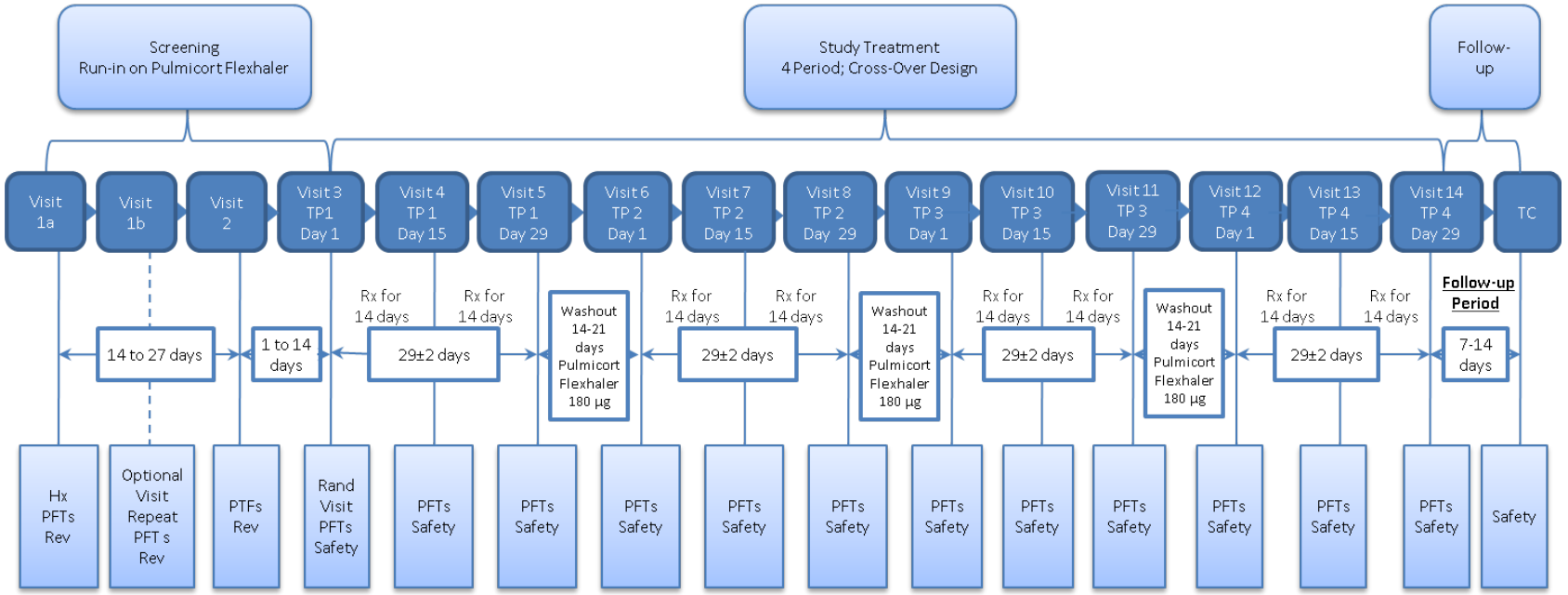
- Sites are encouraged to call the subject on the day before a scheduled visit to remind the subject to:
    - Take their last dose the evening before (12 ± 2 hours) prior to the scheduled visit.
    - Bring their study medications with them to the clinic
    - Withhold all asthma medications (including ICS) for at least 4 hours prior to 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 will be recorded as the time of administration of the *second* puff of study medication.
- 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 test day. Site personnel may request the subject to surrender all non-study asthma medications prior to start of the visit before performing any study procedures and return to subject at 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 done between Treatment Day 13 and Treatment Day 17, inclusive).
- Similarly, every effort must be made to ensure that subjects return to the clinic on Day 29 (4 Weeks) following the initiation of each treatment arm. To accommodate scheduling

conflicts a window of 28 ± 2 days from Treatment Day 1 is permitted (ie., Treatment Day 29 procedures must be done between Treatment Day 27 and Treatment Day 31, inclusive).

Note: If Visit 5, 8 or 11 occurs at Day 31 or later, the site must contact the Sponsor for guidance prior to initiating the next Treatment Period.

A Study Flow Diagram is displayed in Figure 1:

Figure 1. Study Flow Diagram



Hx = Medical History, Rand = Randomization, PFT = Pulmonary Function Test, Rx = Treatment, Rev = Reversibility, TC = Telephone Call, TP = Treatment Period

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

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

1. Give their signed written informed consent to participate.
2. Are ≥18 – 65 years of age at Visit 1.
3. Have a diagnosis of mild to moderate persistent asthma, diagnosed at least 6 months prior to screening visit according to NHLBI EPR 3, (NHLBI, 2007)
   - Asthma symptoms > 2 days per week, or
   - Nighttime awakenings 3–4 times per month or greater due to asthma symptoms, or
   - Use of short-acting beta agonist (SABA) for symptom control (not for prevention of exercise-induced bronchospasm) > 2 days per week, or
4. Asthma Medication History: Must be currently receiving treatment with a low to medium dose of an ICS (as defined in Table 1) ***OR*** a combination of controller medications as defined in Table 2, containing a low (total daily) dose ICS (as defined in Table 1) for at least 4 weeks preceding screening.
5. Pulmonary Function: Must have a pre-albuterol (Ventolin HFA) FEV_1 of ≥ 60% and ≤ 85% of predicted normal value at Screening (Visit 1a or 1b) and at Visits 2 and 3.
6. Reversibility: At Screening (Visits 1a or 1b) and at Visit 2, the subject must have an increase in FEV_1 of ≥ 12% and ≥ 200mL over the pre-albuterol (Ventolin HFA) FEV_1 within 30-60 minutes after the inhalation of 4 puffs of Ventolin HFA. Historic documentation of reversibility will not be permitted (see Section 7.1.2).
7. FEV_1 Baseline Stability Criteria: At Visit 3, 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 2 (see Section 7.1.3).
8. Asthma Symptom Criteria: Have required Ventolin HFA use on at least two of the last seven days and have an Asthma Control Questionnaire (ACQ) total score ≥ 1.5 prior to Randomization (Visit 3) (see Appendix 6).
9. A female is eligible to enter and participate in the study if she is :
   - 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, and agrees to one 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 until 14 days after Visit 14)
     a. Complete abstinence from intercourse from screening until 14 days after Visit 14 ***or***
     b. 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***

c. Injectable progestogen administered for at least 1 month prior to study drug administration and administered for 1 month following study completion; ***or***
d. Oral contraceptive (combined or progestogen only) administered for at least one monthly cycle prior to study drug administration; ***or***
e. Double barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository); ***or***
f. An intrauterine device (IUD), inserted by a qualified physician, with published data showing that the highest expected failure rate is less than 1% per year; or estrogenic vaginal ring; ***or***
g. Percutaneous contraceptive patches.

10. Results from clinical laboratory tests conducted at Screening must be acceptable to the Investigator.

5.2 Exclusion Criteria

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

1. Life-Threatening Asthma: A subject must not have life-threatening asthma. Life-threatening asthma is defined for this protocol 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 screening (Visit 1).
2. Worsening Asthma: A subject must not have experienced a worsening of asthma which involved an emergency department visit, hospitalization or use of oral/parenteral corticosteroids within 6 weeks of Screening (Visit 1).
3. Intermittent, Seasonal, or Exercise-Induced Asthma Alone: Subjects with only intermittent, seasonal or exercise-induced asthma are excluded from participation in this study.
4. Concurrent Respiratory Disease: A subject must not have current evidence or diagnosis of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), or other respiratory abnormalities other than asthma.
5. Concurrent Conditions/Diseases: A subject with historical or current evidence of any clinically significant, co-morbid 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. Pregnant women or nursing mothers.
7. Chronic Obstructive Pulmonary Disease (COPD): A current diagnosis of COPD.
8. Smoking History: Current smokers or subjects with a $\geq$ 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.
9. Respiratory Tract Infection(s): Subjects who have had a respiratory tract infection within 6 weeks prior to Visit 1. 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. 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.
11. Cardiac Conditions/Disease: Subjects with documented myocardial infarction within a year from screening visit 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 three months of screening visit are to be excluded.
12. Clinically significant abnormal ECG: A clinically significant abnormal ECG is defined as (but not limited to) any of the following:
    a. 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).
    b. Clinically significant arrhythmias (eg., atrial fibrillation, ventricular tachycardia)
    c. 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).
    d. Bradycardia with rate < 45 bpm.
    e. Pathological Q waves of 1 year or less
    f. ST-T wave abnormalities (excluding non-specific ST-T wave abnormalities)
    g. Subjects who, in the opinion of the Investigator, have a clinically significant abnormal 12-lead ECG
13. Uncontrolled Hypertension: Subjects who, in the opinion of the Investigator, have clinically significant uncontrolled hypertension.
14. Liver Function: Subjects with abnormal liver function tests defined as aspartate aminotransferase (AST), alanine aminotransferace (ALT), alkaline phosphatase or total bilirubin ≥1.5 times upper limit of normal on repeat testing.
15. 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 have been adequately worked up, are clinically controlled and the subject's participation in the study would not represent a safety concern, are eligible
16. Drug Allergy: Subjects who have a history of hypersensitivity to any component of the MDI.
17. Substance Abuse: Subjects with a known or suspected history of alcohol or drug abuse within the last 2-year period prior to Screening.

18. Medication Prior to Spirometry: Subjects who are medically unable to withhold their short-acting bronchodilators for the 4-hour period required prior to spirometry testing at each study visit will be excluded.
19. Prohibited Asthma Medications: Subjects taking the following medications within the specified time intervals prior to Screening (Visit 1) are to be excluded:
    a. 3 months: depot corticosteroids, intra-articular corticosteroids.
    b. 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.
    c. Initiation or discontinuation of ICS within 30 days of Visit 1.
    d. Subjects treated chronically with oral or systemic corticosteroids are excluded from the study.
    e. 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.
    f. Subjects treated chronically with antibiotics are excluded from the study.
20. Taking other prohibited medications as defined in Table 3.
    a. Anti-tumor necrosis factor α (TNFα) antibodies (eg., infliximab and any other members of this class of drugs)
    b. Antipsychotic drugs (phenothiazines)
    c. Systemic calcineurin inhibitors
    d. Systemic antifungal agents
    e. Protease inhibitors and cimetidine
    f. Immunosuppressants (Methotrexate, Cyclosporins, etc.)
    g. Any oral, inhaled or systemic corticosteroids
    h. Use of any LABA as single agent (as indicated in FDA mandated black box warning for LABAs)
21. Spirometry Performance:
    a. Acceptability Criteria: Subjects who cannot perform acceptable spirometry, (ie., meet ATS/ERS acceptability criteria)
    b. Repeatability Criteria: Subjects who cannot perform technically acceptable spirometry with at least three acceptable flow-volume curves with two or more meeting ATS repeatability criteria for FEV_1 during at least one of the pre-bronchodilator assessments at Visit 2 (-60 minute or -30 minute) and at the post-bronchodilator assessment at Visit 2
    c. FEV_1 Baseline Stability: see Section 5.1)
22. 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]).
23. 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.

24. 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.
25. 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.
26. 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 the Screening Visit (Visit 1). Only subjects continuing to meet entry inclusion/exclusion criteria at Visit 3 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 (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 1**.**

Table 1. Estimated Equipotent Daily Doses of Inhaled Glucocorticosteroids

Drug	Low Dose (µg)	Medium Daily Dose (µg)	High Daily Dose (µg)
Beclomethasone dipropionate - CFC	200 - 500	> 500 - 1000	> 1000 - 2000

Beclomethasone dipropionate - HFA	100 - 250	> 250 - 500	> 500 - 1000
Budesonide	200 - 400	> 400 - 800	> 800 - 1600
Ciclesonide	80 - 160	>160 - 320	> 320 - 1280
Flunisolide	500 - 1000	> 1000 - 2000	> 2000
Fluticasone propionate	100 - 250	> 250 - 500	> 500 - 1000
Mometasone furoate	200	> 400 - 800	> 800
Triamcinolone acetonide	400 - 1000	> 1000 - 2000	> 2000

Note: Comparisons based on efficacy data.
Source: GINA, 2012

Table 2 provides the list of asthma controller medications permitted (low to medium dose) and prohibited (high dose) in this study.

Table 2. Asthma Controller Medications

Low dose ICS + Leukotriene modifiers
Low dose ICS + Theophylline products
Low dose ICS + Inhaled anticholinergics or combination products (eg., Atrovent or Combivent)
Low dose ICS + Long-acting inhaled anticholinergics (ie., Spiriva)
Combination products containing low to medium dose ICS and a long acting beta agonist: **Permitted**: Advair/Seretide DISKUS 100/50 µg and 250/50 µg BID, Advair HFA 90/42 µg (administered as two puffs of 45/21 µg) BID, Advair HFA 230/42 µg (administered as two puffs of 115/21 µg) BID, Symbicort 160/9 µg (administered as two puffs of 80/4.5 µg) BID, Dulera 200/10 µg (administered as two puffs of 100/5 µg) BID.
Combination products containing high dose ICS and a long acting beta agonist: **Prohibited:** Advair/Seretide DISKUS 500/50 µg, Advair HFA 460/42 µg (administered as two puffs of 230/21 µg) BID; Symbicort 320/9 µg (administered as two puffs of 160/4.5 µg) BID; Dulera 400/10 µg (administered as two puffs of 200/5 µg) BID and Breo Ellipta 100/25 µg (administered as one inhalation) QD.

Source: GINA, 2012

Prohibited Medications:

The use of the medications listed in Table 3 is not permitted during this study, if initiated the subject needs to be discontinued immediately. If the subject had previously been prescribed any of the prohibited medications below and was recently discontinued, the minimum Washout Period prior to screening is provided:

Table 3. Prohibited Medications

Prohibited Medications	Minimum Cessation Period Prior to Visit 1 (Screening)
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

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

Illicit drugs or drugs of abuse will not be allowed from the start of Screening (Visit 1) to the end of the study (Visit 14), or to whenever the subject discontinues the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented.

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

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

abnormality. All subjects who prematurely discontinue the study after being randomized, regardless of the cause, should undergo the assessments outlined in Section 8.10 on the date 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 needs to make a determination as to the suitability of continuing the subject in the study.

Changes of concern include:

- Decrease in creatinine clearance to a value below 30 mL/min using CKD-EPI 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 principal Investigator (PI) or designee will need to determine whether the subject is having an asthma exacerbation and will also make a determination as to the suitability of continuing the subject in the specific treatment period.
  d. If a subject requires use of rescue medication 4 or more times per day (ie., ≥ 8 puffs of Ventolin HFA) for three or more consecutive days.
  e. If a subject meets the protocol-defined rescue criteria (Section 7.1.4) during the Treatment Period.
- If a subject does not meet protocol-defined FEV_1 baseline stability criteria (Section 5.1) 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 subject becomes pregnant during the course of the study, the subject will be discontinued. (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 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 as 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
Study Drug			
Budesonide Inhalation Aerosol 320 µg ex-actuator	160 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Budesonide Inhalation Aerosol 160 µg ex-actuator	80 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Budesonide Inhalation Aerosol 80 µg ex-actuator	40 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Budesonide Inhalation Aerosol 40 µg ex-actuator	20 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Open-label Products			
Albuterol Sulfate Inhalation Aerosol[§] 90 µg (Ventolin HFA)	Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece	1 MDI 200 actuations	US source: (Ventolin® HFA) *Supplies are open-label*
Budesonide Inhalation Powder[†] 180 µg (Pulmicort Flexhaler)	Taken as one inhalation. Each inhalation contains 180 µg of budesonide corresponding to 160 µg delivered from the mouthpiece	1 DPI 120 actuations	US source: (Pulmicort Flexhaler®) *Supplies are open-label*
Placebo			
Placebo	Formulation does not contain active ingredient	1 MDI 120 inhalations	Placebo Taken as 2 inhalations from the MDI

[§] Rescue medication and reversibility testing.

[†] Asthma maintenance therapy during Screening and Washout Periods

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

All placebos are created by Pearl Therapeutics in the image of the active test product. The 320, 160, 80, and 40 µg ex-actuator delivery of BD MDI are equivalent to 370.0, 185.0, 92.4, and 46.2 µg ex-valve of BD MDI, respectively.

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

For open-label Pulmicort Flexhaler (budesonide inhalation powder 180 µg), commercial dry powder inhalers (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).

6.3 Primary Packaging and Labeling Information

Investigational materials will be packaged by Pearl Therapeutics.

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

Open-label Supplies: Open-label PulmicortFlexhaler and Ventolin HFA will be provided as individually labeled DPIs and MDIs, respectively. Each inhaler will contain a single investigational label. For Pulmicort Flexhaler, a two-part label will be affixed to the carton. Ventolin MDIs will be packaged in foil pouches. Foil pouches will receive a one-part label. The two-part label will be affixed to the carton holding the foil. Both single and two-part labels will be printed with 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)

6.4 Secondary Packaging and Labeling Information (Box)

Investigational drug supplies will be packaged in boxes as outlined below in Table 6. Open label Ventolin HFA supplies will be provided in boxes, also 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	1DPI

Each box will be labeled with a double panel label printed with black ink and may include the following text (see Table 7).

Table 7. Description of Box Labeling

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

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.

Ventolin HFA supplies: Open-label supplies should also be kept 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.

Pulmicort Flexhaler supplies: Store in a dry place at controlled room temperature 20–25°C (68-77°F) with the cover tightly in place. Keep out of the reach of children. Keep Pulmicort Flexhaler 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 or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained.

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

BD and Placebo MDIs

Individual BD 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 foil overwrap is labeled with a two-part label. Write the subject number and treatment visit number on each of the two-part labels. The 'tear-off' part of the label is to be placed onto the IWRS confirmation report.

All MDIs must be primed before the first use. Priming involves releasing a certain number of sprays (4) into the air before the first use of the inhaler. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that it's ready to use. Site personnel will prime the inhaler device prior to giving to the subject by gently shaking the inhaler for 5-10 seconds and then spraying once into the air away from themself and others. After approximately 30 seconds, the process should be repeated three more times.

The MDI must be primed in a separate room from the subject treatment area. Since the MDI is primed in a separate room before dosing, there is a possibility that there may be a delay between priming and dosing, and therefore to ensure consistency in the administration for all subjects, the MDIs are to be gently shaken (5-10 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 twice daily, 2 puffs in the morning and 2 puffs in the evening approximately 12 hours apart, until the subject returns to the clinic. Refer to Appendix 3 for instructions on the administration of BD and Placebo MDIs.

Pulmicort Flexhaler (budesonide inhalation powder 180 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 during screening and Washout Periods.

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 DPIs 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 during Screening and Washout Periods. 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.

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 this 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 placed in a plastic bag (Ziploc® or similar type bag) and labeled with the subject number. Used subject supplies will be kept at room temperature in a secure and locked cabinet until returned to Pearl Therapeutics or designee.

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

7 STUDY PROCEDURES

It is recommended that whenever possible, all assessments during Visits 3 through 14 be conducted in the following order: vital signs, ECGs, clinical laboratory assessments, and spirometry.

7.1 Efficacy Assessments

7.1.1 Pulmonary Function Tests

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

At each visit, spirometry will be conducted 60 minutes and 30 minutes prior to Ventolin HFA, Pulmicort Flexhaler, or randomized study drug administration. The average of these two assessments will be used to calculate the baseline and pre-dose values for each parameter.

At Visits 3, 6, 9, and 12 (Day 1 of each treatment period) subjects must meet the Baseline Stability Criteria (see Section 5.1) prior to dosing in order to continue in the study.

Refer to Section 5.1 and Section 5.2 for specific spirometry inclusion/exclusion criteria that result in discontinuation from the study.

7.1.2 Characterization of Reversibility

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

- Reversibility testing to Ventolin HFA:
- Perform pre-bronchodilator PFTs prior to administration of Ventolin HFA (albuterol). **Note**: A single pre-dose bronchodilator PFT is collected at Visits 1a/1b. Pre-bronchodilator PFTs are collected at -60 min and -30 min at Visit 2.
- 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 at 30 minutes, a repeat post-bronchodilator PFT may be performed at 60 minutes to assess reversibility.
- Subjects who do not meet reversibility criteria at Visit 1a may, at the discretion of the investigator, be retested for reversibility at Visit 1b. Subjects who fail to meet reversibility criteria at Visit 1b will be screen failed. Subjects who do not meet reversibility criteria at Visit 2 following at least 14 days on Pulmicort Flexhaler will be screen failed.

7.1.3 FEV_1 Baseline Stability Criteria

Baseline stability criteria are as follows:

- At Visit 3, 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 2 (see Section 5.1 for baseline FEV_1 stability inclusion criterion). At Visit 3, 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 two assessments meet the baseline stability requirements (ie., within ± 20%), the initial 60 minute pre-dose assessment will not be used and the last two assessments will be used to establish the eligibility criteria. Subjects who do not meet the FEV_1 baseline stability criteria at Visit 3 must be screen failed.
- At Visits 6, 9, and 12, 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 two assessments meet the baseline stability requirements (ie., within ±20%), the initial 60 minute pre-dose assessment will not be used and the last two assessments will be used to establish the eligibility criteria.
- Subjects must meet the FEV_1 baseline stability criteria to be eligible for dosing at Visits 6, 9 and 12. Subjects who do not meet the FEV_1 baseline stability criteria at Visits 6, 9 and 12 must be rescheduled as soon as is practical but within the protocol-specified washout window (14–21 days between Treatment Periods). Subjects who fail to meet stability criteria after 2 attempts within a Washout Period will be discontinued.

7.1.4 Rescue Criteria for Randomized Subjects

Rescue criteria will be evaluated on Visits 4, 7, 10, and 13 (Day 15 of each Treatment Period), and during any unscheduled visits occurring during any Treatment Period. Subjects meeting rescue criteria will be advanced to the Washout Period and given treatment with Pulmicort Flexhaler 180 µg BID.

The Rescue Criteria are met if the average of the -60 min and -30 min FEV_1 are > 30% below 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 > 30% below the average of Visit 3 baseline FEV_1, but if the -30 min assessment is within 30%, then another assessment may be conducted 30 minutes later (at the Investigator's discretion). If the last two assessments meet the rescue criteria requirements (ie., within ± 30%), the initial 60 minute pre-dose assessment will not be used and the last two assessments will be used to establish the eligibility criteria.

In lieu of FEV_1 criteria, if a Rescue Period is required based on worsening of asthma symptoms (eg., cough, wheeze, nighttime awakenings, increased SABA use, etc.), and in the opinion of the Investigator, the subject may to be transitioned to a Washout Period. The Investigator should make every effort to collect trough PFTs prior to transitioning the subject to a Washout Period.

If a subject is advanced to a Washout Period and that period is completed, subjects may continue in the study to the next Treatment Period provided the Baseline Stability Criteria are met (see Section 5.1).

If the Rescue Criteria are met during the fourth and final Treatment Period, then the procedures for discontinuation should be followed and the subject will be considered to have successfully completed the treatment portion of the study.

Refer to Section 8.9 for instructions on handling subjects who meet Rescue Criteria.

7.1.5 Standardization of Spirometry Collections

All pulmonary function tests, including FEV_1, FVC, PEFR and $FEF_{25–75\%}$ 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 at the Investigator meetings. All technicians will be required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable pulmonary function tests (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 ([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, 4-6 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 2).

7.1.6 Subject eDiary Data Collection

Subjects will be provided with an eDiary to be completed twice daily to record time of study medication administration and Pulmicort Flexhaler, morning and evening asthma symptoms, the use of study medication, Pulmicort Flexhaler and rescue albuterol (Ventolin HFA), and 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 electronic diary and training the subject on the proper use of the eDiary.

Subjects will be issued and trained on an eDiary at Screening Visit (Visit 1a or 1b) and instructed to collect eDiary data during the Screening Period (between Visit 1 to Visit 3).

Site personnel will review the eDiary during the Screening Period to assess the subject's compliance and understanding of how to use the eDiary to maintain a daily record of their time of dosing for Pulmicort Flexhaler, rescue medication use, morning and evening asthma symptoms and collection of daily peak flow rates using a Sponsor-provided portable peak flow meter.

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

At Visits 3, 6, 9, and 12 (Day 1 of each Treatment Period), subjects will receive an eDiary in which they will be asked to maintain twice-daily eDiary records (AM and PM) until the end of the Treatment Period.

Electronic Diary data will be collected during the Washout Periods (between Visits 5 and 6, Visits 8 and 9, and Visits 11 and 12).

Note: At all treatment visits (Visits 3-14), subjects will record pre-dose and 30 minute post-dose home peak flow values and the time of study medication dosing in their eDiary while in the clinic.

At Visits 3, 4, 5, 7, 8, 10, 11, 13 and 14, site personnel must review eDiary data prior to dosing study medication in the clinic (see Table 9).

The eDiary data report will be available to site personnel through the vendor's server. The eDiary data report 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. The subject should be reinstructed, as appropriate, on the importance of recording twice daily entries if missing entries are observed. If the subject demonstrates persistent eDiary compliance issues the subject should be evaluated, at the Investigator's discretion, for further study continuation.

7.1.7 Rescue Ventolin HFA Use

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

7.1.8 Home Peak Expiratory Flow Rate

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

Subjects will be issued and trained on peak flow meter use at Screening Visit (Visit 1a *or* 1b) and instructed to collect peak flow meter data during the Screening Period (between Visit 1 to Visit 3).

At Visits 3, 6, 9, and 12 (Day 1 of each Treatment period), subjects will be given a peak flow meter and be asked to record peak flow readings in their eDiary until the end of the Treatment Period.

Peak flow meter data will be collected during the Washout Periods (between Visits 5 and 6, Visits 8 and 9, and Visits 11 and 12).

The peak flow meter will be used by all subjects for home measurements of pre- and post-dose morning and evening assessments. At each study visit, the Investigator will review the PEFR readings and any findings will be discussed with the subject and clinical relevance determined. Subjects will bring their peak flow meter to the clinic at each visit.

At each treatment visit (Visits 3-14) subjects will measure, in clinic, PEFR immediately before and 30 minutes after dosing with study medication and must record pre and post peak flow values and time of dosing in their eDiary.

Note: The in-clinic 30 minute post-dose PEFR at each treatment visit (Visits 3 – 14) should be obtained after spirometry assessments allowing enough time for the subject to recover from the pulmonary function test maneuvers. The subject will be instructed to forcefully exhale from total lung capacity 3 times into the peak flow meter and confirm the collection of PEFR measurements on the eDiary. These PEFR measurements will be performed from Day 1 to Day 29 of each Treatment Period at home and on in-clinic days.

Subjects will perform PEFR measurements at home in the morning and in the evening immediately before and 30 minutes after dosing during the screening and Treatment Periods.

7.1.9 Medication Compliance

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

7.1.10 Asthma Control Questionnaire (ACQ)

The Asthma Control Questionnaire (ACQ) will be completed at Visits 3 through 14 before any other study procedures are performed.

The ACQ (Juniper, 1999) was developed and validated to measure asthma control in adults (see Appendix 6). It is 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).

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 Asthma Control Questionnaire (ACQ) (Juniper, 1999) was developed 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.

Subjects who do not meet an ACQ minimum score of ≥1.5 at Visit 3 will be screen failed. (see Section 5.1)

7.2 Safety Assessments

The safety assessments include ECGs, vital sign measurements, clinical laboratory tests, monitoring for paradoxical bronchospasm, physical examination findings, AEs and SAEs during the study period.

7.2.1 Medical/Surgical History and Physical Examination

Medical history will be collected at Screening and updated during Visits 1a to Visit 3 (Screening Period). A complete physical examination will be performed at Visit 1a (Screening) and Visit 14 or at the Premature Discontinuation Visit (Early Termination Visit).

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 14. Height will be recorded at Visit 1a (Screening) only.

Note: At Visit 1a, obtain a chest x-ray *only* if the subject has not had a chest x-ray or computed tomography (CT) scan of the chest/lungs within the last 6 months.

7.2.2 Vital Sign Measurements

At all visits (including the Premature Discontinuation Visit), hear rate, systolic and diastolic blood pressure (SBP/DBP) will be assessed. Assessments of HR and BP will be obtained after the subject is supine or seated for 5 – 10 minutes. If, in the opinion of the Investigator, a clinically significant vital sign change occurs, then the measurement should be repeated at medically appropriate intervals until the value returns to within an acceptable range**.**

A single set of vital signs will be obtained at Visits 1a (Screening) and Premature Discontinuation Visit (see Section 8.10).

At Visit 3 to Visit 14, vital signs will be obtained pre-dose within 1 hour of in-clinic dosing and at 30 minutes post-dose. Temperature will be obtained only at pre-dose at all visits and will not be repeated at subsequent time points unless clinically indicated (see Table 9).

Refer to Section 5.2 for specific vital signs exclusion criteria.

7.2.3 12-Lead Electrocardiogram (ECG)

A 12-lead ECG will be obtained at Visit 1a (Screening). At Visits 3, 5, 6, 8, 9, 11, 12, 14 (Day 1 and Day 29 of each Treatment Period), an ECG recording will be obtained pre-dose within 1 hour of in-clinic dosing (see Table 9). 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 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 site phone training sessions. 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 [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: HR, RR interval, PR interval, QRS axis, QRS interval, and QT/QTcF (Fridericia's Formula) interval.

QT intervals and calculated QTcF (Fridericia's Formula) 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. Refer to Section 5.2 for specific QTcF criteria that will prompt the Investigator to exclude subjects from the study. If QTcF interval prolongation exceeds the permissible limits for inclusion in the study, and is verified during treatment, the subject's medical background should be examined closely for risk factors that may have contributed to the event, including genotyping for hereditary long QT syndromes, if appropriate.

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, and prior to dosing at Visits 3, 5, 8, 11, and 14 (see Table 9)

Serum pregnancy testing will be performed in women of child-bearing potential.at Visit 1a (Screening), Visit 14, and, as appropriate, at the Premature Discontinuation Visit. Urine hCG testing will occur at Visits 3, 6, 9 and 12.

See Section 5.2 for specific criteria for clinical chemistry exclusion criteria.

The following clinical laboratory parameters that will be assessed are noted in Table 8.

Table 8. Clinical Laboratory Measures

Hematology	
Hemoglobin	Mean corpuscular hemoglobin (MCH)
Hematocrit	Mean corpuscular hemoglobin concentration (MCHC)
White Blood Cell count with differential	Mean corpuscular volume (MCV)
Red Blood Cell count	
Platelet Count	
Clinical Blood Chemistry	**Other Clinical Blood Chemistry**
Liver Function Tests	Albumin
Alanine aminotransferase (ALT)	Blood urea nitrogen (BUN)[a]
Aspartate aminotransferase (AST)	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 Final Visit only and Urine HCG at appropriate visits for this study as detailed in Table 9.
Creatinine clearance will be estimated by the CKD-EPI published formula. Parameters included in the Basic Metabolic Panel (BMP).

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 case report form and on the AE Reporting Form. If the AE is "alarming", the Investigator must report the AE immediately to Pearl Therapeutics. In addition, certain AEs (as described in Section 7.2.6.2) are classified as "serious" and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as a serious adverse event to Pearl Therapeutics or its designee.

In the case of serious adverse events, after discussing the details of the AE, 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 adverse event (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 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 a serious AE (SAE) as defined in Section 7.2.6.2.

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 adverse event to the study drug administration will be assessed by the Investigator after careful consideration, and according to the following guidelines:

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

7.2.6.6 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 [BUN] and creatinine in the setting of an adverse event of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). In such cases, the laboratory abnormality itself (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 (eg., < *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 adverse event
- 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 patient or 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 adverse event 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 a serious adverse event. At a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report using the appropriate form (eg., SAE Report Form). After the initial report, as necessary, the Investigator must provide any additional information on a SAE to the Medical Monitor within two working days after he/she receives that information. This follow-up information will be a detailed written report that will include copies of hospital records, case reports, and autopsy reports, and other pertinent documents.

Post-study SAEs following the last dose of study drug must be reported to Pearl Therapeutics as described in Section 7.2.6.10.

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

7.2.6.9 Supplemental Investigations of SAEs

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

7.2.6.10 Post-Study Follow-Up of Adverse Events

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

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

7.2.6.11 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 following the last dose of study drug, it must be reported to Pearl Therapeutics, whether or not the event is attributable to study drug. All SAEs must be reported to Pearl Therapeutics no later than 24 hours after the Investigator recognizes/classifies the event as a serious adverse event.

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 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 AEs of Interest

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 PEFR of $\geq$30% from the pre-dose value, with associated asthma symptoms of wheezing, shortness of breath and/or cough. All AEs and SAEs will be recorded as appropriate.

7.2.8 Overdose

An overdose is defined as a dose greater than the high 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, adverse events, 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 notice in advance by the Investigator for any reason as per the terms of the contract with Pearl Therapeutics. The reason should be communicated in writing to Pearl Therapeutics.

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

8 STUDY ACTIVITIES

Detailed schedules for pre- and post-dose procedures to be performed on each study visit are provided (see Table 9).

Table 9. Schedule of Events

Procedures	Screening[a]			Treatment Period 1[a]			Treatment Period 2[a]			Treatment Period 3[a]			Treatment Period 4[a]			Phone Follow-Up
	Visit 1a	Visit 1b (as needed)	Visit 2	Visit 3 Rand. TP 1 Day 1	Visit 4 TP 1 Day 15	Visit 5 TP1 Day 29	Visit 6 TP 2 Day 1	Visit 7 TP 2 Day 15	Visit 8 TP 2 Day 29	Visit 9 TP 3 Day 1	Visit 10 TP 3 Day 15	Visit 11 TP 3 Day 29	Visit 12 TP 4 Day 1	Visit 13 TP 4 Day 15	Visit 14 TP 4 Day 29 or final visit[q]	Telephone Follow-up
Treatment Day[a]	**Up to -28**	**Up to -27**	**-14 to -1**	**1[a]**	**15±2 [a]**	**29±2 [a]**	**1[a]**	**15±2 [a]**	**29±2 [a]**	**1[a]**	**15±2 [a]**	**29±2 [a]**	**1[a]**	**15±2 [a]**	**29±2 [a]**	**7-14 [a]**
Informed Consent	X															
Eligibility Criteria	X	X	X	X												
Verify Cont. Eligibility					X	X	X	X	X	X	X	X	X	X	X	
Ventolin HFA Reversibility[b]	X	X	X													
Demographics, Medical, Surgical History	X	X	X	X												
Switch to Pulmicort Flexhaler 180 µg BID[c]	X					X			X			X				
ACQ[d]				X	X	X	X	X	X	X	X	X	X	X	X	

ACQ=asthma control questionnaire; BID=twice-daily; ECG=electrocardiogram; PEFR= peak expiratory flow rate; TP=Treatment Period

Note: At Visit 1a, obtain a chest x-ray *only* if the subject has not had a chest x-ray or computed tomography (CT) scan of the chest/lungs within the last 6 months.

[a] Visit windows during each Treatment Period are relative to Day 1 of that Treatment Period. Washout Periods occurring between Visits 5 and 6, Visits 8 and 9, and Visits 11 and 12 are 14-21 days. If Visit 5, 8 or 11 occurs at Day 31 or later, the site must contact Sponsor for guidance prior to initiating next treatment period. Visit 1b must occur before Visit 2

[b] See instructions for reversibility assessment in Section 7.1.2

[c] At Screening, stop prohibited asthma medications and change asthma medications as specified in Section 5.4 (ie., Sponsor-provided Pulmicort Flexhaler and Ventolin HFA)

[d] See instructions for administering the ACQ in Section 7.1.10 and Appendix 6

Table 9. Schedule of Events (continued)

Procedures	Screening[a]			Treatment Period 1[a]			Treatment Period 2[a]			Treatment Period 3[a]			Treatment Period 4[a]			Phone Follow-Up
	Visit 1a	Visit 1b (as needed)	Visit 2	Visit 3 Rand. TP 1 Day 1	Visit 4 TP 1 Day 15	Visit 5 TP1 Day 29	Visit 6 TP 2 Day 1	Visit 7 TP 2 Day 15	Visit 8 TP 2 Day 29	Visit 9 TP 3 Day 1	Visit 10 TP 3 Day 15	Visit 11 TP 3 Day 29	Visit 12 TP 4 Day 1	Visit 13 TP 4 Day 15	Visit 14 TP 4 Day 29 or final visit[q]	Telephone Follow-up
Prior Concomitant Medications[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Spirometry[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination[g]	X														X	
Vital Signs[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[i]	X			X		X	X		X	X		X	X		X	
Pregnancy Test[j]	X			X			X			X			X		X	
Clinical Laboratory Testing[k]	X			X		X			X			X			X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inhalation Device Training[l]	X			X			X			X			X			
Study Drug Administration[l]				X	X	X	X	X	X	X	X	X	X	X	X	

[e] See listing of prohibited and concomitant medication in Section 5.4. At all visits beyond Screening, note time of last dose of short-acting bronchodilator and other asthma medications (if <4 hours, visit should be rescheduled).

[f] See Section 7.1.1 and Section 7.1.3 for guidance related to Spirometry assessments and criteria.

[g] Weight, assessed in ordinary indoor clothing with shoes removed at Visit 1a (Screening) and Visit 14. Height will be recorded at Visit 1a (Screening) only. (See Section 7.2.1).

[h] See Section 7.2.2 for guidance on vital signs collection.

[i] See Section 7.2.3 for guidance on ECG assessment

[j] See Section 7.2.5 for guidance on the administration of pregnancy test (women of child- bearing potential only).

[k] See Section 7.2.5 for guidance on clinical laboratory testing.

[l] At the start of each treatment visit, subject must withhold all asthma medications, including study medication and rescue medications (Ventolin HFA) for at least 4 hours prior to start of test day procedures. If appropriate, re-train subject on use of inhalation device.

Table 9. Schedule of Events (continued)

Procedures	Screening[a]			Treatment Period 1a			Treatment Period 2a			Treatment Period 3a			Treatment Period 4a			Phone Follow-Up
	Visit 1a	Visit 1b (as needed)	Visit 2	Visit 3 Rand. TP 1 Day 1	Visit 4 TP 1 Day 15	Visit 5 TP1 Day 29	Visit 6 TP 2 Day 1	Visit 7 TP 2 Day 15	Visit 8 TP 2 Day 29	Visit 9 TP 3 Day 1	Visit 10 TP 3 Day 15	Visit 11 TP 3 Day 29	Visit 12 TP 4 Day 1	Visit 13 TP 4 Day 15	Visit 14 TP 4 Day 29 or final visit[q]	Telephone Follow-up
Dispense Peak Flow Meter[m]	X	X														
Dispense Subject Diary[m]	X	X														
Collect PEFR in Clinic[n]				X	X	X	X	X	X	X	X	X	X	X	X	
Review Subject Diary[m]			X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Dispensing/ Collection	X			X	X	X	X	X	X	X	X	X	X	X	X	
Paradoxical Bronchospasm[o]				X	X	X	X	X	X	X	X	X	X	X	X	
Return to Maintenance Asthma Medications[p]															X	

ACQ=asthma control questionnaire; BID=twice-daily; ECG=electrocardiogram; PEFR= peak expiratory flow rate; TP=Treatment Period

[m] See Section 7.1.6 for guidance on the eDiary use, and Section 7.1.8 for guidance on peak flow meter use.

[n] See Section 7.1.8 for further information on the collection of PEFR.

[o] See Section 7.2.7 for definition of paradoxical bronchospasm.

[p] At the end of the Visit 14, return subject to pre-study or other appropriate inhaled maintenance asthma medications.

[q] If a subject discontinues the study prematurely (early termination), the procedures that should be completed at the final visit are defined in Section 8.10

8.1 Screening Visit (Visits 1a, 1b)

- Obtain informed consent.
- Register subject in IWRS to obtain subject screening number.
- Obtain demographic data, including age, race, smoking history, medical/surgical history, and asthma medication history.
- Verify that subject meets inclusion/exclusion criteria.
- Obtain medication history, including asthma medications.
- Conduct a serum pregnancy test (β (beta)-human chorionic gonadotropin [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 (HR and BP after being supine or seated for 5 – 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's ability to use MDI correctly (provide coaching as needed).
  - Repeat spirometry assessments 30 minutes following 4 puffs Ventolin HFA
  - Confirm subject is reversible (see Section 7.1.2 for Reversibility Criteria)
- Obtain clinical laboratory samples (hematology and chemistry).
- At Visit 1a, obtain a chest x-ray *only* if the subject has not had a chest x-ray or computed tomography (CT) scan of the chest/lungs within the last 6 months.
- Schedule next visit:
  - Visit 1b at Investigator discretion for subjects who fail reversibility criteria at Visit 1a (at least 1 day prior to Visit 2).
  - Visit 2 for subjects who meet eligibility criteria to continue, at least 14 days but no more than 27 days from Visit 1a.
- Stop prohibited asthma medications and change concurrent asthma medications as specified in the protocol (see Section 5.4).
- Subjects who meet entry criteria will have their inhaled asthma medication switched to Pulmicort Flexhaler 180 µg BID and Ventolin HFA for rescue medication.
- 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 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 adverse event unless the event meets the definition of an SAE (see Section 7.2.6.2).

8.2 Visit 1b (At Investigator Discretion)

- Assess continued eligibility criteria
- Record concomitant medications
- Repeat spirometry assessment and reversibility to Ventolin HFA (Section 5.1 and Section 7.1.2.
- Record any AEs that have occurred
- Schedule Visit 2 for subjects who meet eligibility criteria to continue, at least 14 days but no more than 27 days from Visit 1a.

8.3 Visit 2 (Reversibility Testing Following Pulmicort Flexhaler Run-in)

- Review subject eDiary and retrain subject if subject has not met eDiary compliance requirement (see Section 5.2).
- Determine time of last SABA use (if < 4 hours, Visit 2 should be delayed or rescheduled).
- Review inclusion/exclusion criteria and confirm subject eligibility to continue.
- If not previously reviewed, review clinical laboratory testing results from Visit 1a and record any clinically significant findings.
- Record AEs, if any.
- Review all prior medications and adherence to asthma regimen,
- Obtain pre-bronchodilator vital signs.
- Perform reversibility testing to Ventolin HFA (see Section 5.1 and Section 7.1.2).
- Schedule Visit 3 (Randomization Visit) for subjects who meet eligibility criteria to continue. **Note**: Visit 3 can be scheduled at minimum, 1 day after Visit 2, and no later than 28 days after Visit 1a (Screening).

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

- Review subject eDiary and peak flow values. Screen fail subject if subject has not met eDiary compliance requirement (see Section 5.2).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the CRF (if <4 hours, Visit 3 must be rescheduled).
- Assess ACQ (see Appendix 6)
- Record AEs, (if any).
- Review concomitant medications to ensure adherence to study specified regimen.
- Collect Sponsor-provided Pulmicort Flexhaler and Ventolin HFA dispensed during the Screening Period.
- Complete all pre-dose assessments, including vital signs, ECGs, clinical laboratory testing, urine pregnancy testing and spirometry.
- Review inclusion/exclusion criteria, including baseline stability criteria (see Section 5.1) and confirm subject eligibility for Randomization

- Have subjects perform pre-dose eDiary collections including completion of symptom questions and pre-dose PEFR assessments.
- Obtain subject randomization number and 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 15–30 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 first dose of newly assigned study drug at the clinic.
  - The subject is to be considered randomized as soon as the site personnel have received the subject treatment assignment from the IWRS.
- Have subject perform post-dose eDiary collections including PEFR at 30 minutes post-dosing.
- Perform vital signs at 30 minutes post-dosing and assess subject for paradoxical bronchospasm.
- Subjects will be instructed to bring the eDiary, peak flow meter and all study medication to the next visit.
- Schedule Visit 4 within 14 ± 2days, and ensure subject has adequate supply of study drug and rescue Ventolin HFA.

8.5 Visits 6, 9, 12 (Day 1 of Treatment Periods 2, 3 and 4)

- Review subject eDiary and peak flow values, and retrain subject if subject has not met eDiary compliance requirement (see Section 5.2).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the CRF (if <4 hours, the visit must be rescheduled).
- Assess ACQ.
- Record AEs, (if any).
- Review concomitant medications to ensure adherence to study specified regimen.
- Collect Sponsor-provided Pulmicort Flexhaler and Ventolin HFA dispensed for use during the Washout Period.
- Complete all pre-dose assessments, including vital signs, ECGs, urine pregnancy testing, spirometry (60 and 30 minutes prior to dosing).
- Confirm subject eligibility to continue, including baseline stability criteria (see Section 5.1).
- 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 15–30 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 first dose of newly assigned study drug at the clinic.
- Subject record dosing time in the eDiary.
- Have subject perform post-dose eDiary collections including PEFR at 30 minutes post-dosing.
- Perform vital signs at 30 minutes post-dosing and assess subject for paradoxical bronchospasm.
- Subjects will be instructed to bring the eDiary, peak flow meter and all study medication to the next visit.
- 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.

8.6 Visit 4, 7, 10 and 13 (Day 15 of Treatment Periods 1, 2, 3 and 4)

- Review subject eDiary and peak flow values, and retrain subject if subject has not met eDiary compliance requirement (see Section 5.2).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the CRF (if <4 hours, the visit must be rescheduled).
- Assess ACQ.
- Record AEs, (if any).
- Review concomitant medications to ensure adherence to study specified regimen.
- Collect blinded study drug dispensed during the prior visit (Day 1 of the Treatment Period).
- Complete all pre-dose assessments, including vital signs and spirometry (60 and 30 minutes prior to dosing).
- Review subject eligibility to continue.
- 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 15–30 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 first dose of newly assigned study drug at the clinic.
- Record dosing time in the eDiary.
- Have subject perform post-dose eDiary collections including PEFR at 30 minutes post-dosing.
- Perform vital signs at 30 minutes post-dosing and assess subject for paradoxical bronchospasm.
- Obtain new MDI and assignment information from IWRS.

- Subjects will be instructed to bring the eDiary, peak flow meter and all study medication to the next visit.
- Schedule the next visit (Day 29 of the Treatment Period) within 29 ± 2 days from Day 1 of the Treatment Period, and ensure subject has adequate supply of study drug and rescue Ventolin HFA.

8.7 Visit 5, 8 and 11 (Day 29 of Treatment Period 1, 2 and 3)

- Review subject eDiary and peak flow values, and retrain subject if subject has not met eDiary compliance requirement (see Section 5.2).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the CRF (if <4 hours, the visit must be rescheduled).
- Assess ACQ.
- Record AEs, (if any).
- Review concomitant medications to ensure adherence to study specified regimen.
- Collect Sponsor-provided study medication including Ventolin HFA dispensed during the prior visit (Day 15 of the Treatment Period).
- Complete all pre-dose assessments, including vital signs, ECGs, clinical laboratory testing, and spirometry (60 and 30 minutes prior to dosing).
- Review subject eligibility to continue.
- Have subjects perform pre-dose eDiary collections including completion of symptom questions and pre-dose PEFR assessments.
- Subject will administer in-clinic dosing from MDI dispensed at previous visit (Day 15 of Treatment Period).
- Record dosing time in the eDiary.
- Have subject perform post-dose eDiary collections including PEFR at 30 minutes post-dosing.
- Perform vital signs at 30 minutes post-dosing and assess subject for paradoxical bronchospasm (see Section 7.2.7).
- Obtain from IWRS the Pulmicort Flexhaler 180 µg and Ventolin HFA assignment for use during the Washout Period. Subjects will be instructed to bring the Pulmicort Flexhaler and Ventolin HFA to the next visit, and continue to complete their PEFRs and their eDiary at home during the Washout Period.
- Schedule the next visit (Day 1 of the Treatment Period) within 14–21 days from Day 29 of the previous Treatment Period.

8.8 Visit 14 (Final Study Visit, Day 29 of Treatment Period 4)

- Review subject eDiary and peak flow values (see Section 5.2).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the CRF (if <4 hours, the visit must be rescheduled).
- Assess ACQ.
- Record AEs, (if any).

- Review concomitant medications to ensure adherence to study specified regimen.
- Collect Sponsor-provided study medication including Ventolin HFA dispensed during the prior visit (Day 15 of Treatment Period 4).
- Complete all pre-dose assessments, including vital signs (including weight), physical examination, ECGs, clinical laboratory testing, serum pregnancy testing, and spirometry (60 and 30 minutes prior to dosing).
- Review subject eligibility to continue.
- Have subjects perform pre-dose eDiary collections including completion of symptom questions and pre-dose PEFR assessments.
- Subject will administer in-clinic dosing from MDI dispensed at previous visit (Day 15 of Treatment Period).
- Record dosing time in the eDiary.
- Have subject perform post-dose eDiary collections including PEFR at 30 minutes post-dosing.
- Perform vital signs at 30 minutes post-dosing and assess subject for paradoxical bronchospasm (see Section 7.2.7).
- Collect subject eDiary and peak flow meter.
- Return the subject to pre-study or appropriate asthma maintenance medication.
- Schedule a follow-up telephone call 7–14 days from Visit 14.

8.9 Management of Randomized Subjects Who Meet Rescue Criteria

- If rescue criteria are met at a scheduled visit during Treatment Periods 1, 2 and 3 (see Section 7.1.4), the Investigator at their discretion, may complete the remaining scheduled visit procedures (ie., clinical laboratory testing, vital signs, etc.) and transition the subject to rescue period as follows:
  - Obtain from IWRS the Pulmicort Flexhaler 180 µg and Ventolin HFA assignment for use during the Rescue Period. Subjects will be instructed to bring the Pulmicort Flexhaler and Ventolin HFA to the next visit, and continue to complete their PEFRs and their eDiary at home during the Washout Period.
  - Schedule the next visit (Day 1 of the next Treatment Period) within 14–21 days from the day the Washout Period was initiated.
  - After the Washout Period, subjects may continue in the study to the next Treatment Period provided the Baseline Stability Criteria are met (see Section 5.1).
- Except during Treatment Period 4, if an unscheduled visit is required to manage worsening of asthma symptoms, and in the opinion of the Investigator, the subject may be transitioned to the Washout Period, the procedures outlined in Section 8.8 (Day 29) may be conducted at the Investigator's discretion during the unscheduled visit, prior to Washout Period transition described below.
  - Obtain from IWRS the Pulmicort Flexhaler 180 µg and Ventolin HFA assignment for use during the Rescue Period. Subjects will be instructed to bring the Pulmicort Flexhaler and Ventolin HFA to the next visit, and continue to complete their PEFRs and their eDiary at home during the Washout Period.

- Schedule the next visit (Day 1 of the next Treatment Period) within 14–21 days from day the Washout Period was initiated.
- After the Washout Period, subjects may continue in the study to the next Treatment Period provided the Baseline Stability Criteria are met (see Section 5.1).

- If the Rescue is required during the fourth and final Treatment Period, then the procedures for discontinuation should be followed and the subject will be considered to have successfully completed the treatment portion of the study.

8.10 Unscheduled Visits/Premature Discontinuation (Early Termination) Visits

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

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

The following minimum procedures should be completed 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 subject discontinuation reason.
- Schedule a follow-up telephone call 7-14 days post last study drug dosing. If the discontinuation visit is performed >7 days post last study drug dosing a follow-up telephone call will not be required.

8.11 Follow-Up Telephone Call

Subjects will be followed-up through a telephone call 14 days post 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

8.12 Completion of the Study

The Investigator will document the completion or the reason for early withdrawal by a subject 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 did 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 4-period, 5-treatment, incomplete block cross-over design evaluating the following 5 treatments in approximately 150 subjects:

- BD MDI 320 µg
- BD MDI 160 µg
- BD MDI 80 µg
- BD MDI 40 µg
- Placebo MDI

The primary objective of this study will be to demonstrate a lung function benefit of BD MDI BID compared with Placebo MDI in adult subjects with mild to moderate persistent asthma.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

Baseline will use the average of the -60 and -30 min pre-dose values on Day 1 of each treatment period for clinical measured variables and is defined as the average of the non-missing Day 1 pre-dose means (averages of 60 and 30 minute pre-dose assessments) for each subject. 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

- Change from baseline in morning pre-dose trough FEV_1 at the end of the Treatment Period

9.2.1.2 Secondary Efficacy Endpoints

- Change from baseline in mean morning pre-dose and mean evening pre-dose peak flow rate (PEFR) readings taken by the subject and recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in Asthma Control Questionnaire (ACQ) score at the end of the Treatment Period

9.2.1.3 Other Efficacy Endpoints

- Change from baseline in morning pre-dose trough FEV_1 over the Treatment Period and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in mean morning and evening pre- and post-dose daily PEFR readings taken by subjects and recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Percentage of days without rescue Ventolin HFA use over each week of the Treatment Period and over the entire Treatment Period
- Change from baseline in pre-dose trough forced vital capacity (FVC) at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough PEFR at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough forced expiratory flow 25-75% ($FEF_{25-75\%}$) at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in the number of nighttime awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period, over each week of the Treatment Period, and over the entire Treatment Period
- Percentage of nights with awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period and over the entire Treatment Period

9.2.2 Safety Endpoints

The safety assessments include electrocardiograms (ECGs,) vital sign measurements, clinical laboratory tests, monitoring for paradoxical bronchospasm, physical examination findings, AEs and SAEs during the study period.

9.3 Analysis

9.3.1 Primary Efficacy Analysis

The primary efficacy analysis will compare the changes from baseline at the end of the treatment periods in morning pre-dose trough FEV_1 between BD MDI treatments and Placebo MDI using a repeated measures mixed model with a random subject effect for the correlation across periods. The fixed effects will include baseline FEV_1, response to albuterol, and period. Sequence will also be included if it explains significant variability ($p<0.10$). Estimated treatment differences and 95% CI's will be provided for all treatment comparisons. Multiplicity will be controlled for the BD MDI to Placebo MDI comparison using a sequential approach (Refer to Section 9.5). A two-sided alpha level of 0.05 will be employed.

The primary efficacy analysis will compare the changes from baseline at the end of the treatment periods in morning pre-dose trough FEV_1 between BD MDI treatments and Placebo MDI using a repeated measures mixed model with a random subject effect for the correlation across periods. The fixed effects will include baseline FEV_1, response to albuterol, and period. Sequence will also be included if it explains significant variability ($p<0.10$). Estimated treatment differences and 95% CI's will be provided for all treatment comparisons. Multiplicity will be controlled for the BD MDI to Placebo MDI comparison using a sequential approach (Refer to Section 9.5). A two-sided alpha level of 0.05 will be employed.

The primary analysis will be the modified Intent-to-Treat (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 9.7).

9.3.2 Secondary Efficacy Analysis

The secondary endpoints will be analyzed using a similar model as the primary endpoint. Repeated measures mixed models with a random subject effect for the correlation across periods will be fit. The fixed effects will include the relevant baseline and period as covariates. Sequence will also be included if it explains significant variability ($p<0.10$).

Analyses of morning and evening PEFR and rescue Ventolin HFA usage will use the average of the non-missing 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.

9.3.3 Other Efficacy Analysis

The other efficacy endpoints will be analyzed using a similar model as the primary endpoint. Repeated measures mixed models will be fit with an unstructured covariance for the correlation within subject periods and random subject effect for correlation across periods. The fixed effects will include the relevant baseline, response to albuterol, and period as covariates. Sequence will not be included unless it was found to be important and included in the model for the primary endpoint. For analyses that use more than one measure per period, scheduled Treatment Day or Treatment Week will be added to the model as categorical covariates and their interaction with treatment will be included as well.

Additional comparisons will be made for pre-dose trough FEV_1 values between the Day 15 values and the values at the end of the baseline and Washout Periods in order to compare the efficacy of BD MDI to Pulmicort Flexhaler 180 µg. In order to perform these comparisons, a separate model will be fit where the baseline defined previously in Section 9.2.1 will be considered to represent the effect of Pulmicort. These data will be treated as coming from period 0. The model will therefore not include baseline or period since these would be confounded with Pulmicort treatment.

9.3.4 Safety Analysis

9.3.4.1 Adverse Events

Adverse events during each treatment regime will be summarized by the number of subjects experiencing an event. They will be tabulated at the level of the MedDRA preferred term, and the MedDRA System Organ Class. The version of MedDRA current at the time the first subject is randomized will be used throughout the study. Tabulations will be broken down by severity, seriousness, AE's leading to discontinuation, and by relationship to study drug. No hypothesis tests will be performed. Since the washout period includes treatment with Pulmicort Flexhaler, 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.

9.3.4.2 Paradoxical Bronchospasm

Paradoxical Bronchospasm will be considered an adverse event of special interest, and will be tabulated separately. Bronchospasm will be summarized by the number of subjects experiencing the event, during scheduled assessment periods on a test day and during the particular treatment period. We note that tabulations for bronchospasms differ from those for general adverse events, since the tabulation involves tabulating the incidence of paradoxical bronchospasm with onset during a treatment period. Bronchospasm with onset outside a treatment period will be listed separately. No hypothesis tests will be performed, but an appropriate confidence interval may be provided.

9.3.4.3 Clinical Laboratory Measurements

Summary statistics (mean, median, standard deviation and range) of change from baseline for scheduled pre-dose assessments will be tabulated for each laboratory parameter and treatment. 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.

9.3.4.4 Vital Signs

Summary statistics (mean, median, standard deviation and range) of change from baseline will be tabulated by vital sign parameter and treatment 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.

9.3.4.5 ECGs

Summary statistics (mean, median, standard deviation and range) for absolute values and change from baseline will be tabulated by ECG parameter and treatment 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.

9.4 Randomization

Subjects will be randomly assigned to a treatment sequence using an IWRS. Each sequence will include exactly 4 of the 5 treatments included in this study. All subjects will receive BD MDI 320, BD MDI 160 µg, and Placebo MDI in a randomized order, but only half of the subjects will receive BD MDI 40 or BD MDI 80 µg.

The 8 treatment sequences are shown below where A is Placebo MDI, B is BD MDI 320 µg, C is BD MDI 160 µg, D is BD MDI 80 µg, and E is BD MDI 40 µg:

ABCD

ABCE

BDAC

BEAC

CADB

CAEB

DCBA

ECBA

Randomization will be centralized and center will not be used as a stratification factor.

9.5 Experimental Design and Type I Error Control

The experimental design was chosen to be balanced with respect to period and first order carry-over should all subjects complete. The design was selected to limit exposure to 12 weeks of BD MDI treatment at any dose and to focus on the higher doses.

Type I error will be controlled for the primary endpoint by following a sequential approach. First BD MDI 320 µg will be compared to Placebo MDI using a two-sided alpha of 0.05. If the p-value is <0.05 for the comparison of BD MDI 320 µg to Placebo MDI, then the comparison of BD MDI 160 µg to Placebo MDI will be interpreted inferentially using a two-sided alpha=0.05. If the p-value is <0.05 for the comparison of BD MDI 160 µg to Placebo MDI, then the comparison of BD MDI 80 µg to Placebo MDI will be interpreted inferentially using a two-sided alpha of 0.05. Finally, if the p-value is <0.05 for the comparison of BD MDI 80 µg to Placebo MDI, then the comparison of BD MDI 40 µg to Placebo MDI will be interpreted inferentially using a two-sided alpha of 0.05.

Other than the specification of secondary endpoints, no further adjustments for Type I error will be made.

9.6 Sample Size Consideration

Power calculations are based on the properties of the primary endpoint, morning pre-dose trough $FEV_{1,}$ on the last day of each treatment period (end of treatment). An estimate of the total SD of 405 mL is taken from a 12-week trial comparing budesonide to ciclesonide (Boulet, 2006). Assuming that half of the variability comes from within subject and half between (ie., intrasubject correlation=0.5), an estimate of the within subject standard deviation of 285 mL for morning pre-dose trough FEV_1 is obtained. Using this SD and assuming that 150 randomized provides approximately 120 completers, the power to demonstrate a 120 mL difference from Placebo MDI for BD MDI 320 μg or BD MDI 160 μg is approximately 90%. For BD MDI 80 μg and BD MDI 40 μg, the power to demonstrate a difference from Placebo MDI of 140 mL is approximately 80%.

9.7 Data Validation and Transformation

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

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

9.8 Analysis Plan

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

9.9 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 ITT Population including subjects who received treatment and have post-treatment efficacy data from at least two treatment periods. Data judged to be impacted by major protocol deviations will be determined prior to unblinding and excluded. 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 one 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.

9.10 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] (Version 9.2 or higher). 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 (IRB) or Independent Ethics Committee (IEC) 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 (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR parts 50, 54, 56, and 312).
- Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects) [http://www.wma.net/en/10home/index.html].
- Any additional regulatory requirements.

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

Pearl 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 (i.e. Health Insurance Portability and Accountability Act), rules and regulations.

10.6 Quality Control and Assurance

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

10.7 Data Management

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

10.8 Study Monitoring

In accordance with applicable regulations, GCP, and Pearl Therapeutics procedures, clinical monitors will contact the site prior to 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 principal Investigator or sub-Investigators named on the Form FDA 1572 will need to complete a financial disclosure form prior to study initiation, at any time during the study execution if new information needs to be disclosed, and for 1 year after study completion. Investigators should make the IRB/IEC aware of any financial interests that the Investigator has in the investigational product.

10.11 Investigator's Final Report

Shortly after completion of the Investigator's participation in the study, the Investigator will submit a written report to Pearl 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 principal Investigator is responsible for the accuracy and completeness of all data from their site. Pearl Therapeutics (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.

2. **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 nonclinical 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. **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.

11 REFERENCE LIST

Akinbami L. United States Centers for Disease Control. Asthma Prevalence, Health Care Use and Mortality: United States 2003-2005. http://www.cdc.gov/nchs/products/pubs/pubd/hestats/ashtma03-05/asthma03-05.htm.

Clissold SP, Heel RC. Budesonide. A preliminary review of its pharmacodynamic properties and therapeutic efficacy in asthma and rhinitis. *Drugs.* 1984;28(6):485-518.

GINA, 2012 Global Initiative for Asthma GINA, 2012 . Global Strategy for Asthma Management and Prevention. Updated 2012. http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf

Hochaus G. New developments in corticosteroids. *Proc Am Thorac Soc*. 2004;1(3):269-274.

Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14:902-907.

Miller M, Hankinson J, Brusasco V, et al. American Thoracic Society/European Respiratory Society. ATS/ERS Task Force: Standardization of Lung Function Testing: Number 2 in Series. European Respiratory Journal 2005;26(2):319-338.

National Heart, Lung, and Blood Institute (NHBLI). National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report. 2007.

R Development Core Team.R: A language and environment for statistical computing.2003. A Foundation for Statistical Computing, Vienna, Austria.

United States Food and Drug Administration. FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm

WebMD. Drugs and Medications. Budesonide oral. http://www.webmd.com/drugs/drug-22008-budesonide+oral.aspx

World Health Organization (WHO). Asthma Fact Sheet. November 2013. http://www.who.int/mediacentre/factsheets/fs307/en/index.html

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 eight successive FVC maneuvers performed in a 10-minute period without inspiration from the instrument.

Display

For optimal quality control, both flow–volume and volume–time displays are useful, and test operators should visually inspect the performance of each maneuver for quality assurance before proceeding with another maneuver. This inspection requires tracings to meet the minimum size and resolution requirements set forth in this standard. Displays of flow versus volume provide more detail for the initial portion (first 1 s) of the FVC maneuver. Since this portion of the maneuver, particularly the peak expiratory flow 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 two units of flow per one unit of volume

The time scale should be ≥20 mm-s^{-1}, and larger time scales are preferred (≥30 mm-s^{-1}) when manual measurements are made. When the volume–time plot is used in conjunction with a flow–volume curve (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 three different flow ranges
Time	Quarterly	Mechanical recorder check with stop watch
Software	New versions	Log installation date and perform test using "known" subject

Calibration is the procedure for establishing the relationship between sensor-determined values of flow or volume and the actual flow or volume. A calibration check is different from calibration and is the procedure used to validate that the device is within calibration limits, 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 one volume up to their maximum; this can be done by attempting to empty them with the outlet corked. A dropped or damaged syringe should be considered out of calibration until it is checked.

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

Quality Control for Volume-Measuring Devices

The volume accuracy of the spirometer must be checked at least daily, with a single discharge of a 3-L calibrated syringe. Daily calibration checking is highly recommended so that the onset of a problem can be determined within 1 day and also to help define day-to-day laboratory variability. More frequent checks may be required in special circumstances, such as: 1) during industrial surveys or other studies in which a large number of subject maneuvers are carried out, the equipment's calibration should be checked more frequently than daily; and 2) when the ambient temperature is changing (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 one 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 three times to give a range of flows varying between 0.5 and 12 $L\text{-}s^{-1}$ (with 3-L injection times of 6 s and 0.5 s). The volume at each flow should meet the accuracy requirement of ± 3.5%. For devices using disposable flow sensors, a new sensor from the supply used for patient tests should be tested each day.

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

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 one time period to another. The accuracy of a spirometry system depends on characteristics of the entire system, from the volume or flow transducer and the use of an in-line filter, to the recorder, display or processor. Changes in any aspect of the equipment or errors at any step in the process can affect the accuracy of the results. For example, if the BTPS correction factor is wrong, an accurately measured FVC will be incorrectly reported. Spirometers are not required to measure all of the indices in Table A1-1, but must meet the recommendations for those that are measured. Accuracy and repeatability recommendations apply over the entire volume range of the instrument.

Table A1-3. Range and Accuracy Recommendations Specified for Forced Expiratory Maneuvers

Test	Range/Accuracy (BTPS)	Flow Range ($L\text{-}s^{-1}$)	Time (s)	Resistance and Back Pressure	Test Signal
VC	0.5–8 L, ± 3% of reading or ± 0.050 L, whichever is greater	0-14	30		3-L Calibration syringe
FVC	0.5–8 L, ± 3% of reading or ±0.050 L, whichever is greater	0-14	15	<1.5 cm H_2O L^{-1} s^{-1} (0.15 kPa $L^{-1}s^{-1}$)	24 ATS waveforms, 3-L Cal Syringe
FEV_1	0.5–8 L, ± 3% of reading or ± 0.050 L, whichever is greater	0-14	1	<1.5 cm H_2O L^{-1} s^{-1} (0.15 kPa $L^{-1}s^{-1}$)	24 ATS waveforms
Time Zero	The time point from which all FEV_t measurements are taken.			Back extrapolation	

FEVt: forced expiratory volume in t seconds

BTPS correction

All spirometry values should be reported at BTPS by any method (measuring temperature and barometric pressure) proven effective by the manufacturer. For volume-type spirometers,

the temperature inside the spirometer should be measured for each breathing maneuver. Regardless of the BTPS correction technique used, the ambient temperature must always be recorded with an accuracy of ± 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

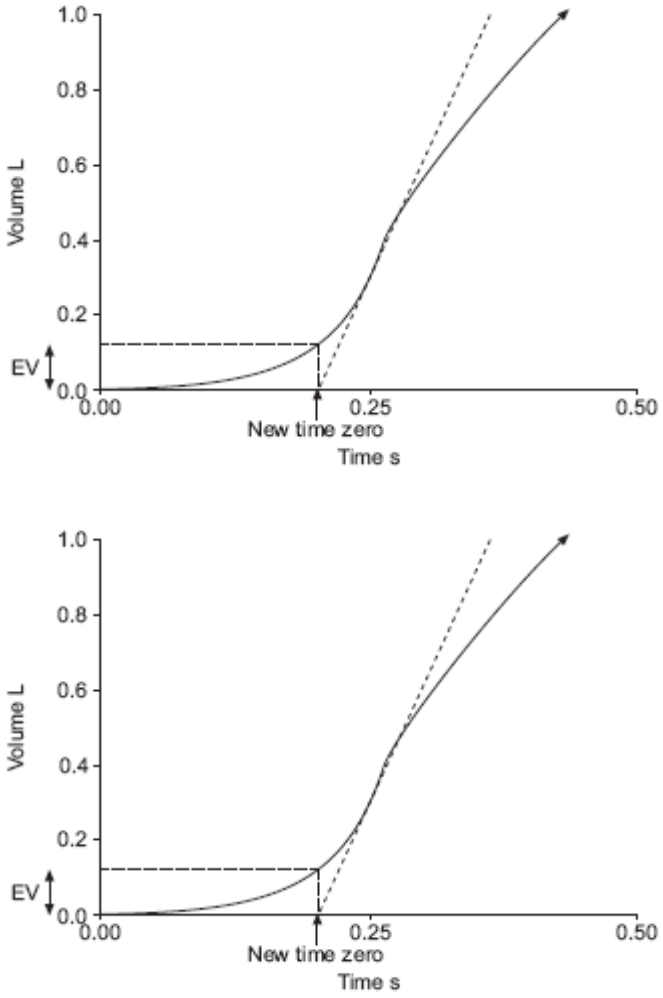
***Acceptable* Tests must meet the following 7 Criteria:**

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 three acceptable spirograms have been obtained, apply the following tests

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

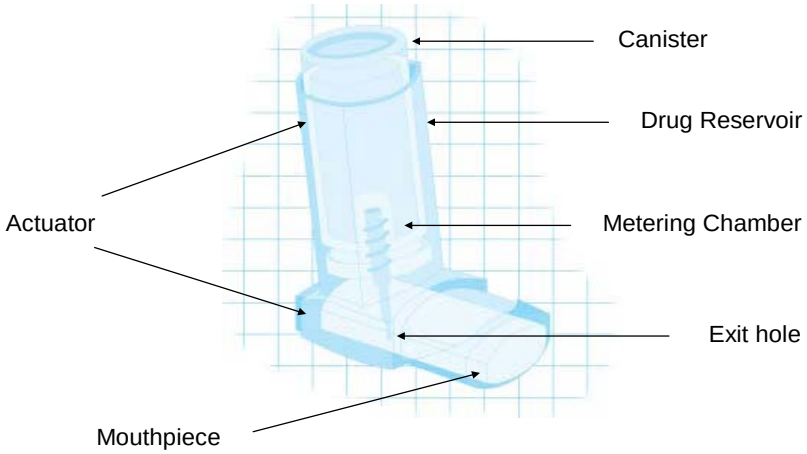
If these criteria are met, the spirometry testing for that time-point may conclude. The highest FEV_1 and the highest FVC obtained at each testing time-point (even if from different reproducible tracings), will be collected.

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 BD 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 three more times.
5. Gently shake the inhaler for 5 to 10 seconds before each spray.
6. Breathe out fully through your mouth, expelling as much air from your lungs as possible. Tilt your head back slightly, place the mouthpiece into your mouth, holding the inhaler with the mouthpiece down, and closing your lips around it. To allow the medication to enter your lungs, keep your tongue flat on the floor of your mouth.
7. While breathing in deeply and slowly through your mouth, fully depress the top of the metal canister with your index finger. Immediately after the spray is delivered, release your finger from the canister. When you have breathed in fully, remove the inhaler from your mouth and close your mouth.
8. Hold your breath as long as possible, up to 10 seconds, and then breathe normally.
9. 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



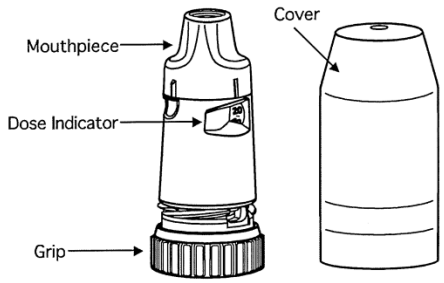
Appendix 4 Instructions for Use of Pulmicort Flexhaler *(budesonide inhalation powder)*

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

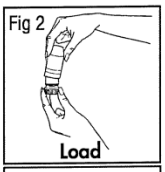


Fig 3

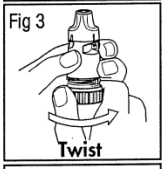


Fig 4

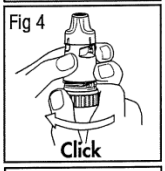
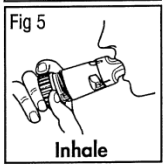


Fig 5



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

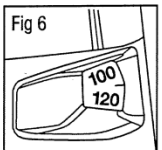
1. Turn your head away from the inhaler and breathe out (exhale). If you accidentally blow into your inhaler after loading a dose, follow the instructions for loading a new dose.
2. Place the mouthpiece in your mouth and close your lips around the mouthpiece. Breathe in (inhale) deeply and forcefully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



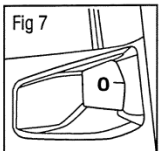
Dose Indicator

- 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

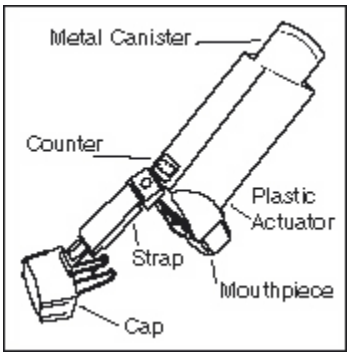

Figure 1

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.

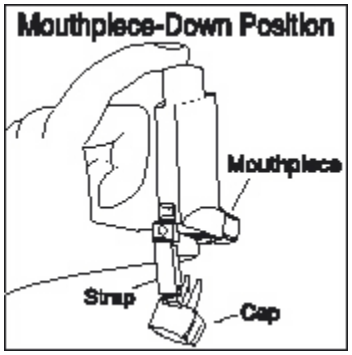

Figure 2

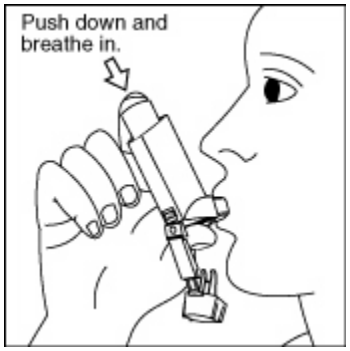

Figure 3

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).

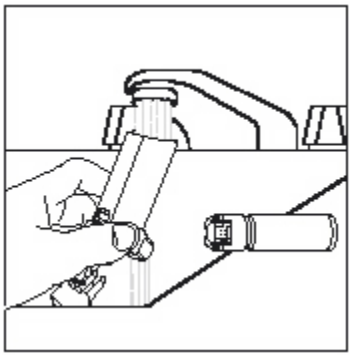

Figure 4

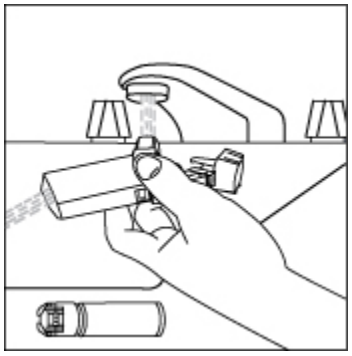

Figure 5

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).

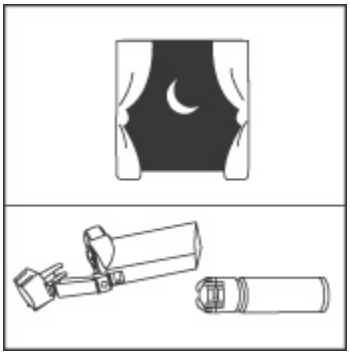

Figure 6

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.

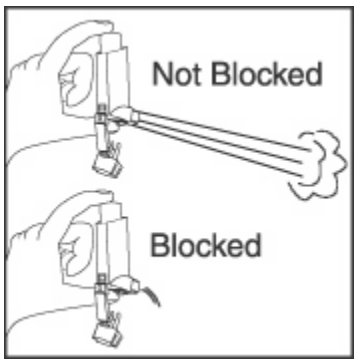

Figure 7

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 Asthma Control Questionnaire

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

ASTHMA CONTROL QUESTIONNAIRE

(SYMPTOMS ONLY)

UK ENGLISH VERSION

[redacted]

For further information:

[redacted]

[redacted]

[redacted]

SYMPTOMS ONLY MODIFIED [redacted]

UK 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 time did you **wheeze?**
   - 0 Never
   - 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]

UK ENGLISH

Appendix 7 Sponsor Signatory

Study Title: A Randomized, Double-Blind, Chronic Dosing (4 weeks), Four-Period, Five-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess the Efficacy and Safety of Four Doses of Budesonide Inhalation Aerosol (BD MDI, PT008) Relative to Placebo MDI in Adult Subjects With Mild to Moderate Persistent Asthma

Study Number: PT008001-01

Final Original Date: [redacted]

Amendment 1 Date: [redacted]

Signature: [redacted] Date: [redacted]

Name: [redacted]

Title: [redacted]

Appendix 8 Investigator's Agreement and Signature Page

Study Title:	A Randomized, Double-Blind, Chronic Dosing (4 weeks), Four-Period, Five-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess the Efficacy and Safety of Four Doses of Budesonide Inhalation Aerosol (BD MDI, PT008) Relative to Placebo MDI in Adult Subjects With Mild to Moderate Persistent Asthma
Study Number:	PT008001-01
Final Amendment 1 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:_____ Date:_____

Name:_____

Affiliation: _____

Clinical Trial Protocol: PT008001-02

Study Title:	A Randomized, Double-Blind, Chronic Dosing (4 weeks), Four-Period, Five-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess the Efficacy and Safety of Four Doses of Budesonide Inhalation Aerosol (BD MDI, PT008) Relative to Placebo MDI in Adult Subjects With Mild to Moderate Persistent Asthma
Study Number:	PT008001-02
Study Phase:	IIb
Product Name:	Budesonide Inhalation Aerosol; PT008
IND Number:	121629
Indication:	Asthma
Investigators:	Multicenter
Sponsor:	Pearl Therapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]

	Version Number	Date
Original Protocol	Version 1.0	[redacted]
Amendment 1	Version 2.0	[redacted]
Amendment 2	Version 3.0	[redacted]

SUMMARY OF CHANGES TO AMENDED PROTOCOL VERSION 2.0, DATED [redacted]

The following changes have been made to PT008001-01 (Version 2.0), and this amended study protocol, PT008001-02 (Version 3.0), includes the following revisions:

- Section 5.1, Inclusion Criteria #5, Pulmonary Function: The FEV_1 criteria was expanded from < 85% to ≤ 90% (Range: FEV_1 ≥60 - ≤90%) of the predicted normal value at Screening (Visit 1a or 1b) and at Visits 2 and 3

    - Rationale for the Change: The upper range of FEV_1% predicted was widened in order to evaluate a broader spectrum of subjects with mild asthma (providing they meet all the inclusion criteria).

- Appendix VI, Asthma Control Questionnaire: The version provided in the protocol is dated [redacted] and is superceded by a more recent version dated [redacted]

- In addition, the opportunity was taken to address other minor protocol inconsistencies and typographical errors, which do not compromise subject safety or the intent of the original design of the study

SYNOPSIS

Pearl Therapeutics, Inc. (Pearl) [redacted]
Names of Finished Products: Budesonide Inhalation Aerosol; PT008
Name of Active Ingredients: Budesonide
Study Title: A Randomized, Double-Blind, Chronic Dosing (4 weeks), Four-Period, Five-Treatment, Incomplete Block, Cross-Over, Multicenter Study to Assess the Efficacy and Safety of Four Doses of Budesonide Inhalation Aerosol (BD MDI, PT008) Relative to Placebo MDI in Adult Subjects With Mild to Moderate Persistent Asthma
Study Number: PT008001-02
Study Phase: IIb
Study Objective(s): **Primary Objective:** To demonstrate a lung function benefit of BD MDI compared with Placebo MDI in adult subjects with mild to moderate persistent asthma. **Secondary Objective:** To characterize the dose response of BD MDI based on lung function in adult subjects with mild to moderate persistent asthma.
Safety Objective: To evaluate the safety and tolerability of BD MDI across all doses evaluated in the study.
Study Design: This is a randomized, double-blind, chronic dosing (4 weeks), four-period, five-treatment, incomplete block, cross-over, multicenter study to assess the efficacy and safety of four doses of BD MDI (320, 160, 80, and 40 µg ex-actuator, twice daily [BID]) and Placebo MDI (BID) in adult subjects with mild to moderate persistent asthma. It is planned to conduct this multi-center study at approximately 45 sites in the United States, with each site contributing approximately 3 subjects. Across these sites, it is planned that approximately 150 adult subjects with mild to moderate persistent asthma who remain symptomatic despite treatment with Pulmicort Flexhaler® 180 µg BID will be randomized into the study to provide approximately 120 completers. The entire study

period is scheduled to take a maximum of 32 weeks for each subject.

Study Population:
Approximately 150 adult subjects with mild to moderate persistent asthma who remain symptomatic despite treatment with Pulmicort Flexhaler (budesonide inhalation powder) 180 µg BID, will be enrolled to provide approximately 120 completers (e.g., 4 treatment periods).

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

Drug/Product Name & Dose	Product Strength	Dosage Form/Fill Count	Comments
Study Drug			
Budesonide Inhalation Aerosol 320 µg ex-actuator	160 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Budesonide Inhalation Aerosol 160 µg ex-actuator	80 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Budesonide Inhalation Aerosol 80 µg ex-actuator	40 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Budesonide Inhalation Aerosol 40 µg ex-actuator	20 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Open-label Products			
Albuterol Sulfate Inhalation Aerosol[§] 90 µg (Ventolin HFA)	Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece	1 MDI 200 actuations	US source: (Ventolin® HFA) *Supplies are open-label*
Budesonide Inhalation Powder[†] 180 µg (Pulmicort Flexhaler)	Taken as one inhalation. Each inhalation contains 180 µg of budesonide corresponding to 160 µg delivered from the mouthpiece	1 DPI 120 actuations	US source: (Pulmicort Flexhaler®) *Supplies are open-label*
Placebo			
Placebo	Formulation does not contain active ingredient	1 MDI 120 inhalations	Taken as 2 inhalations from the MDI

[§] Rescue medication and reversibility testing.

[†] Asthma maintenance therapy during Screening and Washout Periods

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

All placebos are created by Pearl Therapeutics in the image of the active test product. The 320, 160, 80, and 40 µg ex-actuator delivery of BD MDI are equivalent to 370.0, 185.0, 92.4, and 46.2 µg ex-valve of BD MDI, respectively.

Duration of Treatment:
Each subject will receive 4 weeks (28 days) of study treatment with each of their assigned treatments for a total of 4 separate Treatment Periods. A Washout Period of at least 14 days (and up to 21 days) will occur between each Treatment Period. The entire study is scheduled to take a maximum of 32 weeks for each individual subject from the time of screening (see Figure 1).

Efficacy Assessments:

Primary Efficacy Endpoint:

- Change from baseline in morning pre-dose trough forced expiratory volume in one second (FEV_1) at the end of the Treatment Period

- Secondary Efficacy Endpoints:
- Change from baseline in mean morning pre-dose and mean evening pre-dose peak flow rate (PEFR) readings taken by the subject and recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in Asthma Control Questionnaire (ACQ) score at the end of the Treatment Period

Other Efficacy Endpoints:

- Change from baseline in morning pre-dose trough FEV_1 over the Treatment Period and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in mean morning and evening pre- and post-dose daily PEFR readings taken by subjects and recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Percentage of days without rescue Ventolin HFA use over the last week of the Treatment Period and over the entire Treatment Period
- Change from baseline in pre-dose trough forced vital capacity (FVC) at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough PEFR at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough forced expiratory flow 25-75% (FEF_{25-75}) at the end of each Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in the number of nighttime awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period, over each week of the Treatment Period, and over the entire Treatment Period
- Percentage of nights with awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period and over the entire Treatment Period

Safety Endpoints:

The safety assessments include electrocardiograms (ECGs,) vital sign measurements, clinical laboratory tests, monitoring for paradoxical bronchospasm, physical examination findings, AEs and SAEs during the study period.

Statistical Methods:

Sample Size Determination:

Power calculations are based on the properties of the primary endpoint, morning pre-dose trough $FEV_{1,}$ on the last day of each Treatment Period (end of treatment). An estimate of the total standard deviation (SD) of 405 mL is taken from a 12-week trial comparing budesonide to ciclesonide (Boulet, 2006). Assuming that half of the variability comes from within subject and half between (i.e., intrasubject correlation=0.5), an estimate of the within subject standard deviation of 285 mL for morning pre-dose trough FEV_1 is obtained. Using this SD and assuming that 150 randomized subjects will provide approximately 120 completers, the power to demonstrate a 120 mL difference from Placebo MDI for BD MDI 320 μg or BD MDI 160 μg is approximately 90%. For BD MDI 80 μg and BD MDI 40 μg, the power to demonstrate a difference from Placebo MDI of 140 mL is approximately 80%.

Efficacy Analyses:

The primary efficacy analysis will compare the change from baseline at the end of the treatment periods in morning pre-dose trough FEV_1 between BD MDI treatments and Placebo MDI using a repeated measures mixed model with a random subject effect for the correlation across periods. The fixed effects will include baseline FEV_1, response to albuterol, and period. Sequence will also be included if it explains significant variability. The primary population will be a *modified* Intent to Treat (mITT) Population. A two-sided alpha level of 0.05 will be employed. Multiplicity will be controlled using a sequential, dose-ordered approach.

Similar analyses will be conducted using the Intent to Treat (ITT) Population for the primary endpoint as well as for analyses of the secondary and other efficacy endpoints.

Safety Analyses:

Safety analyses will be based on descriptive statistics for ECG, vital sign and laboratory measurements as appropriate, incidence of paradoxical bronchospasm, and on the number of subjects with AEs and SAEs.

Date of Original Approved Protocol: [redacted]

Date of Amendment 1: [redacted]

Date of Amendment 2: [redacted]

TABLE OF CONTENTS

List of In-Text Tables

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ACQ	Asthma Control Questionnaire
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the curve
AV	Atrioventricular block
BD	Budesonide
BID	Bis in die, twice daily
BMP	Basic Metabolic Panel
BP	Blood Pressure
BPM	Beats per minute
BTPS	Body Temperature and Pressure Saturated
BUN	Blood urea nitrogen
$CaCl_2$	Calcium Chloride
CFR	Code of Federal Regulations
CMP	Comprehensive Metabolic Panel
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
CRO	Contract Research Organization
CT	Computed tomography
DBP	Diastolic blood pressure
DSPC	Distearoylphosphatidyl choline
DPI	Dry Powder Inhaler
eg	*Exempli gratia*, for example
ECG	Electrocardiogram
ex-actuator	dose delivered from the actuator (i.e., mouthpiece) of the MDI
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
hCG	Human chorionic gonadotropin
HR	Heart Rate
HFA	Hydrofluoroalkane
ie	*Id est*, that is
IBD	Incomplete Block Design
ICF	Informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IWRS	Interactive Web Response System
L	Liter
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
MAO	Monoamine oxidase inhibitor
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified ITT
mL	Milliliter

Msec (ms)	Millisecond
NHANES III	National Heart, Lung, and Blood Institute Third National Health and Nutrition Examination Survey
OTC	Over-the-counter
PEFR	Peak expiratory flow rate
PFT	Pulmonary function test
PI	Principal Investigator
PIN	Personal identification number
PK	Pharmacokinetic
PP	Per Protocol
PRN	Pro re nata, as needed
PT	Preferred term
REML	Residual or restricted maximum likelihood
RFD	Rescue-free days
Rx	Treatment
QTcF	QT corrected using Fridericia's formula ($QT/(RR^{1/3})$)
SABA	Short-acting beta agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
TNFα	Tumor necrosis factor α
TP	Treatment Period
µg	Microgram
US/USA	United States

TRADEMARK INFORMATION

Trademarks Not Owned By Pearl Therapeutics

Advair

Atrovent

Breo

Combivent

Diskus

Dulera

Ellipta

Pulmicort Flexhaler

Robinul

Robinul Forte

Seretide

Symbicort

Ventolin HFA

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 (e.g., age 50, 60 or even later in life) [GINA, 2012]. Those individuals who develop asthma as adults are said to have adult onset asthma.

The current National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report-3, 2007 [NHBLI, 2007] recommends long-term treatment with inhaled corticosteroids (ICS) because of their superior effectiveness in managing the chronic airway inflammation that characterizes persistent asthma [February 2010 that long-acting beta agonists (LABAs) should never be used alone to treat asthma, and specifying that when they are used as part of a combination therapy, they should be administered only for the shortest duration possible and then discontinued and then patient should be maintained on a controller medication [FDA, 2007].

The NHLBI EPR-3 Guidelines recommend a stepwise approach to asthma treatment: inhaled corticosteroid (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 [NHBLI, 2007].

Regular treatment with ICS improves symptoms, lung function , 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, 2012].

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 BD when used to treat chronic asthma, and a large range outcome measures have been used to assess its efficacy and safety.

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 (DSPC) and calcium chloride ($CaCl_2$) that are cosuspended

with crystalline active drug substances and formulated into suspension-based hydrofluoroalkane (HFA) metered dose inhalers (MDIs). The safety of porous particles is previously demonstrated in over 1000 patients with COPD.

Pearl Therapeutics is developing a broad range of MDI-based inhalation aerosols using its porous particle technology platform. These inhaled therapies include Glycopyrrolate (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) for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. GFF MDI is currently being evaluated in the PINNACLE 1 and PINNACLE 2 Phase III trials; and in a recently completed Phase I pharmacokinetic (PK) study with budesonide as a component in a fixed "triple" combination therapy with GP and FF.

1.1 Study Rationale

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

2 STUDY OBJECTIVES

2.1 Primary Objective

To demonstrate lung function benefit of BD MDI compared with Placebo MDI in adult subjects with mild to moderate persistent asthma.

2.2 Secondary Objective

To characterize the dose response of BD MDI based on lung function in adult subjects with mild to moderate persistent asthma.

2.3 Safety Objective

To evaluate the safety and tolerability of BD MDI across all doses evaluated in the study.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoint

- Change from baseline in morning pre-dose trough forced expiratory volume in one second (FEV_1) at the end of the Treatment Period

3.1.2 Secondary Efficacy Endpoints

- Change from baseline in mean morning pre-dose and mean evening pre-dose peak flow rate (PEFR) readings taken by the subject and recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in Asthma Control Questionnaire (ACQ) score at the end of the Treatment Period

3.1.3 Other Efficacy Endpoints

- Change from baseline in morning pre-dose trough FEV_1 over each Treatment Period and at Day 15 and Day 29 of each Treatment Period
- Change from baseline in mean morning and evening pre- and post-dose daily PEFR readings taken by subjects and recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
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- Change from baseline in pre-dose trough forced vital capacity (FVC) at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
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- Change from baseline in pre-dose trough forced expiratory flow 25-75% (FEF_{25-75}) at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in the number of nighttime awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period, over the week of the Treatment Period, and over the entire Treatment Period

- Percentage of nights with awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period and over the entire Treatment Period

3.2 Safety Endpoints

The safety assessments include electrocardiograms (ECGs), vital sign measurements, clinical laboratory tests, monitoring for paradoxical bronchospasm, physical examination findings, AEs and SAEs during the study period.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind, chronic dosing (4 weeks) four-period, five-treatment, incomplete block, cross-over, multi-center study to assess the efficacy and safety of four doses of BD MDI (320, 160, 80, and 40 µg BID) and Placebo MDI (BID) in adult subjects with mild to moderate persistent asthma.

This multi-center study will be conducted at approximately 45 sites in the United States (US), contributing approximately 3 subjects per site. Across these sites, it is planned that approximately 150 adult subjects with mild to moderate persistent asthma, who remain symptomatic despite treatment with Pulmicort Flexhaler® 180 µg will be randomized into the study to provide approximately 120 subjects to complete the study. The entire study period is scheduled to take a maximum of 32 weeks for each individual subject (see Figure 1). The study is anticipated to run for approximately 12 months and should not exceed 18 months.

At the Screening Visit (Visit 1a), all subjects are to sign an informed consent form (ICF) prior to the conduct of any screening assessments. The Investigator or designee will obtain a medical history, physical examination, and all required documentation in order to determine eligibility for participation (inclusion/exclusion criteria). Pre-bronchodilator pulmonary function tests (PFTs) will be assessed prior to administration of Ventolin HFA (albuterol). Post-bronchodilator testing may be performed to assess reversibility (see Section 7.1.2).

At the Investigators' discretion, subjects who do not meet the spirometry and/or reversibility entry criteria at Visit 1a can return for a repeat spirometry and/or reversibility assessment at an optional Screening visit (Visit 1b). **Note**: Visit 1b is to be used only for repeat spirometry entry criteria at any time between Visit 1a and Visit 2. All other repeat assessments, if needed, will be captured as an unscheduled visit. Repeat spirometry can be done anytime post Visit 1a and Visit 2, however, the subject must be in the 2-week run in period with Pulmicort Flexhaler 180 µg.

Providing the subject meets all eligibility criteria at Screening (Visit 1a or optional Visit 1b), the Investigator or designee will review current asthma medications and, if necessary, will adjust the prohibited asthma therapy to protocol-allowable asthma therapy as described in Section 5.4.

Subjects who meet all entry criteria but are using certain prohibited asthma medications (e.g., oral β_2-agonists, corticosteroids, corticosteroid/LABA fixed dose combination products, and leukotriene antagonists [e.g., zafirlukast, montelukast, zileuton]) will discontinue these medications for the duration of the trial.

During the Screening Period (between Visit 1 to Visit 3), all subjects will be prescribed open-label Pulmicort Flexhaler 180 µg BID provided by the Sponsor and open-label rescue Ventolin HFA 108 µg MDI provided by the Sponsor, as needed, to control symptoms.

Subjects will be issued and trained in the use of an electronic diary (eDiary) and peak flow meter at Visit 1 (Screening). Subjects will be instructed to collect practice data during the Screening Period (between Visit 1 and Visit 3).

In order to standardize asthma maintenance medications and to determine disease severity, eligible subjects will undergo a run-in period of at least 14 days (2 weeks) but not greater than 28 days in duration, using Sponsor-provided open-label Pulmicort Flexhaler 180 µg BID and Sponsor-provided rescue Ventolin HFA MDI, as needed, to control symptoms prior to returning to the clinic for Visit 2.

At Visit 2, reversibility to Ventolin HFA will be evaluated (see Section 7.1.2) and Visit 2 procedures completed (see Section 8.3). Subjects who successfully meet study entry criteria at Visit 2 will be scheduled for Visit 3 (Randomization Visit) at least 1 day from Visit 2, but no later than 28 days from Visit 1a (Screening).

At Visit 3 (Randomization Visit; Treatment Period 1, Day 1), subject eDiary compliance will be reviewed and all sponsor-provided Pulmicort Flexhaler and Ventolin HFA provided during the Screening Period will be discontinued and collected by site personnel for accountability. Eligible subjects will complete an Asthma Control Questionnaire (ACQ) (Juniper, 1999) (see Section 7.1.10 and Appendix 6) at Visit 3 prior to Randomization.

Subjects must have a minimum ACQ score of ≥1.5 and eDiary compliance of ≥70% in the last 7 days preceding Visit 3 and meet the FEV_1 baseline stability criteria (see Section 5.1) to be eligible for Randomization at Visit 3. Subjects who do not meet the ACQ minimum score, eDiary compliance and/or FEV_1 baseline stability criteria described above must be screen failed at Visit 3.

Subjects who continue to meet all entry inclusion/exclusion criteria at Visit 3 and those who remain eligible for participation in the study will be randomized to one of the pre-defined treatment sequences. Each sequence will include exactly 4 of the 5 treatments included in this study. All subjects will receive BD MDI 320, BD MDI 160 µg, and Placebo MDI in a randomized order, but only half of the subjects will be randomized to receive BD MDI 40 µg or BD MDI 80 µg.

The subject, clinical site personnel, and Pearl Therapeutics will be unaware of the treatment dose sequence assigned to each subject, and it will not be possible to differentiate between study treatments as all blinded clinical supplies will be identical in image in all aspects.

Randomization will be centralized, through the use of an IWRS (Interactive Web Response System). Study treatments will be administered twice daily. Each of the 4 treatments will be administered for 28 ±2 days with a Washout Period of at least 14 days (up to 21 days) during which subjects will administer Pulmicort Flexhaler 180 µg, BID and Ventolin HFA, as needed, in between Treatment Periods.

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 (≥4 hours) of short acting bronchodilators. 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 last post-dose PEFR assessment (see Section 8.4). Subjects will then be discharged from the clinic and will continue to administer study medication and complete their eDiary entries at home for 14 days (2 weeks) 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 (2 weeks) of chronic Treatment 1 dosing at home and complete Visit 4 procedures (see Section 8.6). Subjects will then be discharged from the clinic and will continue to administer study medication and complete their eDiary entries for 14 days (2 weeks) at home until Visit 5 (Treatment Period 1, Day 29).

Subjects will return to the clinic following approximately 14 days (2 weeks) of chronic Treatment 1 dosing for Visit 5 (Treatment 1, Day 29) and complete the procedures for Visit 5 (see Section 8.7). On discharge, subjects will undergo a study medication Washout Period of at least 14 Days (2 weeks) but no more than 21 Days (3 weeks) duration, using Sponsor-provided open-label Pulmicort Flexhaler 180 µg BID and Sponsor-provided rescue Ventolin HFA MDI, as needed, to control symptoms, prior to initiating Treatment 2 in their assigned treatment sequence at Visit 6.

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

At Visits 6, 9 and 12 (Day 1 of Treatment Periods 2, 3 and 4, respectively), subjects will return to the clinic following their Washout Period and if eligible to continue, complete all Day 1 procedures for the Treatment Period (see Section 8.5). Pre-dose assessments will be performed and continued eligibility will be determined. Subjects must meet the FEV_1 baseline stability criteria (see Section 5.1) to be eligible for dosing at Visits 6, 9 and 12. Subjects who do not meet the FEV_1 baseline stability criteria at Visits 6, 9 and 12 must be rescheduled as soon as is practical, but within the protocol-specified washout window (14-21 days between Treatment Periods). Subjects who fail to meet stability criteria after two attempts within a Washout Period will be discontinued from the study.

Eligible subjects (e.g., subjects who meet FEV_1 baseline stability criteria and have withheld all asthma medications for 4 hours prior to the study visit) will be dispensed study drug relative to the IWRS and administer their first dose of study drug in the clinic under site supervision. The post-dose PEFR will be performed and the subject discharged to continue daily study drug administration and eDiary completion at home until the next scheduled visit at 14 $\pm$2 days from Treatment Day 1 of the Treatment Period (see Section 8.5).

At Visits 7, 10, and 13 (Day 15 of Treatment Periods 2, 3 and 4, respectively), eligible subjects (e.g., subjects who have withheld all asthma medications for 4 hours prior to the study visit) will complete all pre-dose assessments and continued eligibility will be

determined (see Section 8.6). Providing the subject does not meet rescue criteria (see Section 7.1.4), new study drug as assigned by IWRS will be dispensed, the subject will take their study medication under site supervision, and a post-dose PEFR will be obtained. The subject will be discharged to continue daily study drug administration and eDiary completion at home until the next scheduled visit at approximately 28±2 days from Treatment Day 1 of the Treatment Period.

At Visits 8 and 11 (Day 29 of Treatment Periods 2 and 3, respectively), eligible subjects (e.g., subjects who have withheld all asthma medications for 4 hours prior to the study visit) will complete all pre-dose assessments and continued eligibility will be determined (see Section 8.7). Subjects will administer their last dose of study drug from the MDI assigned at Visits 7 and 10, respectively, and post-dose PEFR and vital signs will be obtained. The subject will be discharged to undergo a Washout Period of at least 14 Days (2 weeks) up to 21 Days (3 weeks) on Sponsor-provided open-label Pulmicort Flexhaler 180 µg BID and Ventolin HFA, as needed, for relief of asthma symptoms, prior to initiating Treatment Periods 3 and 4 at Visit 9 (Treatment Period 3, Day 1) and Visit 12 (Treatment Period 4, Day 1), respectively.

At Visit 14 (Day 29 of Treatment Period 4), eligible subjects (e.g., subjects who have withheld all asthma medications for 4 hours prior to the study visit) will complete all pre-dose assessments and continued eligibility determined (see Section 8.8). Subjects will administer their last dose of study drug from the MDI assigned at Visit 13, and post-dose PEFR and vital signs will be obtained. Following completion of Visit 14 assessments, the subject will be discharged and returned to pre-study or appropriate inhaled asthma maintenance medication(s). Subjects completing Visit 14 (Day 29 of Treatment Period 4), or who require a Premature Discontinuation Visit, will be scheduled for a post-study follow-up telephone call (see Section 8.11) at least 7 days and up to 14 days from the date of last study dose.

General Guidance for Treatment During In-clinic Visits 3 through 14

- 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 study medication and rescue medications (e.g., Ventolin HFA [albuterol]) for at least 4 hours, by confirming the last time of dosing for all asthma medication(s).

  Note: Subjects who inadvertently took rescue medication(s) within 4 hours of the start of study procedures must be rescheduled as soon as is practical but within the specified visit window. In addition, before the in-clinic dose is administered, the site must confirm the subject met all other protocol specified requirements (e.g., FEV_1 baseline stability). Subjects will remain in the clinic until 30 minutes post-dose, for observation (safety).

- Subjects must not ingest caffeine-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 a dosing schedule at home consistent with their in clinic dosing time.
    - Subjects will be required to take their study medication twice a day: 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.

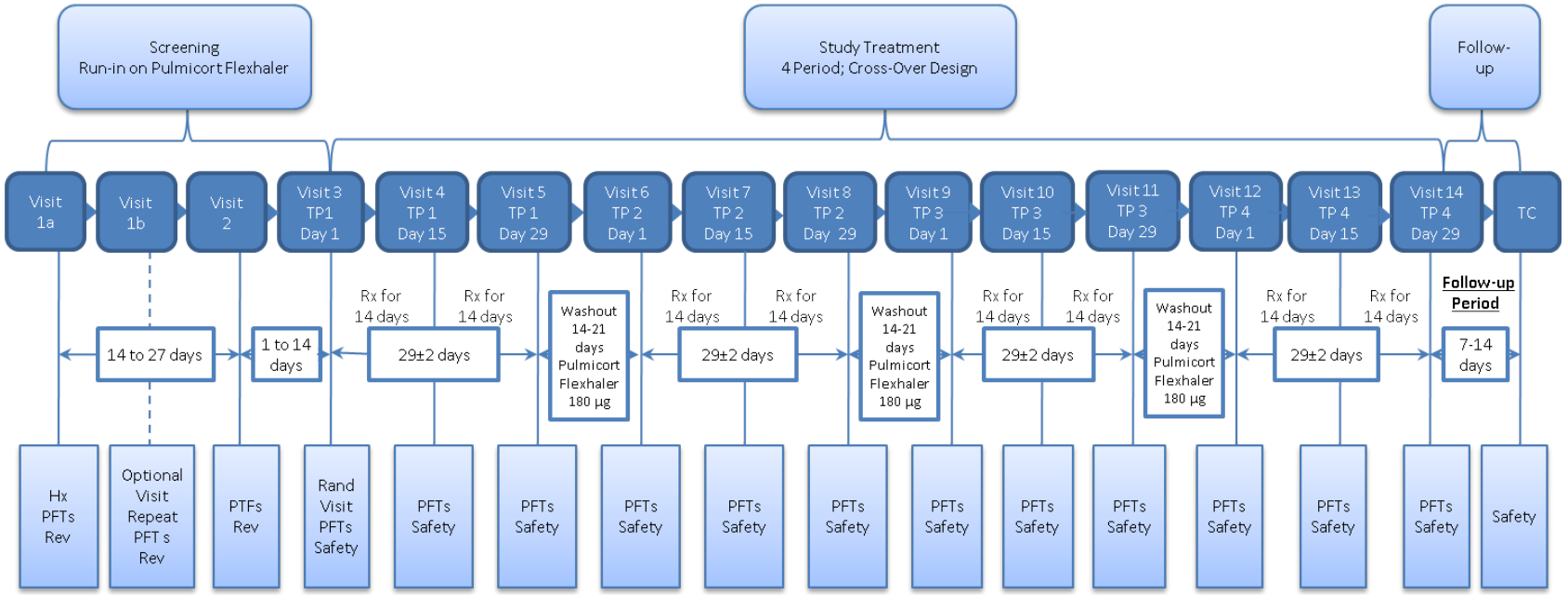
- Sites are encouraged to call the subject on the day before a scheduled visit to remind the subject to:
    - Take their last dose the evening before (12 ± 2 hours) prior to the scheduled visit.
    - Bring their study medications with them to the clinic
    - Withhold all asthma medications (including ICS) for at least 4 hours prior to 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 will be recorded as the time of administration of the *second* puff of study medication.
- 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 test day. Site personnel may request the subject to surrender all non-study asthma medications prior to start of the visit before performing any study procedures and return to subject at 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 (i.e., Treatment Day 15 procedures must be done between Treatment Day 13 and Treatment Day 17, inclusive).
- Similarly, every effort must be made to ensure that subjects return to the clinic on Day 29 (4 Weeks) following the initiation of each treatment arm. To accommodate scheduling

conflicts a window of 28 ± 2 days from Treatment Day 1 is permitted (i.e.,Treatment Day 29 procedures must be done between Treatment Day 27 and Treatment Day 31, inclusive).

Note: If Visit 5, 8 or 11 occurs at Day 31 or later, the site must contact the Sponsor for guidance prior to initiating the next Treatment Period.

A Study Flow Diagram is displayed in Figure 1:

Figure 1. Study Flow Diagram



Hx = Medical History, Rand = Randomization, PFT = Pulmonary Function Test, Rx = Treatment, Rev = Reversibility, TC = Telephone Call, TP = Treatment Period

5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

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

1. Give their signed written informed consent to participate.
2. Are ≥18 – 65 years of age at Visit 1.
3. Have a diagnosis of mild to moderate persistent asthma, diagnosed at least 6 months prior to screening visit according to NHLBI EPR 3, (NHLBI, 2007)
   - Asthma symptoms > 2 days per week, or
   - Nighttime awakenings 3–4 times per month or greater due to asthma symptoms, or
   - Use of short-acting beta agonist (SABA) for symptom control (not for prevention of exercise-induced bronchospasm) > 2 days per week, or
4. Asthma Medication History: Must be currently receiving treatment with a low to medium dose of an ICS (as defined in Table 1) ***OR*** a combination of controller medications as defined in Table 2, containing a low (total daily) dose ICS (as defined in Table 1) for at least 4 weeks preceding screening.
5. Pulmonary Function: Must have a pre-albuterol (Ventolin HFA) FEV_1 of ≥60% and ≤90% of predicted normal value at Screening (Visit 1a or 1b) and at Visits 2 and 3.
6. Reversibility: At Screening (Visits 1a or 1b) and at Visit 2, the subject must have an increase in FEV_1 of ≥ 12% and ≥ 200mL over the pre-albuterol (Ventolin HFA) FEV_1 within 30-60 minutes after the inhalation of 4 puffs of Ventolin HFA. Historic documentation of reversibility will not be permitted (see Section 7.1.2).
7. FEV_1 Baseline Stability Criteria: At Visit 3, 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 2 (see Section 7.1.3).
8. Asthma Symptom Criteria: Have required Ventolin HFA use on at least two of the last seven days and have an Asthma Control Questionnaire (ACQ) total score ≥ 1.5 prior to Randomization (Visit 3) (see Appendix 6).
9. A female is eligible to enter and participate in the study if she is :
   - Non-child bearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal); ***or***
   - Child bearing potential, has a negative serum pregnancy test at screening, and agrees to one of the following acceptable contraceptive methods used consistently and correctly (i.e., in accordance with the approved product label and the instructions of the physician for the duration of the study from Screening until 14 days after Visit 14)
     a. Complete abstinence from intercourse from screening until 14 days after Visit 14 ***or***
     b. 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***

c. Injectable progestogen administered for at least 1 month prior to study drug administration and administered for 1 month following study completion; ***or***
d. Oral contraceptive (combined or progestogen only) administered for at least one monthly cycle prior to study drug administration; ***or***
e. Double barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository); ***or***
f. An intrauterine device (IUD), inserted by a qualified physician, with published data showing that the highest expected failure rate is less than 1% per year; or estrogenic vaginal ring; ***or***
g. Percutaneous contraceptive patches.

10. Results from clinical laboratory tests conducted at Screening must be acceptable to the Investigator.

5.2 Exclusion Criteria

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

1. Life-Threatening Asthma: A subject must not have life-threatening asthma. Life-threatening asthma is defined for this protocol 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 screening (Visit 1).
2. Worsening Asthma: A subject must not have experienced a worsening of asthma which involved an emergency department visit, hospitalization or use of oral/parenteral corticosteroids within 6 weeks of Screening (Visit 1).
3. Intermittent, Seasonal, or Exercise-Induced Asthma Alone: Subjects with only intermittent, seasonal or exercise-induced asthma are excluded from participation in this study.
4. Concurrent Respiratory Disease: A subject must not have current evidence or diagnosis of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), or other respiratory abnormalities other than asthma.
5. Concurrent Conditions/Diseases: A subject with historical or current evidence of any clinically significant, co-morbid 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. Pregnant women or nursing mothers.
7. Chronic Obstructive Pulmonary Disease (COPD): A current diagnosis of COPD.
8. Smoking History: Current smokers or subjects with a $\geq$ 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.

9. Respiratory Tract Infection(s): Subjects who have had a respiratory tract infection within 6 weeks prior to Visit 1. 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. 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.
11. Cardiac Conditions/Disease: Subjects with documented myocardial infarction within a year from screening visit 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 three months of screening visit are to be excluded.
12. Clinically significant abnormal ECG: A clinically significant abnormal ECG is defined as (but not limited to) any of the following:
    a. Clinically significant conduction abnormalities (e.g., left bundle branch block, Wolff-Parkinson-White syndrome or evidence of second degree (Mobitz Type II) or third degree atrioventricular (AV) block).
    b. Clinically significant arrhythmias (e.g., atrial fibrillation, ventricular tachycardia)
    c. A mean corrected QT interval using Fridericia's correction factor (QTcF) value at screening > 450 ms for males and > 470 ms for females or an ECG that is not suitable for QT measurements (e.g., poorly defined termination of the T wave).
    d. Bradycardia with rate < 45 bpm.
    e. Pathological Q waves of 1 year or less
    f. ST-T wave abnormalities (excluding non-specific ST-T wave abnormalities)
    g. Subjects who, in the opinion of the Investigator, have a clinically significant abnormal 12-lead ECG
13. Uncontrolled Hypertension: Subjects who, in the opinion of the Investigator, have clinically significant uncontrolled hypertension.
14. Liver Function: Subjects with abnormal liver function tests defined as aspartate aminotransferase (AST), alanine aminotransferace (ALT), alkaline phosphatase or total bilirubin ≥1.5 times upper limit of normal on repeat testing.
15. 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 have been adequately worked up, are clinically controlled and the subject's participation in the study would not represent a safety concern, are eligible
16. Drug Allergy: Subjects who have a history of hypersensitivity to any component of the MDI.

17. Substance Abuse: Subjects with a known or suspected history of alcohol or drug abuse within the last 2-year period prior to Screening.
18. Medication Prior to Spirometry: Subjects who are medically unable to withhold their short-acting bronchodilators for the 4-hour period required prior to spirometry testing at each study visit will be excluded.
19. Prohibited Asthma Medications: Subjects taking the following medications within the specified time intervals prior to Screening (Visit 1) are to be excluded:
    a. 3 months: depot corticosteroids, intra-articular corticosteroids.
    b. 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.
    c. Initiation or discontinuation of ICS within 30 days of Visit 1.
    d. Subjects treated chronically with oral or systemic corticosteroids are excluded from the study.
    e. 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.
    f. Subjects treated chronically with antibiotics are excluded from the study.
20. Taking other prohibited medications as defined in Table 3.
    a. Anti-tumor necrosis factor α (TNFα) antibodies (e.g., infliximab and any other members of this class of drugs)
    b. Antipsychotic drugs (phenothiazines)
    c. Systemic calcineurin inhibitors
    d. Systemic antifungal agents
    e. Protease inhibitors and cimetidine
    f. Immunosuppressants (Methotrexate, Cyclosporins, etc.)
    g. Any oral, inhaled or systemic corticosteroids
    h. Use of any LABA as single agent (as indicated in FDA mandated black box warning for LABAs)
21. Spirometry Performance:
    a. Acceptability Criteria: Subjects who cannot perform acceptable spirometry, (i.e., meet ATS/ERS acceptability criteria)
    b. Repeatability Criteria: Subjects who cannot perform technically acceptable spirometry with at least three acceptable flow-volume curves with two or more meeting ATS repeatability criteria for FEV_1 during at least one of the pre-bronchodilator assessments at Visit 2 (-60 minute or -30 minute) and at the post-bronchodilator assessment at Visit 2
    c. FEV_1 Baseline Stability: see Section 5.1)
22. Non-compliance: Subjects unable to comply with study procedures, including non-compliance with eDiary completion (i.e., <70% subject completion of eDiary assessment in the last 7 days preceding Visit 3 [Randomization Visit]).

23. 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.
24. 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.
25. 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.
26. 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 the Screening Visit (Visit 1). Only subjects continuing to meet entry inclusion/exclusion criteria at Visit 3 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 (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 1**.**

Table 1. Estimated Equipotent Daily Doses of Inhaled Glucocorticosteroids

Drug	Low Dose (µg)	Medium Daily Dose (µg)	High Daily Dose (µg)
Beclomethasone dipropionate - CFC	200 - 500	> 500 - 1000	> 1000 - 2000
Beclomethasone dipropionate - HFA	100 - 250	> 250 - 500	> 500 - 1000
Budesonide	200 - 400	> 400 - 800	> 800 - 1600
Ciclesonide	80 - 160	>160 - 320	> 320 - 1280
Flunisolide	500 - 1000	> 1000 - 2000	> 2000
Fluticasone propionate	100 - 250	> 250 - 500	> 500 - 1000
Mometasone furoate	200	> 400 - 800	> 800
Triamcinolone acetonide	400 - 1000	> 1000 - 2000	> 2000

Note: Comparisons based on efficacy data.
Source: GINA, 2012

Table 2 provides the list of asthma controller medications permitted (low to medium dose) and prohibited (high dose) in this study.

Table 2. Asthma Controller Medications

Low dose ICS + Leukotriene modifiers
Low dose ICS + Theophylline products
Low dose ICS + Inhaled anticholinergics or combination products (e.g., Atrovent or Combivent)
Low dose ICS + Long-acting inhaled anticholinergics (i.e., Spiriva)
Combination products containing low to medium dose ICS and a long acting beta agonist: **Permitted**: Advair/Seretide DISKUS 100/50 µg and 250/50 µg BID, Advair HFA 90/42 µg (administered as two puffs of 45/21 µg) BID, Advair HFA 230/42 µg (administered as two puffs of 115/21 µg) BID, Symbicort 160/9 µg (administered as two puffs of 80/4.5 µg) BID, Dulera 200/10 µg (administered as two puffs of 100/5 µg) BID.
Combination products containing high dose ICS and a long acting beta agonist: **Prohibited:** Advair/Seretide DISKUS 500/50 µg, Advair HFA 460/42 µg (administered as two puffs of 230/21 µg) BID; Symbicort 320/9 µg (administered as two puffs of 160/4.5 µg) BID; Dulera 400/10 µg (administered as two puffs of 200/5 µg) BID and Breo Ellipta 100/25 µg (administered as one inhalation) QD.

Source: GINA, 2012

Prohibited Medications:

The use of the medications listed in Table 3 is not permitted during this study, if initiated the subject needs to be discontinued immediately. If the subject had previously been prescribed any of the prohibited medications below and was recently discontinued, the minimum Washout Period prior to screening is provided:

Table 3. Prohibited Medications

Prohibited Medications	Minimum Cessation Period Prior to Visit 1 (Screening)
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 (e.g., infliximab and any other members of this class of drugs)	30 days or 5 half-lives, whichever is longer
Monoclonal antibodies	30 days or 5 half-lives, whichever is longer
Antipsychotic drugs (phenothiazines)	30 days
Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors and cimetidine	30 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

Illicit drugs or drugs of abuse will not be allowed from the start of Screening (Visit 1) to the end of the study (Visit 14), or to whenever the subject discontinues the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented.

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

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

abnormality. All subjects who prematurely discontinue the study after being randomized, regardless of the cause, should undergo the assessments outlined in Section 8.10 on the date 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 needs to make a determination as to the suitability of continuing the subject in the study.

Changes of concern include:

- Decrease in creatinine clearance to a value below 30 mL/min using CKD-EPI 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 principal Investigator (PI) or designee will need to determine whether the subject is having an asthma exacerbation and will also make a determination as to the suitability of continuing the subject in the specific treatment period.
  d. If a subject requires use of rescue medication 4 or more times per day (i.e., ≥ 8 puffs of Ventolin HFA) for three or more consecutive days.
  e. If a subject meets the protocol-defined rescue criteria (Section 7.1.4) during the Treatment Period.
- If a subject does not meet protocol-defined FEV_1 baseline stability criteria (Section 5.1) 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 subject becomes pregnant during the course of the study, the subject will be discontinued. (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 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 as 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
Study Drug			
Budesonide Inhalation Aerosol 320 µg ex-actuator	160 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Budesonide Inhalation Aerosol 160 µg ex-actuator	80 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Budesonide Inhalation Aerosol 80 µg ex-actuator	40 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Budesonide Inhalation Aerosol 40 µg ex-actuator	20 µg per actuation	1 MDI 120 inhalations	Taken as 2 inhalations
Open-label Products			
Albuterol Sulfate Inhalation Aerosol[§] 90 µg (Ventolin HFA)	Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece	1 MDI 200 actuations	US source: (Ventolin® HFA) *Supplies are open-label*
Budesonide Inhalation Powder[†] 180 µg (Pulmicort Flexhaler)	Taken as one inhalation. Each inhalation contains 180 µg of budesonide corresponding to 160 µg delivered from the mouthpiece	1 DPI 120 actuations	US source: (Pulmicort Flexhaler®) *Supplies are open-label*
Placebo			
Placebo	Formulation does not contain active ingredient	1 MDI 120 inhalations	Placebo Taken as 2 inhalations from the MDI

[§] Rescue medication and reversibility testing.

[†] Asthma maintenance therapy during Screening and Washout Periods

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

All placebos are created by Pearl Therapeutics in the image of the active test product. The 320, 160, 80, and 40 µg ex-actuator delivery of BD MDI are equivalent to 370.0, 185.0, 92.4, and 46.2 µg ex-valve of BD MDI, respectively.

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

For open-label Pulmicort Flexhaler (budesonide inhalation powder 180 µg), commercial dry powder inhalers (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).

6.3 Primary Packaging and Labeling Information

Investigational materials will be packaged by Pearl Therapeutics.

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

Open-label Supplies: Open-label PulmicortFlexhaler and Ventolin HFA will be provided as individually labeled DPIs and MDIs, respectively. Each inhaler will contain a single investigational label. For Pulmicort Flexhaler, a two-part label will be affixed to the carton. Ventolin MDIs will be packaged in foil pouches. Foil pouches will receive a one-part label. The two-part label will be affixed to the carton holding the foil. Both single and two-part labels will be printed with 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)

6.4 Secondary Packaging and Labeling Information (Box)

Investigational drug supplies will be packaged in boxes as outlined below in Table 6. Open label Ventolin HFA supplies will be provided in boxes, also 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	1DPI

Each box will be labeled with a double panel label printed with black ink and may include the following text (see 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)

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.

Ventolin HFA supplies: Open-label supplies should also be kept 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.

Pulmicort Flexhaler supplies: Store in a dry place at controlled room temperature 20–25°C (68-77°F) with the cover tightly in place. Keep out of the reach of children. Keep Pulmicort Flexhaler 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 or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained.

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

BD and Placebo MDIs

Individual BD 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 foil overwrap is labeled with a two-part label. Write the subject number and treatment visit number on each of the two-part labels. The 'tear-off' part of the label is to be placed onto the IWRS confirmation report.

All MDIs must be primed before the first use. Priming involves releasing a certain number of sprays (4) into the air before the first use of the inhaler. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that it's ready to use. Site personnel will prime the inhaler device prior to giving to the subject by gently shaking the inhaler for 5-10 seconds and then spraying once into the air away from themself and others. After approximately 30 seconds, the process should be repeated three more times.

The MDI must be primed in a separate room from the subject treatment area. Since the MDI is primed in a separate room before dosing, there is a possibility that there may be a delay between priming and dosing, and therefore to ensure consistency in the administration for all subjects, the MDIs are to be gently shaken (5-10 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 twice daily, 2 puffs in the morning and 2 puffs in the evening approximately 12 hours apart, until the subject returns to the clinic. Refer to Appendix 3 for instructions on the administration of BD and Placebo MDIs.

Pulmicort Flexhaler (budesonide inhalation powder 180 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 during screening and Washout Periods.

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 DPIs 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 during Screening and Washout Periods. 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.

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 this 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 placed in a plastic bag (Ziploc® or similar type bag) and labeled with the subject number. Used subject supplies will be kept at room temperature in a secure and locked cabinet until returned to Pearl Therapeutics or designee.

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

7 STUDY PROCEDURES

It is recommended that whenever possible, all assessments during Visits 3 through 14 be conducted in the following order: vital signs, ECGs, clinical laboratory assessments, and spirometry.

7.1 Efficacy Assessments

7.1.1 Pulmonary Function Tests

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

Except at Visits 1A and 1B, spirometry will be conducted at each visit 60 minutes and 30 minutes prior to Ventolin HFA, Pulmicort Flexhaler, or randomized study drug administration. The average of these two assessments will be used to calculate the baseline and pre-dose values for each parameter. At Visits 1A and 1B, the pre-bronchodilator PFT will be performed prior to administration of Ventolin HFA (albuterol).

At Visits 3, 6, 9, and 12 (Day 1 of each treatment period) subjects must meet the Baseline Stability Criteria (see Section 5.1) prior to dosing in order to continue in the study.

Refer to Section 5.1 and Section 5.2 for specific spirometry inclusion/exclusion criteria that result in discontinuation from the study.

7.1.2 Characterization of Reversibility

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

- Reversibility testing to Ventolin HFA:
- Perform pre-bronchodilator PFTs prior to administration of Ventolin HFA (albuterol). **Note**: A single pre-dose bronchodilator PFT is collected at Visits 1a/1b. Pre-bronchodilator PFTs are collected at -60 min and -30 min at Visit 2.
- 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 at 30 minutes, a repeat post-bronchodilator PFT may be performed at 60 minutes to assess reversibility.
- Subjects who do not meet reversibility criteria at Visit 1a may, at the discretion of the investigator, be retested for reversibility at Visit 1b. Subjects who fail to meet reversibility criteria at Visit 1b will be screen failed. Subjects who do not meet reversibility criteria at Visit 2 following at least 14 days on Pulmicort Flexhaler will be screen failed.

7.1.3 FEV_1 Baseline Stability Criteria

Baseline stability criteria are as follows:

- At Visit 3, 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 2 (see Section 5.1 for baseline FEV_1 stability inclusion criterion). At Visit 3, 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 two assessments meet the baseline stability requirements (i.e., within ± 20%), the initial 60 minute pre-dose assessment will not be used and the last two assessments will be used to establish the eligibility criteria. Subjects who do not meet the FEV_1 baseline stability criteria at Visit 3 must be screen failed.
- At Visits 6, 9, and 12, 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 two assessments meet the baseline stability requirements (i.e., within ±20%), the initial 60 minute pre-dose assessment will not be used and the last two assessments will be used to establish the eligibility criteria.
- Subjects must meet the FEV_1 baseline stability criteria to be eligible for dosing at Visits 6, 9 and 12. Subjects who do not meet the FEV_1 baseline stability criteria at Visits 6, 9 and 12 must be rescheduled as soon as is practical but within the protocol-specified washout window (14–21 days between Treatment Periods). Subjects who fail to meet stability criteria after 2 attempts within a Washout Period will be discontinued.

7.1.4 Rescue Criteria for Randomized Subjects

Rescue criteria will be evaluated on Visits 4, 7, 10, and 13 (Day 15 of each Treatment Period), and during any unscheduled visits occurring during any Treatment Period. Subjects meeting rescue criteria will be advanced to the Washout Period and given treatment with Pulmicort Flexhaler 180 µg BID.

The Rescue Criteria are met if the average of the -60 min and -30 min FEV_1 are > 30% below 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 > 30% below the average of Visit 3 baseline FEV_1, but if the -30 min assessment is within 30%, then another assessment may be conducted 30 minutes later (at the Investigator's discretion). If the last two assessments meet the rescue criteria requirements (i.e., within ± 30%), the initial 60 minute pre-dose assessment will not be used and the last two assessments will be used to establish the eligibility criteria.

In lieu of FEV_1 criteria, if a Rescue Period is required based on worsening of asthma symptoms (e.g., cough, wheeze, nighttime awakenings, increased SABA use, etc.), and in the opinion of the Investigator, the subject may to be transitioned to a Washout Period. The Investigator should make every effort to collect trough PFTs prior to transitioning the subject to a Washout Period.

If a subject is advanced to a Washout Period and that period is completed, subjects may continue in the study to the next Treatment Period provided the Baseline Stability Criteria are met (see Section 5.1).

If the Rescue Criteria are met during the fourth and final Treatment Period, then the procedures for discontinuation should be followed and the subject will be considered to have successfully completed the treatment portion of the study.

Refer to Section 8.9 for instructions on handling subjects who meet Rescue Criteria.

7.1.5 Standardization of Spirometry Collections

All pulmonary function tests, including FEV_1, FVC, PEFR and $FEF_{25–75\%}$ 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 at the Investigator meetings. All technicians will be required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable pulmonary function tests (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 [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 i.e., at <2 L/sec, 4-6 L/sec and >8 L/sec with temperature and barometric pressure correction. The calibration syringe must meet ATS specifications and must not be used beyond the expiry date. Required accuracy is ± 3%, i.e., 3.09 L to 2.91 L (ATS/ERS). The results will be printed and maintained in a calibration log, which will be monitored for compliance during the monitoring visits (see Appendix 2).

7.1.6 Subject eDiary Data Collection

Subjects will be provided with an eDiary to be completed twice daily to record time of study medication administration and Pulmicort Flexhaler, morning and evening asthma symptoms, the use of study medication, Pulmicort Flexhaler and rescue albuterol (Ventolin HFA), and 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 electronic diary and training the subject on the proper use of the eDiary.

Subjects will be issued and trained on an eDiary at Screening Visit (Visit 1a or 1b) and instructed to collect eDiary data during the Screening Period (between Visit 1 to Visit 3).

Site personnel will review the eDiary during the Screening Period to assess the subject's compliance and understanding of how to use the eDiary to maintain a daily record of their time of dosing for Pulmicort Flexhaler, rescue medication use, morning and evening asthma symptoms and collection of daily peak flow rates using a Sponsor-provided portable peak flow meter.

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

At Visits 3, 6, 9, and 12 (Day 1 of each Treatment Period), subjects will receive an eDiary in which they will be asked to maintain twice-daily eDiary records (AM and PM) until the end of the Treatment Period.

Electronic Diary data will be collected during the Washout Periods (between Visits 5 and 6, Visits 8 and 9, and Visits 11 and 12).

Note: At all treatment visits (Visits 3-14), subjects will record pre-dose and 30 minute post-dose home peak flow values and the time of study medication dosing in their eDiary while in the clinic.

At Visits 3, 4, 5, 7, 8, 10, 11, 13 and 14, site personnel must review eDiary data prior to dosing study medication in the clinic (see Table 9).

The eDiary data report will be available to site personnel through the vendor's server. The eDiary data report 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. The subject should be reinstructed, as appropriate, on the importance of recording twice daily entries if missing entries are observed. If the subject demonstrates persistent eDiary compliance issues the subject should be evaluated, at the Investigator's discretion, for further study continuation.

7.1.7 Rescue Ventolin HFA Use

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

7.1.8 Home Peak Expiratory Flow Rate

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

Subjects will be issued and trained on peak flow meter use at Screening Visit (Visit 1a *or* 1b) and instructed to collect peak flow meter data during the Screening Period (between Visit 1 to Visit 3).

At Visits 3, 6, 9, and 12 (Day 1 of each Treatment period), subjects will be given a peak flow meter and be asked to record peak flow readings in their eDiary until the end of the Treatment Period.

Peak flow meter data will be collected during the Washout Periods (between Visits 5 and 6, Visits 8 and 9, and Visits 11 and 12).

The peak flow meter will be used by all subjects for home measurements of pre- and post-dose morning and evening assessments. At each study visit, the Investigator will review the PEFR readings and any findings will be discussed with the subject and clinical relevance determined. Subjects will bring their peak flow meter to the clinic at each visit.

At each treatment visit (Visits 3-14) subjects will measure, in clinic, PEFR immediately before and 30 minutes after dosing with study medication and must record pre and post peak flow values and time of dosing in their eDiary.

Note: The in-clinic 30 minute post-dose PEFR at each treatment visit (Visits 3 – 14) should be obtained after spirometry assessments allowing enough time for the subject to recover from the pulmonary function test maneuvers. The subject will be instructed to forcefully exhale from total lung capacity 3 times into the peak flow meter and confirm the collection of PEFR measurements on the eDiary. These PEFR measurements will be performed from Day 1 to Day 29 of each Treatment Period at home and on in-clinic days.

Subjects will perform PEFR measurements at home in the morning and in the evening immediately before and 30 minutes after dosing during the screening and Treatment Periods.

7.1.9 Medication Compliance

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

7.1.10 Asthma Control Questionnaire (ACQ)

The Asthma Control Questionnaire (ACQ) will be completed at Visits 3 through 14 before any other study procedures are performed.

The ACQ (Juniper, 1999) was developed and validated to measure asthma control in adults (see Appendix 6). It is 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).

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 Asthma Control Questionnaire (ACQ) (Juniper, 1999) was developed 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.

Subjects who do not meet an ACQ minimum score of ≥1.5 at Visit 3 will be screen failed. (see Section 5.1)

7.2 Safety Assessments

The safety assessments include ECGs, vital sign measurements, clinical laboratory tests, monitoring for paradoxical bronchospasm, physical examination findings, AEs and SAEs during the study period.

7.2.1 Medical/Surgical History and Physical Examination

Medical history will be collected at Screening and updated during Visits 1a to Visit 3 (Screening Period). A complete physical examination will be performed at Visit 1a (Screening) and Visit 14 or at the Premature Discontinuation Visit (Early Termination Visit).

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 14. Height will be recorded at Visit 1a (Screening) only.

Note: At Visit 1a, obtain a chest x-ray *only* if the subject has not had a chest x-ray or computed tomography (CT) scan of the chest/lungs within the last 6 months.

7.2.2 Vital Sign Measurements

At all visits (including the Premature Discontinuation Visit), hear rate, systolic and diastolic blood pressure (SBP/DBP) will be assessed. Assessments of HR and BP will be obtained after the subject is supine or seated for 5 – 10 minutes. If, in the opinion of the Investigator, a clinically significant vital sign change occurs, then the measurement should be repeated at medically appropriate intervals until the value returns to within an acceptable range**.**

A single set of vital signs will be obtained at Visits 1a (Screening) and Premature Discontinuation Visit (see Section 8.10).

At Visit 3 to Visit 14, vital signs will be obtained pre-dose within 1 hour of in-clinic dosing and at 30 minutes post-dose. Temperature will be obtained only at pre-dose at all visits and will not be repeated at subsequent time points unless clinically indicated (see Table 9).

Refer to Section 5.2 for specific vital signs exclusion criteria.

7.2.3 12-Lead Electrocardiogram (ECG)

A 12-lead ECG will be obtained at Visit 1a (Screening). At Visits 3, 5, 6, 8, 9, 11, 12, 14 (Day 1 and Day 29 of each Treatment Period), an ECG recording will be obtained pre-dose within 1 hour of in-clinic dosing (see Table 9). 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 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 site phone training sessions. 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 [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: HR, RR interval, PR interval, QRS axis, QRS interval, and QT/QTcF (Fridericia's Formula) interval.

QT intervals and calculated QTcF (Fridericia's Formula) 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. Refer to Section 5.2 for specific QTcF criteria that will prompt the Investigator to exclude subjects from the study. If QTcF interval prolongation exceeds the permissible limits for inclusion in the study, and is verified during treatment, the subject's medical background should be examined closely for risk factors that may have contributed to the event, including genotyping for hereditary long QT syndromes, if appropriate.

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, and prior to dosing at Visits 3, 5, 8, 11, and 14 (see Table 9)

Serum pregnancy testing will be performed in women of child-bearing potential.at Visit 1a (Screening), Visit 14, and, as appropriate, at the Premature Discontinuation Visit. Urine hCG testing will occur at Visits 3, 6, 9 and 12.

See Section 5.2 for specific criteria for clinical chemistry exclusion criteria.

The following clinical laboratory parameters that will be assessed are noted in Table 8.

Table 8. Clinical Laboratory Measures

Hematology	
Hemoglobin	Mean corpuscular hemoglobin (MCH)
Hematocrit	Mean corpuscular hemoglobin concentration (MCHC)
White Blood Cell count with differential	Mean corpuscular volume (MCV)
Red Blood Cell count	
Platelet Count	
Clinical Blood Chemistry	**Other Clinical Blood Chemistry**
Liver Function Tests	Albumin
Alanine aminotransferase (ALT)	Blood urea nitrogen (BUN)[a]
Aspartate aminotransferase (AST)	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 Final Visit only and Urine HCG at appropriate visits for this study as detailed in Table 9.
Creatinine clearance will be estimated by the CKD-EPI published formula. Parameters included in the Basic Metabolic Panel (BMP).

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 case report form and on the AE Reporting Form. If the AE is "alarming", the Investigator must report the AE immediately to Pearl Therapeutics. In addition, certain AEs (as described in Section 7.2.6.2) are classified as "serious" and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as a serious adverse event to Pearl Therapeutics or its designee.

In the case of serious adverse events, after discussing the details of the AE, 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 adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any

judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Adverse events include, but are not limited to:

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

An AE does **not** include:

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

7.2.6.3 Pre-Randomization Adverse Events

Adverse events that occur between the time the subject signs the ICF for the study and the time when that subject is randomized will be summarized as medical history and not as a treatment emergent adverse event unless the event meets the definition of a serious AE (SAE) as defined in Section 7.2.6.2.

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 adverse event to the study drug administration will be assessed by the Investigator after careful consideration, and according to the following guidelines:

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

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

Criteria for a "clinically significant" laboratory abnormality are:

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

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

7.2.6.7 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 adverse event
- 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 patient or 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 adverse event 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 a serious adverse event. At a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report using the appropriate form (e.g., SAE Report Form). After the initial report, as necessary, the Investigator must provide any additional information on a SAE to the Medical Monitor within two working days after he/she receives that information. This follow-up information will be a detailed written report that will include copies of hospital records, case reports, and autopsy reports, and other pertinent documents.

Post-study SAEs following the last dose of study drug must be reported to Pearl Therapeutics as described in Section 7.2.6.10.

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

7.2.6.9 Supplemental Investigations of SAEs

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

7.2.6.10 Post-Study Follow-Up of Adverse Events

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

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

7.2.6.11 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 following the last dose of study drug, it must be reported to Pearl Therapeutics, whether or not the event is attributable to study drug. All SAEs must be reported to Pearl Therapeutics no later than 24 hours after the Investigator recognizes/classifies the event as a serious adverse event.

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 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 AEs of Interest

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 PEFR of $\geq$30% from the pre-dose value, with associated asthma symptoms of wheezing, shortness of breath and/or cough. All AEs and SAEs will be recorded as appropriate.

7.2.8 Overdose

An overdose is defined as a dose greater than the high 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, adverse events, 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 notice in advance by the Investigator for any reason as per the terms of the contract with Pearl Therapeutics. The reason should be communicated in writing to Pearl Therapeutics.

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

8 STUDY ACTIVITIES

Detailed schedules for pre- and post-dose procedures to be performed on each study visit are provided (see Table 9).

Table 9. Schedule of Events

Procedures	Screening[a]			Treatment Period 1[a]			Treatment Period 2[a]			Treatment Period 3[a]			Treatment Period 4[a]			Phone Follow-Up
	Visit 1a	Visit 1b (as needed)	Visit 2	Visit 3 Rand. TP 1 Day 1	Visit 4 TP 1 Day 15	Visit 5 TP1 Day 29	Visit 6 TP 2 Day 1	Visit 7 TP 2 Day 15	Visit 8 TP 2 Day 29	Visit 9 TP 3 Day 1	Visit 10 TP 3 Day 15	Visit 11 TP 3 Day 29	Visit 12 TP 4 Day 1	Visit 13 TP 4 Day 15	Visit 14 TP 4 Day 29 or final visit[q]	Telephone Follow-up
Treatment Day[a]	**Up to -28**	**Up to -27**	**-14 to -1**	**1[a]**	**15±2 [a]**	**29±2 [a]**	**1[a]**	**15±2 [a]**	**29±2 [a]**	**1[a]**	**15±2 [a]**	**29±2 [a]**	**1[a]**	**15±2 [a]**	**29±2 [a]**	**7-14 [a]**
Informed Consent	X															
Eligibility Criteria	X	X	X	X												
Verify Cont. Eligibility					X	X	X	X	X	X	X	X	X	X	X	
Ventolin HFA Reversibility[b]	X	X	X													
Demographics, Medical, Surgical History	X	X	X	X												
Switch to Pulmicort Flexhaler 180 µg BID[c]	X					X			X			X				
ACQ[d]				X	X	X	X	X	X	X	X	X	X	X	X	

ACQ=asthma control questionnaire; BID=twice-daily; ECG=electrocardiogram; PEFR= peak expiratory flow rate; TP=Treatment Period

Note: At Visit 1a, obtain a chest x-ray *only* if the subject has not had a chest x-ray or computed tomography (CT) scan of the chest/lungs within the last 6 months.

[a] Visit windows during each Treatment Period are relative to Day 1 of that Treatment Period. Washout Periods occurring between Visits 5 and 6, Visits 8 and 9, and Visits 11 and 12 are 14-21 days. If Visit 5, 8 or 11 occurs at Day 31 or later, the site must contact Sponsor for guidance prior to initiating next treatment period. Visit 1b must occur before Visit 2

[b] See instructions for reversibility assessment in Section 7.1.2

[c] At Screening, stop prohibited asthma medications and change asthma medications as specified in Section 5.4 (i.e., Sponsor-provided Pulmicort Flexhaler and Ventolin HFA)

[d] See instructions for administering the ACQ in Section 7.1.10 and Appendix 6

Table 9. Schedule of Events (continued)

Procedures	Screening[a]			Treatment Period 1[a]			Treatment Period 2[a]			Treatment Period 3[a]			Treatment Period 4[a]			Phone Follow-Up
	Visit 1a	Visit 1b (as needed)	Visit 2	Visit 3 Rand. TP 1 Day 1	Visit 4 TP 1 Day 15	Visit 5 TP1 Day 29	Visit 6 TP 2 Day 1	Visit 7 TP 2 Day 15	Visit 8 TP 2 Day 29	Visit 9 TP 3 Day 1	Visit 10 TP 3 Day 15	Visit 11 TP 3 Day 29	Visit 12 TP 4 Day 1	Visit 13 TP 4 Day 15	Visit 14 TP 4 Day 29 or final visit[q]	Telephone Follow-up
Prior Concomitant Medications[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Spirometry[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination[g]	X														X	
Vital Signs[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[i]	X			X		X	X		X	X		X	X		X	
Pregnancy Test[j]	X			X			X			X			X		X	
Clinical Laboratory Testing[k]	X			X		X			X			X			X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inhalation Device Training[l]	X			X			X			X			X			
Study Drug Administration[l]				X	X	X	X	X	X	X	X	X	X	X	X	

[e] See listing of prohibited and concomitant medication in Section 5.4. At all visits beyond Screening, note time of last dose of short-acting bronchodilator and other asthma medications (if <4 hours, visit should be rescheduled).

[f] See Section 7.1.1 and Section 7.1.3 for guidance related to Spirometry assessments and criteria.

[g] Weight, assessed in ordinary indoor clothing with shoes removed at Visit 1a (Screening) and Visit 14. Height will be recorded at Visit 1a (Screening) only. (See Section 7.2.1).

[h] See Section 7.2.2 for guidance on vital signs collection.

[i] See Section 7.2.3 for guidance on ECG assessment

[j] See Section 7.2.5 for guidance on the administration of pregnancy test (women of child- bearing potential only).

[k] See Section 7.2.5 for guidance on clinical laboratory testing.

[l] At the start of each treatment visit, subject must withhold all asthma medications, including study medication and rescue medications (Ventolin HFA) for at least 4 hours prior to start of test day procedures. If appropriate, re-train subject on use of inhalation device.

Table 9. Schedule of Events (continued)

Procedures	Screening[a]			Treatment Period 1a			Treatment Period 2a			Treatment Period 3a			Treatment Period 4a			Phone Follow-Up
	Visit 1a	Visit 1b (as needed)	Visit 2	Visit 3 Rand. TP 1 Day 1	Visit 4 TP 1 Day 15	Visit 5 TP1 Day 29	Visit 6 TP 2 Day 1	Visit 7 TP 2 Day 15	Visit 8 TP 2 Day 29	Visit 9 TP 3 Day 1	Visit 10 TP 3 Day 15	Visit 11 TP 3 Day 29	Visit 12 TP 4 Day 1	Visit 13 TP 4 Day 15	Visit 14 TP 4 Day 29 or final visit[q]	Telephone Follow-up
Dispense Peak Flow Meter[m]	X	X														
Dispense Subject Diary[m]	X	X														
Collect PEFR in Clinic[n]				X	X	X	X	X	X	X	X	X	X	X	X	
Review Subject Diary[m]			X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Dispensing/ Collection	X			X	X	X	X	X	X	X	X	X	X	X	X	
Paradoxical Bronchospasm[o]				X	X	X	X	X	X	X	X	X	X	X	X	
Return to Maintenance Asthma Medications[p]															X	

ACQ=asthma control questionnaire; BID=twice-daily; ECG=electrocardiogram; PEFR= peak expiratory flow rate; TP=Treatment Period

[m] See Section 7.1.6 for guidance on the eDiary use, and Section 7.1.8 for guidance on peak flow meter use.

[n] See Section 7.1.8 for further information on the collection of PEFR.

[o] See Section 7.2.7 for definition of paradoxical bronchospasm.

[p] At the end of the Visit 14, return subject to pre-study or other appropriate inhaled maintenance asthma medications.

[q] If a subject discontinues the study prematurely (early termination), the procedures that should be completed at the final visit are defined in Section 8.10

8.1 Screening Visit (Visits 1a, 1b)

- Obtain informed consent.
- Register subject in IWRS to obtain subject screening number.
- Obtain demographic data, including age, race, smoking history, medical/surgical history, and asthma medication history.
- Verify that subject meets inclusion/exclusion criteria.
- Obtain medication history, including asthma medications.
- Conduct a serum pregnancy test (β (beta)-human chorionic gonadotropin [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 (i.e., 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 (HR and BP after being supine or seated for 5 – 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's ability to use MDI correctly (provide coaching as needed).
  - Repeat spirometry assessments 30 minutes following 4 puffs Ventolin HFA
  - Confirm subject is reversible (see Section 7.1.2 for Reversibility Criteria)
- Obtain clinical laboratory samples (hematology and chemistry).
- At Visit 1a, obtain a chest x-ray *only* if the subject has not had a chest x-ray or computed tomography (CT) scan of the chest/lungs within the last 6 months.
- Schedule next visit:
  - Visit 1b at Investigator discretion for subjects who fail reversibility criteria at Visit 1a (at least 1 day prior to Visit 2).
  - Visit 2 for subjects who meet eligibility criteria to continue, at least 14 days but no more than 27 days from Visit 1a.
- Stop prohibited asthma medications and change concurrent asthma medications as specified in the protocol (see Section 5.4).
- Subjects who meet entry criteria will have their inhaled asthma medication switched to Pulmicort Flexhaler 180 µg BID and Ventolin HFA for rescue medication.
- 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 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 adverse event unless the event meets the definition of an SAE (see Section 7.2.6.2).

8.2 Visit 1b (At Investigator Discretion)

- Assess continued eligibility criteria
- Record concomitant medications
- Repeat spirometry assessment and reversibility to Ventolin HFA (Section 5.1 and Section 7.1.2.
- Record any AEs that have occurred
- Schedule Visit 2 for subjects who meet eligibility criteria to continue, at least 14 days but no more than 27 days from Visit 1a.

8.3 Visit 2 (Reversibility Testing Following Pulmicort Flexhaler Run-in)

- Review subject eDiary and retrain subject if subject has not met eDiary compliance requirement (see Section 5.2).
- Determine time of last SABA use (if < 4 hours, Visit 2 should be delayed or rescheduled).
- Review inclusion/exclusion criteria and confirm subject eligibility to continue.
- If not previously reviewed, review clinical laboratory testing results from Visit 1a and record any clinically significant findings.
- Record AEs, if any.
- Review all prior medications and adherence to asthma regimen,
- Obtain pre-bronchodilator vital signs.
- Perform reversibility testing to Ventolin HFA (see Section 5.1 and Section 7.1.2).
- Schedule Visit 3 (Randomization Visit) for subjects who meet eligibility criteria to continue. **Note**: Visit 3 can be scheduled at minimum, 1 day after Visit 2, and no later than 28 days after Visit 1a (Screening).

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

- Review subject eDiary and peak flow values. Screen fail subject if subject has not met eDiary compliance requirement (see Section 5.2).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the CRF (if <4 hours, Visit 3 must be rescheduled).
- Assess ACQ (see Appendix 6)
- Record AEs, (if any).
- Review concomitant medications to ensure adherence to study specified regimen.
- Collect Sponsor-provided Pulmicort Flexhaler and Ventolin HFA dispensed during the Screening Period.
- Complete all pre-dose assessments, including vital signs, ECGs, clinical laboratory testing, urine pregnancy testing and spirometry.
- Review inclusion/exclusion criteria, including baseline stability criteria (see Section 5.1) and confirm subject eligibility for Randomization

- Have subjects perform pre-dose eDiary collections including completion of symptom questions and pre-dose PEFR assessments.
- Obtain subject randomization number and 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 15–30 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 first dose of newly assigned study drug at the clinic.
  - The subject is to be considered randomized as soon as the site personnel have received the subject treatment assignment from the IWRS.
- Have subject perform post-dose eDiary collections including PEFR at 30 minutes post-dosing.
- Perform vital signs at 30 minutes post-dosing and assess subject for paradoxical bronchospasm.
- Subjects will be instructed to bring the eDiary, peak flow meter and all study medication to the next visit.
- Schedule Visit 4 within 14 ± 2days, and ensure subject has adequate supply of study drug and rescue Ventolin HFA.

8.5 Visits 6, 9, 12 (Day 1 of Treatment Periods 2, 3 and 4)

- Review subject eDiary and peak flow values, and retrain subject if subject has not met eDiary compliance requirement (see Section 5.2).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the CRF (if <4 hours, the visit must be rescheduled).
- Assess ACQ.
- Record AEs, (if any).
- Review concomitant medications to ensure adherence to study specified regimen.
- Collect Sponsor-provided Pulmicort Flexhaler and Ventolin HFA dispensed for use during the Washout Period.
- Complete all pre-dose assessments, including vital signs, ECGs, urine pregnancy testing, spirometry (60 and 30 minutes prior to dosing).
- Confirm subject eligibility to continue, including baseline stability criteria (see Section 5.1).
- 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 15–30 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 first dose of newly assigned study drug at the clinic.
- Subject record dosing time in the eDiary.
- Have subject perform post-dose eDiary collections including PEFR at 30 minutes post-dosing.
- Perform vital signs at 30 minutes post-dosing and assess subject for paradoxical bronchospasm.
- Subjects will be instructed to bring the eDiary, peak flow meter and all study medication to the next visit.
- 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.

8.6 Visit 4, 7, 10 and 13 (Day 15 of Treatment Periods 1, 2, 3 and 4)

- Review subject eDiary and peak flow values, and retrain subject if subject has not met eDiary compliance requirement (see Section 5.2).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the CRF (if <4 hours, the visit must be rescheduled).
- Assess ACQ.
- Record AEs, (if any).
- Review concomitant medications to ensure adherence to study specified regimen.
- Collect blinded study drug dispensed during the prior visit (Day 1 of the Treatment Period).
- Complete all pre-dose assessments, including vital signs and spirometry (60 and 30 minutes prior to dosing).
- Review subject eligibility to continue.
- 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 15–30 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 first dose of newly assigned study drug at the clinic.
- Record dosing time in the eDiary.
- Have subject perform post-dose eDiary collections including PEFR at 30 minutes post-dosing.
- Perform vital signs at 30 minutes post-dosing and assess subject for paradoxical bronchospasm.
- Obtain new MDI and assignment information from IWRS.

- Subjects will be instructed to bring the eDiary, peak flow meter and all study medication to the next visit.
- Schedule the next visit (Day 29 of the Treatment Period) within 29 ± 2 days from Day 1 of the Treatment Period, and ensure subject has adequate supply of study drug and rescue Ventolin HFA.

8.7 Visit 5, 8 and 11 (Day 29 of Treatment Period 1, 2 and 3)

- Review subject eDiary and peak flow values, and retrain subject if subject has not met eDiary compliance requirement (see Section 5.2).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the CRF (if <4 hours, the visit must be rescheduled).
- Assess ACQ.
- Record AEs, (if any).
- Review concomitant medications to ensure adherence to study specified regimen.
- Collect Sponsor-provided study medication including Ventolin HFA dispensed during the prior visit (Day 15 of the Treatment Period).
- Complete all pre-dose assessments, including vital signs, ECGs, clinical laboratory testing, and spirometry (60 and 30 minutes prior to dosing).
- Review subject eligibility to continue.
- Have subjects perform pre-dose eDiary collections including completion of symptom questions and pre-dose PEFR assessments.
- Subject will administer in-clinic dosing from MDI dispensed at previous visit (Day 15 of Treatment Period).
- Record dosing time in the eDiary.
- Have subject perform post-dose eDiary collections including PEFR at 30 minutes post-dosing.
- Perform vital signs at 30 minutes post-dosing and assess subject for paradoxical bronchospasm (see Section 7.2.7).
- Obtain from IWRS the Pulmicort Flexhaler 180 µg and Ventolin HFA assignment for use during the Washout Period. Subjects will be instructed to bring the Pulmicort Flexhaler and Ventolin HFA to the next visit, and continue to complete their PEFRs and their eDiary at home during the Washout Period.
- Schedule the next visit (Day 1 of the Treatment Period) within 14–21 days from Day 29 of the previous Treatment Period.

8.8 Visit 14 (Final Study Visit, Day 29 of Treatment Period 4)

- Review subject eDiary and peak flow values (see Section 5.2).
- Determine time of last dose of short-acting bronchodilator and other asthma medications on the CRF (if <4 hours, the visit must be rescheduled).
- Assess ACQ.
- Record AEs, (if any).

- Review concomitant medications to ensure adherence to study specified regimen.
- Collect Sponsor-provided study medication including Ventolin HFA dispensed during the prior visit (Day 15 of Treatment Period 4).
- Complete all pre-dose assessments, including vital signs (including weight), physical examination, ECGs, clinical laboratory testing, serum pregnancy testing, and spirometry (60 and 30 minutes prior to dosing).
- Review subject eligibility to continue.
- Have subjects perform pre-dose eDiary collections including completion of symptom questions and pre-dose PEFR assessments.
- Subject will administer in-clinic dosing from MDI dispensed at previous visit (Day 15 of Treatment Period).
- Record dosing time in the eDiary.
- Have subject perform post-dose eDiary collections including PEFR at 30 minutes post-dosing.
- Perform vital signs at 30 minutes post-dosing and assess subject for paradoxical bronchospasm (see Section 7.2.7).
- Collect subject eDiary and peak flow meter.
- Return the subject to pre-study or appropriate asthma maintenance medication.
- Schedule a follow-up telephone call 7–14 days from Visit 14.

8.9 Management of Randomized Subjects Who Meet Rescue Criteria

- If rescue criteria are met at a scheduled visit during Treatment Periods 1, 2 and 3 (see Section 7.1.4), the Investigator at their discretion, may complete the remaining scheduled visit procedures (i.e., clinical laboratory testing, vital signs, etc.) and transition the subject to rescue period as follows:
  - Obtain from IWRS the Pulmicort Flexhaler 180 µg and Ventolin HFA assignment for use during the Rescue Period. Subjects will be instructed to bring the Pulmicort Flexhaler and Ventolin HFA to the next visit, and continue to complete their PEFRs and their eDiary at home during the Washout Period.
  - Schedule the next visit (Day 1 of the next Treatment Period) within 14–21 days from the day the Washout Period was initiated.
  - After the Washout Period, subjects may continue in the study to the next Treatment Period provided the Baseline Stability Criteria are met (see Section 5.1).
- Except during Treatment Period 4, if an unscheduled visit is required to manage worsening of asthma symptoms, and in the opinion of the Investigator, the subject may be transitioned to the Washout Period, the procedures outlined in Section 8.8 (Day 29) may be conducted at the Investigator's discretion during the unscheduled visit, prior to Washout Period transition described below.
  - Obtain from IWRS the Pulmicort Flexhaler 180 µg and Ventolin HFA assignment for use during the Rescue Period. Subjects will be instructed to bring the Pulmicort Flexhaler and Ventolin HFA to the next visit, and continue to complete their PEFRs and their eDiary at home during the Washout Period.

- Schedule the next visit (Day 1 of the next Treatment Period) within 14–21 days from day the Washout Period was initiated.
- After the Washout Period, subjects may continue in the study to the next Treatment Period provided the Baseline Stability Criteria are met (see Section 5.1).

- If the Rescue is required during the fourth and final Treatment Period, then the procedures for discontinuation should be followed and the subject will be considered to have successfully completed the treatment portion of the study.

8.10 Unscheduled Visits/Premature Discontinuation (Early Termination) Visits

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

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

The following minimum procedures should be completed 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 subject discontinuation reason.
- Schedule a follow-up telephone call 7-14 days post last study drug dosing. If the discontinuation visit is performed >7 days post last study drug dosing a follow-up telephone call will not be required.

8.11 Follow-Up Telephone Call

Subjects will be followed-up through a telephone call 14 days post 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

8.12 Completion of the Study

The Investigator will document the completion or the reason for early withdrawal by a subject 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 (e.g., 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 did 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 4-period, 5-treatment, incomplete block cross-over design evaluating the following 5 treatments in approximately 150 subjects:

- BD MDI 320 µg
- BD MDI 160 µg
- BD MDI 80 µg
- BD MDI 40 µg
- Placebo MDI

The primary objective of this study will be to demonstrate a lung function benefit of BD MDI BID compared with Placebo MDI in adult subjects with mild to moderate persistent asthma.

9.2 Protocol Variables

9.2.1 Efficacy Endpoints

Baseline will use the average of the -60 and -30 min pre-dose values on Day 1 of each treatment period for clinical measured variables and is defined as the average of the non-missing Day 1 pre-dose means (averages of 60 and 30 minute pre-dose assessments) for each subject. 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

- Change from baseline in morning pre-dose trough FEV_1 at the end of the Treatment Period

9.2.1.2 Secondary Efficacy Endpoints

- Change from baseline in mean morning pre-dose and mean evening pre-dose peak flow rate (PEFR) readings taken by the subject and recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over the last week of the Treatment Period
- Change from baseline in Asthma Control Questionnaire (ACQ) score at the end of the Treatment Period

9.2.1.3 Other Efficacy Endpoints

- Change from baseline in morning pre-dose trough FEV_1 over the Treatment Period and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in mean morning and evening pre- and post-dose daily PEFR readings taken by subjects and recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Change from baseline in the mean number of puffs of rescue Ventolin HFA recorded in the subject eDiary over each week of the Treatment Period and over the entire Treatment Period
- Percentage of days without rescue Ventolin HFA use over each week of the Treatment Period and over the entire Treatment Period
- Change from baseline in pre-dose trough forced vital capacity (FVC) at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough PEFR at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in pre-dose trough forced expiratory flow 25-75% ($FEF_{25-75\%}$) at the end of the Treatment Period, over the entire Treatment Period, and at Day 15 and Day 29 of the Treatment Period
- Change from baseline in the number of nighttime awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period, over each week of the Treatment Period, and over the entire Treatment Period
- Percentage of nights with awakenings due to asthma symptoms recorded in the subject eDiary over the last week of the Treatment Period and over the entire Treatment Period

9.2.2 Safety Endpoints

The safety assessments include electrocardiograms (ECGs,) vital sign measurements, clinical laboratory tests, monitoring for paradoxical bronchospasm, physical examination findings, AEs and SAEs during the study period.

9.3 Analysis

9.3.1 Primary Efficacy Analysis

The primary efficacy analysis will compare the changes from baseline at the end of the treatment periods in morning pre-dose trough FEV_1 between BD MDI treatments and Placebo MDI using a repeated measures mixed model with a random subject effect for the correlation across periods. The fixed effects will include baseline FEV_1, response to albuterol, and period. Sequence will also be included if it explains significant variability ($p<0.10$). Estimated treatment differences and 95% CI's will be provided for all treatment comparisons. Multiplicity will be controlled for the BD MDI to Placebo MDI comparison using a sequential approach (Refer to Section 9.5). A two-sided alpha level of 0.05 will be employed.

The primary efficacy analysis will compare the changes from baseline at the end of the treatment periods in morning pre-dose trough FEV_1 between BD MDI treatments and Placebo MDI using a repeated measures mixed model with a random subject effect for the correlation across periods. The fixed effects will include baseline FEV_1, response to albuterol, and period. Sequence will also be included if it explains significant variability ($p<0.10$). Estimated treatment differences and 95% CI's will be provided for all treatment comparisons. Multiplicity will be controlled for the BD MDI to Placebo MDI comparison using a sequential approach (Refer to Section 9.5). A two-sided alpha level of 0.05 will be employed.

The primary analysis will be the modified Intent-to-Treat (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 9.7).

9.3.2 Secondary Efficacy Analysis

The secondary endpoints will be analyzed using a similar model as the primary endpoint. Repeated measures mixed models with a random subject effect for the correlation across periods will be fit. The fixed effects will include the relevant baseline and period as covariates. Sequence will also be included if it explains significant variability ($p<0.10$).

Analyses of morning and evening PEFR and rescue Ventolin HFA usage will use the average of the non-missing 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.

9.3.3 Other Efficacy Analysis

The other efficacy endpoints will be analyzed using a similar model as the primary endpoint. Repeated measures mixed models will be fit with an unstructured covariance for the correlation within subject periods and random subject effect for correlation across periods. The fixed effects will include the relevant baseline, response to albuterol, and period as covariates. Sequence will not be included unless it was found to be important and included in the model for the primary endpoint. For analyses that use more than one measure per period, scheduled Treatment Day or Treatment Week will be added to the model as categorical covariates and their interaction with treatment will be included as well.

Additional comparisons will be made for pre-dose trough FEV_1 values between the Day 15 values and the values at the end of the baseline and Washout Periods in order to compare the efficacy of BD MDI to Pulmicort Flexhaler 180 µg. In order to perform these comparisons, a separate model will be fit where the baseline defined previously in Section 9.2.1 will be considered to represent the effect of Pulmicort. These data will be treated as coming from period 0. The model will therefore not include baseline or period since these would be confounded with Pulmicort treatment.

9.3.4 Safety Analysis

9.3.4.1 Adverse Events

Adverse events during each treatment regime will be summarized by the number of subjects experiencing an event. They will be tabulated at the level of the MedDRA preferred term, and the MedDRA System Organ Class. The version of MedDRA current at the time the first subject is randomized will be used throughout the study. Tabulations will be broken down by severity, seriousness, AE's leading to discontinuation, and by relationship to study drug. No hypothesis tests will be performed. Since the washout period includes treatment with Pulmicort Flexhaler, 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.

9.3.4.2 Paradoxical Bronchospasm

Paradoxical Bronchospasm will be considered an adverse event of special interest, and will be tabulated separately. Bronchospasm will be summarized by the number of subjects experiencing the event, during scheduled assessment periods on a test day and during the particular treatment period. We note that tabulations for bronchospasms differ from those for general adverse events, since the tabulation involves tabulating the incidence of paradoxical bronchospasm with onset during a treatment period. Bronchospasm with onset outside a treatment period will be listed separately. No hypothesis tests will be performed, but an appropriate confidence interval may be provided.

9.3.4.3 Clinical Laboratory Measurements

Summary statistics (mean, median, standard deviation and range) of change from baseline for scheduled pre-dose assessments will be tabulated for each laboratory parameter and treatment. 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.

9.3.4.4 Vital Signs

Summary statistics (mean, median, standard deviation and range) of change from baseline will be tabulated by vital sign parameter and treatment 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.

9.3.4.5 ECGs

Summary statistics (mean, median, standard deviation and range) for absolute values and change from baseline will be tabulated by ECG parameter and treatment 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.

9.4 Randomization

Subjects will be randomly assigned to a treatment sequence using an IWRS. Each sequence will include exactly 4 of the 5 treatments included in this study. All subjects will receive BD MDI 320, BD MDI 160 µg, and Placebo MDI in a randomized order, but only half of the subjects will receive BD MDI 40 or BD MDI 80 µg.

The 8 treatment sequences are shown below where A is Placebo MDI, B is BD MDI 320 µg, C is BD MDI 160 µg, D is BD MDI 80 µg, and E is BD MDI 40 µg:

ABCD

ABCE

BDAC

BEAC

CADB

CAEB

DCBA

ECBA

Randomization will be centralized and center will not be used as a stratification factor.

9.5 Experimental Design and Type I Error Control

The experimental design was chosen to be balanced with respect to period and first order carry-over should all subjects complete. The design was selected to limit exposure to 12 weeks of BD MDI treatment at any dose and to focus on the higher doses.

Type I error will be controlled for the primary endpoint by following a sequential approach. First BD MDI 320 µg will be compared to Placebo MDI using a two-sided alpha of 0.05. If the p-value is <0.05 for the comparison of BD MDI 320 µg to Placebo MDI, then the comparison of BD MDI 160 µg to Placebo MDI will be interpreted inferentially using a two-sided alpha=0.05. If the p-value is <0.05 for the comparison of BD MDI 160 µg to Placebo MDI, then the comparison of BD MDI 80 µg to Placebo MDI will be interpreted inferentially using a two-sided alpha of 0.05. Finally, if the p-value is <0.05 for the comparison of BD MDI 80 µg to Placebo MDI, then the comparison of BD MDI 40 µg to Placebo MDI will be interpreted inferentially using a two-sided alpha of 0.05.

Other than the specification of secondary endpoints, no further adjustments for Type I error will be made.

9.6 Sample Size Consideration

Power calculations are based on the properties of the primary endpoint, morning pre-dose trough $FEV_{1,}$ on the last day of each treatment period (end of treatment). An estimate of the total SD of 405 mL is taken from a 12-week trial comparing budesonide to ciclesonide (Boulet, 2006). Assuming that half of the variability comes from within subject and half between (i.e., intrasubject correlation=0.5), an estimate of the within subject standard deviation of 285 mL for morning pre-dose trough FEV_1 is obtained. Using this SD and assuming that 150 randomized provides approximately 120 completers, the power to demonstrate a 120 mL difference from Placebo MDI for BD MDI 320 μg or BD MDI 160 μg is approximately 90%. For BD MDI 80 μg and BD MDI 40 μg, the power to demonstrate a difference from Placebo MDI of 140 mL is approximately 80%.

9.7 Data Validation and Transformation

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

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

9.8 Analysis Plan

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

9.9 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 ITT Population including subjects who received treatment and have post-treatment efficacy data from at least two treatment periods. Data judged to be impacted by major protocol deviations will be determined prior to unblinding and excluded. 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 one 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.

9.10 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] (Version 9.2 or higher). 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 (IRB) or Independent Ethics Committee (IEC) 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 (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR parts 50, 54, 56, and 312).
- Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects) [http://www.wma.net/en/10home/index.html].
- Any additional regulatory requirements.

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

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

10.3 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 (i.e. Health Insurance Portability and Accountability Act), rules and regulations.

10.6 Quality Control and Assurance

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

10.7 Data Management

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

10.8 Study Monitoring

In accordance with applicable regulations, GCP, and Pearl Therapeutics procedures, clinical monitors will contact the site prior to 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 principal Investigator or sub-Investigators named on the Form FDA 1572 will need to complete a financial disclosure form prior to study initiation, at any time during the study execution if new information needs to be disclosed, and for 1 year after study completion. Investigators should make the IRB/IEC aware of any financial interests that the Investigator has in the investigational product.

10.11 Investigator's Final Report

Shortly after completion of the Investigator's participation in the study, the Investigator will submit a written report to Pearl 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 principal Investigator is responsible for the accuracy and completeness of all data from their site. Pearl Therapeutics (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.

2. **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 nonclinical 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, e.g., protocol and amendments, data tabulations, *etc*. The journal and reviewers will need to make arrangements to maintain the confidentiality of such supplemental information, where relevant, and 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. **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.

11 REFERENCE LIST

Akinbami L. United States Centers for Disease Control. Asthma Prevalence, Health Care Use and Mortality: United States 2003-2005. http://www.cdc.gov/nchs/products/pubs/pubd/hestats/ashtma03-05/asthma03-05.htm.

Clissold SP, Heel RC. Budesonide. A preliminary review of its pharmacodynamic properties and therapeutic efficacy in asthma and rhinitis. *Drugs.* 1984;28(6):485-518.

GINA, 2012 Global Initiative for Asthma GINA, 2012 . Global Strategy for Asthma Management and Prevention. Updated 2012. http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf

Hochaus G. New developments in corticosteroids. *Proc Am Thorac Soc*. 2004;1(3):269-274.

Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14:902-907.

Miller M, Hankinson J, Brusasco V, et al. American Thoracic Society/European Respiratory Society. ATS/ERS Task Force: Standardization of Lung Function Testing: Number 2 in Series. European Respiratory Journal 2005;26(2):319-338.

National Heart, Lung, and Blood Institute (NHBLI). National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report. 2007.

R Development Core Team.R: A language and environment for statistical computing.2003. A Foundation for Statistical Computing, Vienna, Austria.

United States Food and Drug Administration. FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm

WebMD. Drugs and Medications. Budesonide oral. http://www.webmd.com/drugs/drug-22008-budesonide+oral.aspx

World Health Organization (WHO). Asthma Fact Sheet. November 2013. http://www.who.int/mediacentre/factsheets/fs307/en/index.html

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 ≥15 s (longer times are recommended) and measuring volumes of ≥8 L (body temperature (i.e., 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 eight successive FVC maneuvers performed in a 10-minute period without inspiration from the instrument.

Display

For optimal quality control, both flow–volume and volume–time displays are useful, and test operators should visually inspect the performance of each maneuver for quality assurance before proceeding with another maneuver. This inspection requires tracings to meet the minimum size and resolution requirements set forth in this standard. Displays of flow versus volume provide more detail for the initial portion (first 1 s) of the FVC maneuver. Since this portion of the maneuver, particularly the peak expiratory flow 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 ≥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 two units of flow per one unit of volume

The time scale should be ≥20 mm-s^{-1}, and larger time scales are preferred (≥30 mm-s^{-1}) when manual measurements are made. When the volume–time plot is used in conjunction with a flow–volume curve (i.e., both display methods are provided for interpretations and no hand measurements are performed), the time scale requirement is reduced to 10 mm-s^{-1} from the usually required minimum of 20 mm-s^{-1} (Table 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 (e.g., industrial surveys), calibration checks and quality-control procedures must be repeated before further testing begins.

Key aspects of equipment quality control are summarized in Table A1-2.

Table A1-2. Summary of Equipment Quality Control

Test	Minimal Interval	Action
Volume	Daily	Calibration check with a 3 L syringe
Leak	Daily	2 cm H_2O (0.3 kPa) constant pressure for 1 minute
Volume Linearity	Quarterly	1 L increments with a calibrating syringe measured over the entire volume range
Flow Linearity	Weekly	Test at least three different flow ranges
Time	Quarterly	Mechanical recorder check with stop watch
Software	New versions	Log installation date and perform test using "known" subject

Calibration is the procedure for establishing the relationship between sensor-determined values of flow or volume and the actual flow or volume. A calibration check is different from calibration and is the procedure used to validate that the device is within calibration limits, e.g., ± 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 (e.g., monthly) leak tested at more than one volume up to their maximum; this can be done by attempting to empty them with the outlet corked. A dropped or damaged syringe should be considered out of calibration until it is checked.

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

Quality Control for Volume-Measuring Devices

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

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

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

Volume-type spirometer systems must be evaluated for leaks every day. The importance of undertaking this daily test cannot be overstressed. Leaks can be detected by applying a constant positive pressure of ≥3.0 cmH2O (0.3 kPa) with the spirometer outlet occluded (preferably at or including the mouthpiece). Any observed volume loss of .30 mL after 1 minute indicates a leak and needs to be corrected.

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

Quality Control for Flow-Measuring Devices

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

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

Equipment

For measurements of VC and IC, the spirometer or flow meter must comply with the requirements for FVC (as described previously) and be capable of accumulating volume for ≥30 s. Expiratory maneuvers or, ideally, both inspiratory and expiratory maneuvers should be included in the display of VC maneuver. Regardless of whether the inspiratory or expiratory maneuver is used for deriving measurements, a display of the entire recorded VC maneuver must be provided. The maximal expiratory volume must be assessed to determine

whether the subject has obtained a plateau in the expiratory effort. For display of the slow VC, the time scale may be reduced to 5 mm-s^{-1}.

TECHNICAL CONSIDERATIONS

Minimal recommendations for spirometry systems

Accurate results require accurate equipment. Spirometer equipment recommendations apply to all spirometers and are minimal requirements. In some circumstances, it may be appropriate to exceed these requirements (i.e., in some research/surveillance applications). Instrumentation recommendations should be followed to provide accurate spirometric data and information that is comparable from laboratory to laboratory and from one time period to another. The accuracy of a spirometry system depends on characteristics of the entire system, from the volume or flow transducer and the use of an in-line filter, to the recorder, display or processor. Changes in any aspect of the equipment or errors at any step in the process can affect the accuracy of the results. For example, if the BTPS correction factor is wrong, an accurately measured FVC will be incorrectly reported. Spirometers are not required to measure all of the indices in Table A1-1, but must meet the recommendations for those that are measured. Accuracy and repeatability recommendations apply over the entire volume range of the instrument.

Table A1-3. Range and Accuracy Recommendations Specified for Forced Expiratory Maneuvers

Test	Range/Accuracy (BTPS)	Flow Range ($L\text{-}s^{-1}$)	Time (s)	Resistance and Back Pressure	Test Signal
VC	0.5–8 L, ± 3% of reading or ± 0.050 L, whichever is greater	0-14	30		3-L Calibration syringe
FVC	0.5–8 L, ± 3% of reading or ±0.050 L, whichever is greater	0-14	15	<1.5 cm H_2O L^{-1} s^{-1} (0.15 kPa $L^{-1}s^{-1}$)	24 ATS waveforms, 3-L Cal Syringe
FEV_1	0.5–8 L, ± 3% of reading or ± 0.050 L, whichever is greater	0-14	1	<1.5 cm H_2O L^{-1} s^{-1} (0.15 kPa $L^{-1}s^{-1}$)	24 ATS waveforms
Time Zero	The time point from which all FEV_t measurements are taken.			Back extrapolation	

FEVt: forced expiratory volume in t seconds

BTPS correction

All spirometry values should be reported at BTPS by any method (measuring temperature and barometric pressure) proven effective by the manufacturer. For volume-type spirometers,

the temperature inside the spirometer should be measured for each breathing maneuver. Regardless of the BTPS correction technique used, the ambient temperature must always be recorded with an accuracy of ± 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

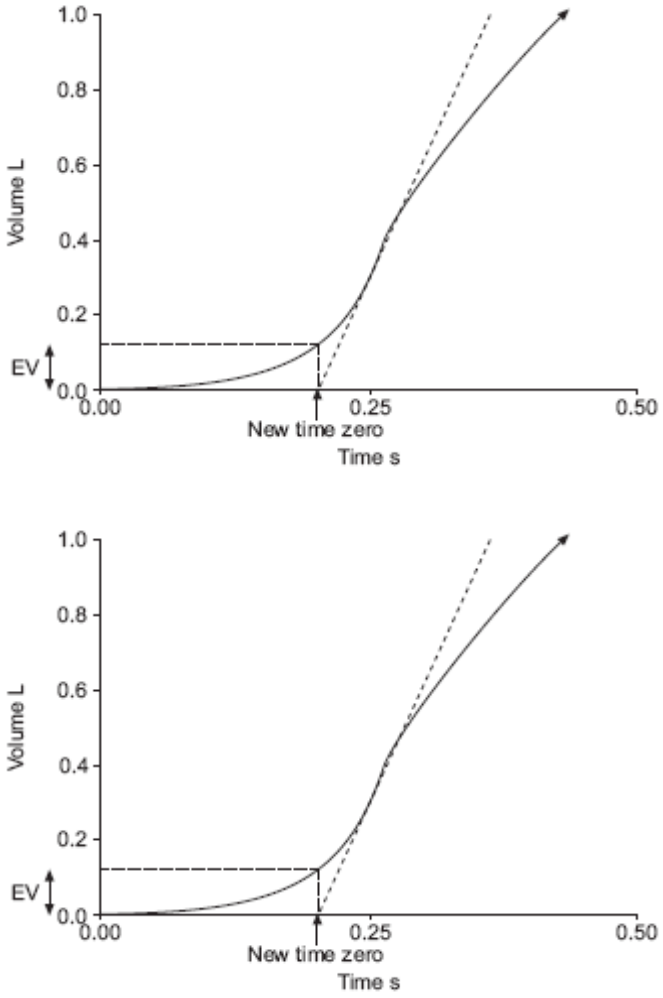
***Acceptable* Tests must meet the following 7 Criteria:**

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, i.e., the volume-time curve shows no change in volume (<0.025 L) for ≥ 1s, and the patient has tried to exhale for at least 6 seconds.

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

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

Figure A2-1. Example of a Usable Spirogram



The expanded version of the early part of a subject's volume-time spirogram, illustrating back extrapolation through the steepest part of the curve, where flow is peak expiratory flow 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 three acceptable spirograms have been obtained, apply the following tests

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

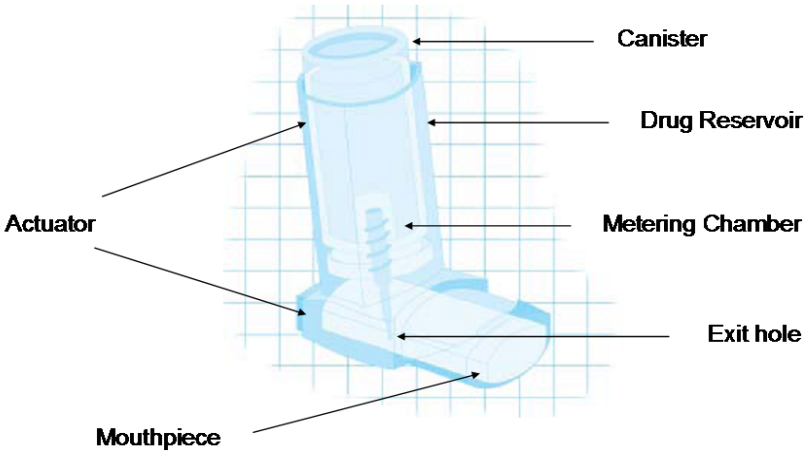
If these criteria are met, the spirometry testing for that time-point may conclude. The highest FEV_1 and the highest FVC obtained at each testing time-point (even if from different reproducible tracings), will be collected.

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 BD 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 three more times.
5. Gently shake the inhaler for 5 to 10 seconds before each spray.
6. Breathe out fully through your mouth, expelling as much air from your lungs as possible. Tilt your head back slightly, place the mouthpiece into your mouth, holding the inhaler with the mouthpiece down, and closing your lips around it. To allow the medication to enter your lungs, keep your tongue flat on the floor of your mouth.
7. While breathing in deeply and slowly through your mouth, fully depress the top of the metal canister with your index finger. Immediately after the spray is delivered, release your finger from the canister. When you have breathed in fully, remove the inhaler from your mouth and close your mouth.
8. Hold your breath as long as possible, up to 10 seconds, and then breathe normally.
9. 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



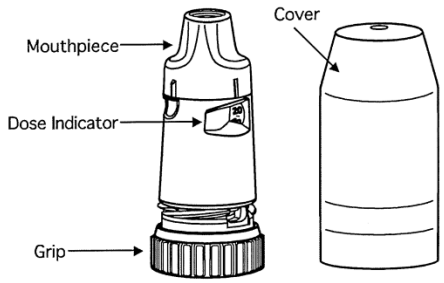
Appendix 4 Instructions for Use of Pulmicort Flexhaler *(budesonide inhalation powder)*

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

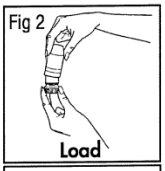


Fig 3

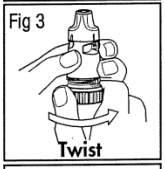


Fig 4

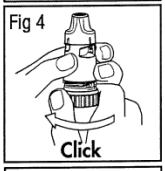
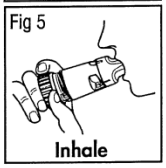


Fig 5



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

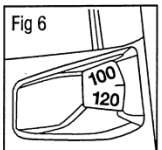
1. Turn your head away from the inhaler and breathe out (exhale). If you accidentally blow into your inhaler after loading a dose, follow the instructions for loading a new dose.
2. Place the mouthpiece in your mouth and close your lips around the mouthpiece. Breathe in (inhale) deeply and forcefully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



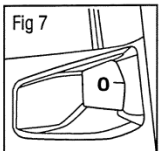
Dose Indicator

- 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

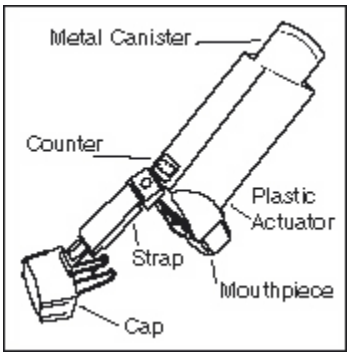

Figure 1

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.

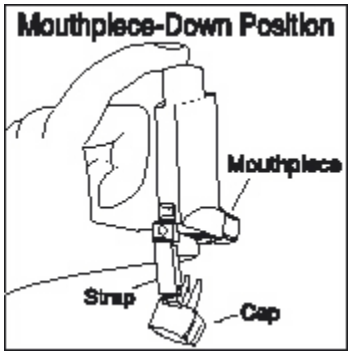

Figure 2

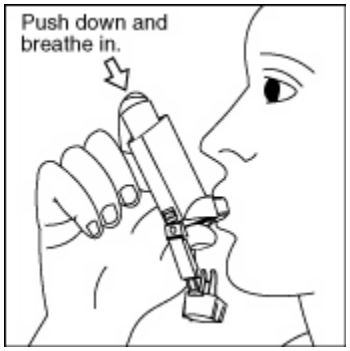

Figure 3

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).

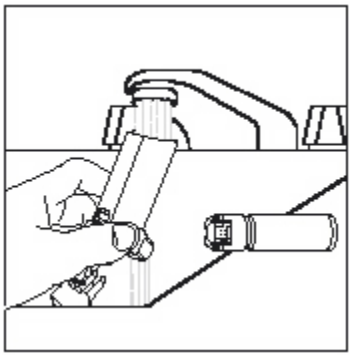

Figure 4

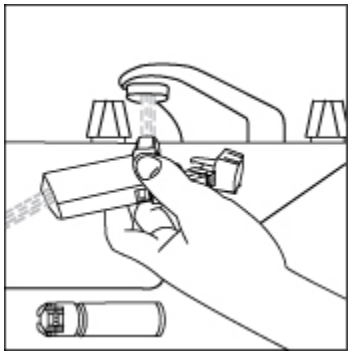

Figure 5

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).

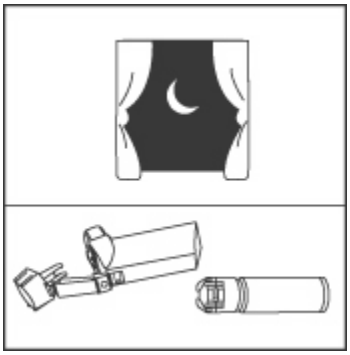

Figure 6

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.

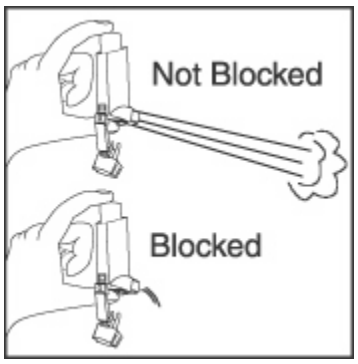

Figure 7

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 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]

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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]

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Appendix 7 Sponsor Signatory

Study Title: A Randomized, Double-Blind, Chronic Dosing (4 weeks), Four-Period, Five-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess the Efficacy and Safety of Four Doses of Budesonide Inhalation Aerosol (BD MDI, PT008) Relative to Placebo MDI in Adult Subjects With Mild to Moderate Persistent Asthma

Study Number: PT008001-02

Final Original Date: [redacted]

Amendment 2 Date: [redacted]

Signature: [redacted] Date: [redacted]

Name: [redacted]

Title: [redacted]

Appendix 8 Investigator's Agreement and Signature Page

Study Title:	A Randomized, Double-Blind, Chronic Dosing (4 weeks), Four-Period, Five-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess the Efficacy and Safety of Four Doses of Budesonide Inhalation Aerosol (BD MDI, PT008) Relative to Placebo MDI in Adult Subjects With Mild to Moderate Persistent Asthma
Study Number:	PT008001-02
Final Amendment 2 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:_____ Date:_____

Name:_____

Affiliation: _____

Dear [redacted]

We want to make you aware of two administrative changes for the Pearl Protocol PT008001 **(version no. 01)** ([redacted]). The changes have no impact on on-subject safety or data quality and will be corrected in a future protocol amendment.

1. **The current protocol states:**

Reversibility testing to Ventolin HFA: - Visits 1a and 1b.
Perform pre-bronchodilator PFTs -60 min and -30 min prior to administration of Ventolin HFA (albuterol).

The correct language should be: **Perform pre-bronchodilator PFTs prior to administration of Ventolin HFA (albuterol).**

2. **Table 3**

Prohibited Medications – amiodarone 3 months is listed with immunosuppressant, and will be deleted.

3. **The current protocol states in the following section**:

Section 7.2.1 -Perform a Chest X-ray or CT scan if one has not been performed on the subject within the last 6 months at Visit 1a.

The correct language should be**: Perform a Chest X-ray if a chest x-ray or CT scan has not been performed within the last 6 months prior to Visit 1a**

4. **Dry Mouth and Tremor:** is listed in the first paragraph of section 7.2. It is not captured in 7.2.6 AEs of interest

This will be corrected and **dry mouth and tremor will be deleted from section 7.2.6.**

5**. Table 10 Schedule of Events**

The table located on pg. 87-90 is labeled incorrectly. On pages 89 this Table is labeled Table 11 and on page 90 this table is labeled Table 12. However, the Table should be labeled and referred to as Table 10 only.

6**. Line above Table no. 1** on page 31 need a clarification – The introductory sentence should read as follows:

The definition of the doses of ICS considered “low”, “medium” and **“high”** is provided below in

7**. Diary Compliance:**

Section 4.1, Page 20: diary compliance of >70% in the last 7 days preceding V3

This will be corrected to read diary compliance of **≥70%** in the last 7 days preceding V3

Section 5.2, # 22, Page 30: [i.e. less than 70% subject completion of eDiary

This will be corrected to read **equal to and greater than 70%.’**

8**. Rescue Ventolin Use:**

Section 7.1.3, Page 44: Subjects requiring more than 8 puffs per day on 3 or more consecutive days

This will be corrected to read **‘equal to or more than 8 puffs.**’

Section 8.4, Page 61: Have subject record dosing time in the eDiary.’

This will be corrected to read **the subject does not record dose time. The dose time is recorded by the eDiary by the subject completing session 1 and 2.**

It is our opinion that these changes will not require changes to the currently approved Informed Consent Form for the PT008001 Trial.

Sincerely,

[redacted]