1.0 TITLE PAGE

Drug Product	Albuterol Sulfate Inhalation Aerosol, eq 90 mcg base
Population	Approximately 123 males and non-pregnant females, 18-65 years of age inclusive, with stable mild asthma
Study Design	A randomized, single-dose, double-blind, double-dummy, four-period, four-sequence, four-treatment, placebo and active controlled, comparative, multiple-center, crossover-design, bronchoprovocation bioequivalence study with pharmacodynamic endpoints
Sponsor	Sun Pharmaceuticals Industries Limited
Protocol Number	CLR_17_08
[redacted]	[redacted]
Protocol Date	04/05/2018

NIIRB
April 17, 2018
APPROVED

2.0 KEY STUDY PERSONNEL AND FACILITIES

Sponsor: Sun Pharmaceuticals Industries Limited
Formulation Development Department
Tandalja, Baroda
Gujarat, 390020, India

CRO: [redacted]

[redacted]

CRO Representative: [redacted]

Medical Monitor: [redacted]

Biostatistician: [redacted]

3.0 SIGNATURE PAGE

We, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study. The study will be performed according to this protocol, all applicable FDA regulations, ICH guidelines and Good Clinical Practice standards.

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

PRINCIPAL INVESTIGATOR'S SIGNATURE

I _____, agree to conduct protocol CLR_17_08 in accordance with FDA regulations, ICH guidelines and Good Clinical Practice. I understand that no deviations from the protocol may be made without the prior permission of the Sponsor (Sun Pharmaceuticals Industries Limited) or [redacted] the company managing the study.

_____ _____
Principal Investigator Date

4.0 TABLE OF CONTENTS

5.0 SYNOPSIS

Protocol Number	[redacted]
Title	A Randomized, Single-Dose, Double-Blind, Double-Dummy, Four-Period, Four-Sequence, Four-Treatment, Placebo and Active Controlled, Comparative, Multiple-Center, Crossover-Design, Bronchoprovocation Study to Evaluate the Pharmacodynamic Equivalence of Albuterol Sulfate Inhalation Aerosol, eq 90 mcg base (Sun Pharmaceuticals Industries Limited) to PROAIR® HFA (albuterol sulfate) Inhalation Aerosol, eq 90 mcg base (Teva Respiratory, LLC) in Subjects With Stable, Mild Asthma
Objectives	1. Demonstrate the pharmacodynamic equivalence of the Test formulation of albuterol sulfate inhalation aerosol, eq 90 mcg base (Sun Pharmaceuticals Industries Limited) to the marketed product PROAIR® HFA (albuterol sulfate) Inhalation Aerosol, eq 90 mcg base (Teva Respiratory, LLC) using methacholine bronchoprovocation in subjects with stable, mild asthma based on National Asthma Education and Prevention Program (NAEPP) guidelines. 2. Compare the safety of Test, low-dose Reference, high-dose Reference, and Placebo treatments in subjects with stable, mild asthma based on NAEPP guidelines.
Sponsor	Sun Pharmaceuticals Industries Limited
Study Products	• **Test (T active)**: Albuterol Sulfate Inhalation Aerosol, eq 90 mcg base per inhalation (Sun Pharmaceuticals Industries Limited) • **Reference (R active)**: PROAIR® HFA (albuterol sulfate) Inhalation Aerosol, eq 90 mcg base per inhalation (Teva Respiratory, LLC) • **Test Placebo (T Placebo)**: Placebo for Albuterol Sulfate Inhalation Aerosol (i.e., vehicle canister with T active actuator [Sun Pharmaceuticals Industries Limited]) • **Reference Placebo (R Placebo)**: Placebo for Albuterol Sulfate Inhalation Aerosol (i.e., vehicle canister with R active actuator [Sun Pharmaceuticals Industries Limited])

<table>
<tr><td>Treatments</td><td>During each period, subjects will receive four puffs of study product from four different inhalers (each dose from a separate inhaler). Treatments will be as follows:
<table>
<tr><td>Treatment A: Zero-dose
Two different Reference Placebo inhalers and two different Test Placebo inhalers</td><td>1 puff Inhaler 1
1 puff Inhaler 2
1 puff Inhaler 3
1 puff Inhaler 4</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Treatment B: 90 mcg of Reference
One Reference inhaler, one Reference Placebo inhaler, and two different Test Placebo inhalers</td><td>1 puff Inhaler 1
1 puff Inhaler 2
1 puff Inhaler 3
1 puff Inhaler 4</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Treatment C: 180 mcg of Reference
Two different Reference inhalers and two different Test Placebo inhalers</td><td>1 puff Inhaler 1
1 puff Inhaler 2
1 puff Inhaler 3
1 puff Inhaler 4</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Treatment D: 90 mcg of Test
One Test inhaler, one Test Placebo inhaler, and two different Reference Placebo inhalers</td><td>1 puff Inhaler 1
1 puff Inhaler 2
1 puff Inhaler 3
1 puff Inhaler 4</td></tr>
</table></td></tr>
<tr><td>Study Design</td><td>A randomized, single-dose, double-blind, double-dummy, four-period, four-sequence, four-treatment, placebo and active controlled, comparative, multiple-center, crossover-design, bronchoprovocation bioequivalence study with pharmacodynamic endpoints</td></tr>
<tr><td>Study Population</td><td>Approximately 123 males and non-pregnant females, 18-65 years of age inclusive, with stable, mild asthma</td></tr>
<tr><td>Confinement</td><td>Subjects will remain confined to clinic for approximately 3-9 hours during each dosing and clinical assessment period (Visits 2-5).</td></tr>
<tr><td>Study Conduct</td><td>Eligible subjects will complete 5 clinic visits as follows:
Visit 1: Screening (Day -14 to -1)
Visit 2: Period 1
Visit 3: Period 2
Visit 4: Period 3
Visit 5: Period 4
Clinical assessments will include Forced Expiratory Volume in 1 second</td></tr>
</table>

	(FEV_1) taken at each visit. If reattempts are necessary, an acceptable FEV_1 is defined as the highest of three to four acceptable curves obtained at each time point. Forced Volume Vital Capacity (FVC) and FEV_1/FVC ratio [(FEV_1/FVC) x 100] will also be recorded along with FEV_1 measurements at each visit. **Screening** Screening evaluations will be performed in accordance with the study schematic. Clinical assessments will include: vital sign measurement, height, weight, physical examination, urine pregnancy test (for all women of childbearing potential), 12-lead electrocardiogram (ECG), and pulse oximetry (during methacholine bronchoprovocation challenges). Chest x-ray may be performed at discretion of the Investigator. Qualifying FEV_1 at Screening must be $\geq$ 80% of predicted value. Once Qualifying FEV_1 is obtained, a normal sterile saline control will be administered to the subject through a nebulizer. Spirometry will be performed following the saline administration. Post-saline FEV_1 should not drop more than 10% from pre-saline (Qualifying) FEV_1 and should be $\geq$ 70% of predicted value. If the subject fails to meet any of these requirements, the procedures must be stopped, rescue albuterol administered, and the visit should be rescheduled. All clinical assessments except height and weight will be performed at each rescheduled visit. Subjects who fail three consecutive visits will not be eligible to participate in the study. Subjects meeting post-saline FEV_1 criteria will undergo methacholine bronchoprovocation challenge with progressively increasing concentrations to determine the subject's baseline provocation concentration of inhaled methacholine required to reduce FEV_1 by 20% (PC_{20}) relative to the post-saline value. The maximum concentration of methacholine to be administered in this step will be 8 mg/mL. Subjects who do not respond to methacholine doses at or below 8 mg/mL will not be eligible for enrollment in the study. Once the procedures have been completed, two puffs (180 mcg; 90 mcg per puff) of rescue albuterol will be administered and spirometry will be performed approximately 15 minutes later until the subject's FEV_1 returns to within 90% of the best post-saline FEV_1 or until the Principal Investigator determines that the FEV_1 has stabilized and it is safe to allow the subject to leave the site. Vital signs will also be repeated. **Dosing Visits** Eligible subjects will return for four treatment visits. The first dosing visit will occur no more than 14 days after Screening procedures and the interval (washout period) between dosing visits should be at least 48 hours. At each treatment visit, the following will be performed before

	dosing: • Vital sign measurement • 12-lead ECG • Pulse oximetry (during methacholine bronchoprovocation challenges) • Concomitant medication update (confirming washouts) • Adverse event (AE) review • Urine pregnancy test for all women of childbearing potential A pre-treatment evaluation will be performed. This will confirm that pre-challenge FEV_1 is ≥ 80% of predicted and within 88 and 112% of qualifying spirometry value at Screening visit. After the first inhalation of saline control is administered, the FEV_1 should not drop more than 10% compared to pre-challenge FEV_1 value and should be ≥ 70% of the predicted value. If the subject fails to meet any of these requirements, the procedures must be stopped, rescue albuterol administered, and the visit should be rescheduled. A minimum washout of 48 hours is required between visits. Subjects who fail three consecutive visits should be dropped from the study. Subsequently, review of inhaler dosing technique, priming and preparation of inhalers will be performed. The subject will receive one of the four randomized study treatments. The time of last actuation will be recorded, as well as the adequacy of inhaler technique. Approximately 15 minutes after the last inhalation of study treatment, a methacholine bronchoprovocation challenge will be given with progressive concentrations to determine the PC_{20}. The 20% reduction in FEV_1 will be determined relative to the post-saline FEV_1 measured before the administration of study product. After the procedures have been completed, two puffs (180 mcg; 90 mcg per puff) of rescue albuterol will be administered to reverse airway obstruction and subjects will be followed until FEV_1 returns to within 90% of the best post-saline FEV_1 captured on that study day or until the Principal Investigator determines that the FEV_1 has stabilized and it is safe to allow the subject to leave the site. Vital signs will also be repeated. Subjects who withdraw prematurely will be evaluated at a final visit, but spirometry, chest x-rays, and methacholine administration do not need to be performed. The spirometry procedures and the methacholine bronchoprovocation challenges in this study are to be performed in accordance with the American Thoracic Society (ATS) Guidelines for Methacholine and Exercise Challenge Testing. The maximum methacholine dose administered will be 8 mg/mL at Screening and 128 mg/mL for treatment

	visits.
Inclusion Criteria	1. Men or non-pregnant women 18 to 65 years of age. 2. Signed informed consent form that meets all criteria of current Food and Drug Administration (FDA) regulations. 3. Females of childbearing potential must not be pregnant or lactating (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin). Women of childbearing potential must agree to the use of a reliable method of contraception (e.g., total abstinence, intrauterine device, a double-barrier method, oral, transdermal, injected or implanted non- or hormonal contraceptive), throughout the study. A sterile sexual partner is not considered an adequate form of birth control. Subjects on hormonal contraceptives must have been on the same hormonal contraceptive for at least one month before the Screening and continue throughout the duration of the study. 4. Male subjects who are considered potent must be willing to avoid passage of semen to their partner and use an acceptable barrier method of contraception throughout the duration of the study. Each man will be considered potent unless surgically sterilized (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). 5. Subjects with a diagnosis of stable, mild asthma (based on NAEPP guidelines), confirmed by prior medical records, for at least 6 months before Screening. The subjects should fulfill the following NAEPP criteria: a. **Symptoms**: > 2 days per week but not daily b. **Nighttime awakenings**: 3-4 times per month c. **Short-acting beta$_2$-agonist (SABA) use for symptom control (other than for exercise-induced bronchospasm)**: > 2 days per week but not daily AND no more than one time on any day. d. **Interference with Normal Activity**: Minor limitation 6. $FEV_1 \geq 80\%$ of predicted at Screening day and no more than 10% drop in FEV_1 and no less than 70% of predicted post-saline control. 7. Airway responsiveness to methacholine demonstrated by a pre-albuterol dose $PC_{20} \leq 8$ mg/mL at Screening. 8. Able to perform valid and reproducible pulmonary function tests including no evidence of spirometry effort-induced bronchoconstriction.

	9. Non-smoker for at least 6 months before Screening and a maximum smoking history of five pack-years (i.e., one pack per day for five years). 10. Ability to use inhalation aerosol correctly.
Exclusion Criteria	1. Allergy or significant history of hypersensitivity or idiosyncratic reactions or intolerance to albuterol sulfate, $beta_2$ receptor-agonist drug, HFA and/or any related compounds. 2. Need for daily oral corticosteroids in the past three months. 3. History of seasonal asthma exacerbations, in which case the subject should be studied outside of the relevant allergen season. 4. History of cystic fibrosis, bronchiectasis, or co-morbid respiratory or sinus diseases, including chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, tuberculosis, pulmonary carcinoma, pulmonary fibrosis, pulmonary hypertension that, in the opinion of the Investigator, would compromise subject safety or interfere with the evaluations. 5. Evidence of conditions that could alter airway reactivity to methacholine, including upper or lower respiratory tract infections (e.g., pneumonia, viral bronchitis, allergic rhinitis, sinobronchitis, etc.) within 6 weeks before Screening. 6. Treatment in emergency room or hospitalization for acute asthmatic symptoms within 3 months before Screening. 7. Current cardiovascular disorders, including uncontrolled hypertension, known aortic or cerebral aneurysm, myocardial infarction or stroke in the last 6 months, and/or current coronary insufficiency that, in the opinion of the Investigator, would compromise subject safety or interfere with the evaluations. 8. Cardiac arrhythmia or 12-lead electrocardiogram (ECG) abnormalities, that in the opinion of the Investigator would compromise subject safety or interfere with the evaluations, or a QTc > 440 ms for males and > 460 ms for females using Fredericia formula. 9. Subjects receiving beta blocker via any route or who may require beta blockers during the study. 10. History of narrow angle glaucoma. 11. Any clinically significant finding on physical exam, ECG, or chest x-ray (to be performed at Investigator's discretion) that, in the opinion of the Investigator, would compromise subject's safety or data integrity. 12. History of significant renal, hepatic, cardiovascular (including ECG

	with evidence of ischemic heart disease, congestive heart failure), neurologic, endocrine dysfunction, or any other significant medical illness or disorder in the opinion of the Investigator, would compromise subject safety or interfere with the evaluations. 13. History of convulsive disorders or hyperthyroidism. 14. History of uncontrolled diabetes. 15. History of paradoxical bronchospasm. 16. SABAs use within 8 hours before Screening. 17. Use of muscarinic $beta_2$-agonists (MABAs), ipratropium bromide, or ipratropium bromide with albuterol within 24 hours before Screening. 18. Use of cromolyn sodium within 8 hours before Screening. 19. Use of nedocromil within 48 hours before Screening 20. Use of antihistamines (hydroxyzine, cetirizine, etc.) within 24 hours before Screening. 21. Use of long-acting $beta_2$-agonists (LABAs) (e.g., salmeterol, formoterol) or combination products containing bronchodilators (e.g., Symbicort) within 48 hours before Screening. 22. Use of tiotropium within one week before Screening. 23. Inhalation corticosteroids must have remained at a constant dosage for the previous 4 weeks; their withholding is at discretion of the Investigator. 24. Use of theophylline medications within 24 hours before Screening. 25. Consumption of caffeine containing products such as coffee, tea, cola drinks, energy drinks or chocolate on the day of Screening. 26. Exercise within 6 hours before Screening. 27. Use of beta blockers, non-potassium sparing diuretics, digoxin, monoamine oxidase inhibitors, cholinesterase inhibitors or tri-cyclic anti-depressants within 30 days before Screening. 28. Use of leukotriene modifiers within 24 hours before Screening. 29. Any surgery within 6 months before Screening that, in the opinion of the Investigator, would compromise subject safety or integrity of the study data. 30. Receipt of any drug as part of a research study within 30 days before Screening. 31. Employees of the Investigator or research center or their immediate family members. 32. Previous participation in this study. 33. Inability to understand the requirements of the study and the relative

	information and are unable or not willing to comply with the study protocol.
Route of Administration	Oral inhalation
Primary Pharmacodynamic Endpoint	The primary pharmacodynamic endpoint will be the post-dose PC_{20}, which is the provocative concentration of the methacholine challenge agent required to reduce the FEV_1 by 20% following administration of differing doses of albuterol (or placebo) by inhalation. The 20% reduction in FEV_1 will be determined relative to the post-saline FEV_1 measure before the placebo or albuterol administration.
Statistical Analysis	The primary bioequivalence analysis will use the Pharmacodynamic (PD) population. A secondary analysis will test the primary pharmacodynamic endpoint using the Per-Protocol (PP) population. Pharmacodynamic equivalence will be based on the Dose-Scale method of analysis of the post-dose $PC_{20}FEV_1$ (mg/mL) data using non-linear E_{max} modeling, as outlined in the FDA Draft Guidance on Orlistat capsule.[1] The methacholine $PC_{20}FEV_1$ will be calculated by linear interpolation from the observed data relating the % decrease in FEV_1 from the post-saline FEV_1 to the concentration of methacholine that provokes at least a 20% decrease in FEV_1. The $PC_{20}FEV_1$ data will be log-transformed if they are log-normally distributed. If the 90% confidence interval for the relative bioavailability (F) falls within 67.00-150.00% then pharmacodynamic equivalence will be considered to have been demonstrated. F is the potency ratio of the doses of Test and Reference formulations that produce an equivalent pharmacodynamic response at the ED_{50} of the Reference dose-response E_{max} curve. The 90% confidence interval for F will be estimated by a bootstrap procedure using Efron's bias-corrected and accelerated (BCA) method.
Safety Analysis	All study subjects who receive at least one actuation of any of the study products will be included in the comparative safety analysis. Adverse events will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 21.0 or higher and presented by treatment group. Summary tables listing the type, date of onset, date of resolution, incidence, severity, outcome, action taken, and Investigator's opinion of relationship to the study product will be presented by treatment group for AEs reported after randomization. Signs and symptoms of asthma will not be considered AEs, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/subject considers that it is in the

	subject's best interest to be dropped from continued participation in the study and given alternative therapy for their condition. If sufficient data exist, then AEs frequencies will be compared among treatments using Fisher's exact test. Concomitant medication used during the study will be tabulated by treatment by subject.
Sample Size Determination	The sample size estimation for this study was based on data from the study by Newhouse et al. that reported the bronchoprotective effect of inhaled salbutamol (albuterol) on methacholine $PC_{20}FEV_1$.[2] The highest within-subject coefficient of variability (COV) value for ln-transformed PC_{20} was estimated as 0.846 from the mean ratio and SD values for the PC_{20} at the 200 and 100 mcg doses (Table 1 in reference 2). Based on this COV, 98 evaluable subjects would be required in the PD population to demonstrate pharmacodynamic equivalence (i.e., 90% confidence interval on F is within the bioequivalence limits of 0.67 to 1.50) with 90% power for a crossover study, assuming a true ratio of F = 1.1. To allow for approximately 20% of subjects that may discontinue from the study or have major protocol violations, and therefore not qualify for the PD population, up to 123 subjects will be randomized in the study.

6.0 STUDY SCHEMATIC

Procedures	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening	Period 1	Period 2	Period 3	Period 4 End of Study
Informed Consent	X				
Baseline Demographics	X				
Medical History	X				
Vital Signs*	X	X	X	X	X
Height and Weight	X				
Physical Exam	X				X
Urine Pregnancy Test**	X	X	X	X	X
12-Lead ECG	X	X†	X†	X†	X†
Chest X-Ray‡	X				
Concomitant Medication	X	X	X	X	X
Spirometry (FEV_1 and FVC)§	X	X	X	X	X
Saline Control Administration	X	X	X	X	X
Methacholine Challenge	X	X	X	X	X
Pulse Oximetry	X	X	X	X	X
Inclusion/Exclusion Criteria Review	X				
Prime, dispense study product and instructions		X	X	X	X
Dosing‖		X	X	X	X
Assessment of Compliance		X	X	X	X
Adverse Events	X	X	X	X	X
Provide Diary	X	X	X	X	
Collect /Review Diary		X	X	X	X
Schedule next visit	X	X	X	X	

* Vital signs will be measured before and after methacholine bronchoprovocation challenges at all visits.

** Female subjects of childbearing potential.

† 12-lead ECG to be performed at Screening may be repeated before methacholine bronchoprovocation challenges at discretion of Investigator.

‡ Chest X-ray is to be performed at discretion of Investigator.

§ FEV_1 and FVC measurements will be performed before saline control, after saline control, and after methacholine administration. If reattempts are necessary, an acceptable FEV_1 is defined as the highest of three to four acceptable curves obtained at each time point.

‖ Subjects will receive four puffs of study product from four different inhalers (each dose from a separate inhaler).

7.0 LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Term
µg	microgram
ADaM	Analysis Dataset Model
AE	Adverse Event
ANDA	Abbreviated New Drug Application
ATS	American Thoracic Society
BCA	Bias-corrected and accelerated
BP	Blood Pressure
C	Celsius
CDISC	Clinical Data Standards Interchange Consortium
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CRO	Clinical Research Organization
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eCTD	Electronic Common Technical Document
EIB	Exercise-Induced Bronchospasm
°F	Fahrenheit
F	Relative bioavailability
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume (flow rate) in 1 second
FVC	Forced Volume Vital Capacity
HFA	Hydrofluoroalkane
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroid
IRB	Institutional Review Board
kg	Kilograms
LABA	Long-Acting $Beta_2$-Agonist
MABA	Muscarinic-Acting $Beta_2$-Agonist
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
mL	Milliliter
NAEPP	National Asthma Education and Prevention Program
OGD	Office of Generic Drugs
PC_{20}	Concentration (mg/mL) of methacholine required to reduce FEV_1 by 20%
PD	Pharmacodynamic
PE	Pulmonary Embolism
PFT	Pulmonary Function Tests
PP	Per-Protocol
RR	Respiratory Rate
SABA	Short-Acting $Beta_2$-Agonist
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SDTM	Study Data Tabulation Model
SUSAR	Suspected Unsuspected Serious Adverse Reaction
US	United States
USP	United States Pharmacopeia

8.0 INTRODUCTION

8.1 Disease Being Treated

Asthma is a common lung disease that affects an estimated 25 million Americans including more than 6 million children.[3-5] The prevalence of this disease makes it one of the most costly diseases in the United States, costing approximately $56 billion per year. The financial burden of the disease extends from medical costs to missed work days and lost productivity. Subjects with uncontrolled asthma have health care costs that are two times higher than those with controlled asthma.[3,5,6]

Asthma is a serious and potentially life-threatening condition characterized by varying symptoms including obstructed airflow, bronchial hyper-responsiveness and underlying inflammation, which can result in difficulty breathing, coughing, chest tightness, pain, chest pressure or wheezing.[7-9] Exacerbation of symptoms may be triggered by a variety of factors including infections, allergens, exercise, inhaled irritants, or emotional episodes.[3,10]

Asthma diagnosis and severity ranking are carried out on the basis of pulmonary function testing using a spirometer, a device that measures Forced Expiratory Volume in 1 second (FEV_1), the volume of air that can forcibly be blown out in one second, after full inspiration. Lung function is typically compromised in asthma subjects (FEV_1 predicted value < 85%). Reversibility (full or partial) of airway obstruction is an essential component of asthma diagnosis to rule out differential diagnoses including Chronic Obstructive Pulmonary Disease (COPD), Congestive Heart Failure (CHF) or pulmonary embolism (PE). This is determined by an increase in predicted FEV_1 > 200 mL or > 12% from baseline measure after inhalation of short-acting $beta_2$-agonist (SABA).[8]

The severity of asthma is rated on a scale of intermittent, mild persistent, moderate persistent or severely persistent. The rating depends on various factors including degree of impairment in lung function, the frequency and intensity of symptoms, susceptibility to future asthma attacks or medication side effects. Asthma management focuses on reducing both impairment and risk for the subject.[11,12]

8.2 Availability and Efficacy of Already Approved Therapies

There are two types of therapies currently available for the treatment of asthma, long-term control medications and quick relief medications.[13,14] Inhaled corticosteroids (ICSs) have been shown to be the most effective long-term treatment of persistent asthma.[15] Quick relief medications or short-acting beta-agonists (SABAs), for e.g., albuterol sulfate (PROAIR® HFA, PROVENTIL® HFA) and levalbuterol tartrate (XOPENEX HFA®) are used to relax airway smooth muscle to promote bronchodilation within minutes of administration. These medications typically provide relief for up to 6 hours. SABAs activate the beta adrenergic receptors on bronchial smooth muscle to rapidly dilate airway passages and provide relief from bronchospasm. SABAs are typically the preferred treatment to prevent exercise-induced bronchospasm (EIB) and for the treatment of acute exacerbations of asthma. The medications are typically provided as metered dose inhalers (MDIs) or dry powder inhalers (oral inhalation). Additionally, anti-cholinergic medications (i.e., ipratropium) and systemic, intravenous or oral corticosteroids are used to treat acute asthma exacerbations.

8.3 Scientific and Statistical Considerations

The methacholine $PC_{20}FEV_1$ (mg/mL) will be calculated by linear interpolation from the observed data relating the % decrease in FEV_1 from the post-saline FEV_1 to the concentration of methacholine that provokes at least a 20% decrease in FEV_1. In the event that subjects receiving the maximum concentration of methacholine (128 mg/mL) at any treatment visit (Visits 2-5) do not achieve at least a 20% fall in FEV_1, then they will have their $PC_{20}FEV_1$ data interpolated as though they had achieved positivity at 128 mg/mL (i.e., PC_{20FEV1} will be imputed as 128 mg/mL) and will be included in the Per-Protocol (PP) population. The $PC_{20}FEV_1$ data will be log-transformed if they are log-normally distributed.

$PD_{20}FEV_1$ (mg) may also be evaluated to correct for the dose of methacholine delivered if different volumes of methacholine are administered as result of different nebulizer flow rate, number of breaths, or nebulizer time. The maximum methacholine dose administered will be 8 mg/mL at Screening and 128 mg/mL (i.e., $PC_{20}FEV_1$ will be imputed as 128 mg/mL) for treatment visits. The use of 128 mg/mL of methacholine is necessary to allow for a minimum 4-fold decrease in sensitivity; however, this dose is higher than the 25 mg/mL dose approved for administration of methacholine chloride in the United States. Therefore, a Bio-IND application is being filed with the United States (US) Food and Drug Administration (FDA) Office of Generic Drugs (OGD) for use of Provocholine® (methacholine chloride USP) concentrations that may exceed the labeled 25.0 mg/mL concentration.

8.4 Justification for Use of Placebo

A Placebo treatment arm is required for application of the Dose-Scale method for a bronchoprovocation study. The Placebo treatment will provide the baseline response in the absence of the drug for fitting of the E_{max} model to the dose-response $PC_{20}FEV_1$ data of the Reference product.

All subjects will undergo one zero-dose treatment (four inhalations of placebo) across the four periods of the study. The lack of a bronchoprotective effect provided by either the Reference or the Test product at higher doses of methacholine implies that the bronchoprovocation challenge test delivered during the zero-dose does not differ from a regular methacholine bronchoprovocation test and does not compromise subject's safety. Bronchoprovocation challenge tests represent a valuable and well validated tool for the diagnosis of respiratory conditions. All methacholine bronchoprovocation challenges are performed in accordance with the American Thoracic Society (ATS) Guidelines for Methacholine and Exercise Challenge Testing in order to ensure subjects' safety and good quality testing. Mainly, the challenge test is initiated exclusively if the subject shows an acceptable functional pulmonary profile (a baseline FEV_1 above 70% of predicted) and it is interrupted if a safety threshold is met (drop in $FEV_1 \geq 20\%$). At the end of each challenge, each subject will be administered a rescue medication (albuterol) in order to ensure proper reversion of the bronchoconstriction, if present; under the Principal Investigator's supervision, the subject will be leaving the investigative site only when an acceptable FEV_1 is reached.

8.5 Risks and Benefits

The risks and benefits to subjects enrolled in clinical research studies that include a Placebo treatment group must be carefully considered based on three main criteria, namely: the disease being treated, the availability, efficacy and safety of already approved therapies and the scientific and statistical requirements of the desired outcome of the research study. The Office of Human Rights Protection, a Division of the USA Federal Government's Department of Health and Human Services, has issued a detailed guidebook to Institutional Review Boards (IRBs) that includes discussion on the use of Placebos in clinical studies.[16]

All subjects enrolled in this study will receive the benefit of free specialized medical care beyond standard medical treatment that would be expected through most health insurance plans. In addition, the subject will receive a stipend for participation to cover costs and expenses associated with trips to the medical facility.

9.0 STUDY OBJECTIVES

1. Demonstrate the pharmacodynamic equivalence of the Test formulation albuterol sulfate HFA inhalation aerosol, eq 90 mcg base (Sun Pharmaceuticals Industries Limited) to the marketed product PROAIR® HFA (albuterol sulfate) Inhalation Aerosol, eq 90 mcg base (Teva Respiratory, LLC) in subjects with stable, mild asthma based on National Asthma Education and Prevention Program (NAEPP) guidelines.
2. Compare the safety of Test, low-dose Reference, high-dose Reference, and Placebo treatments in subjects with stable, mild asthma based on NAEPP guidelines.

10.0 INVESTIGATIONAL PLAN

10.1 Study Design and Plan Description

This randomized, single-dose, double-blind, double-dummy, four-period, four-sequence, four-treatment, Placebo and active controlled, comparative, multiple-center, crossover-design bronchoprovocation study has been designed to evaluate the pharmacodynamic equivalence of albuterol sulfate HFA inhalation aerosol, eq 90 mcg base per inhalation (Sun Pharmaceuticals Industries Limited) to PROAIR® HFA (albuterol sulfate) Inhalation Aerosol, eq 90 mcg base per inhalation (Teva Respiratory, LLC) in subjects with stable, mild asthma.

Approximately 123 subjects with persistent bronchial asthma will be randomized. To qualify for inclusion in the study, subjects must be at least 18 years of age, with a documented diagnosis of mild asthma as defined by the NAEPP guidelines at least 6 months before Screening.

Randomized subjects who withdraw from the study will not be replaced.

Before any study-specific procedures are performed, all subjects will read and sign the IRB-approved informed consent form.

Eligible subjects will complete 5 clinic visits as follows:

- Visit 1: Screening (Day -14 to -1)

- Visit 2: Period 1
- Visit 3: Period 2
- Visit 4: Period 3
- Visit 5: Period 4

Clinical assessments will include FEV_1 taken at each visit. If reattempts are necessary, an acceptable FEV_1 is defined as the highest of three to four acceptable curves obtained at each time point. FVC and FEV_1/FVC ratio [(FEV_1/FVC) x 100] will also be recorded along with FEV_1 measurements at each visit.

Screening

Screening evaluations will be performed in accordance with the study calendar. Clinical assessments will include: vital sign measurement, height, weight, physical examination, urine pregnancy test (for all women of childbearing potential), 12-lead electrocardiogram (ECG), and pulse oximetry (during methacholine bronchoprovocation challenges). Chest x-ray may be performed at discretion of the Investigator. Qualifying FEV_1 at Screening must be ≥ 80% of predicted value. Once Qualifying FEV_1 is obtained, a sterile, saline control will be administered to the subject through a nebulizer. Spirometry will be performed following the saline administration. Post-saline FEV_1 should not drop more than 10% from pre-saline FEV_1 and should be ≥ 70% of predicted value. If the subject fails to meet any of these requirements, the procedures must be stopped, rescue albuterol administered, and the visit should be rescheduled. All clinical assessments except height and weight will be performed at each rescheduled visit. Subjects who fail three consecutive visits will not be eligible to participate in the study. Subjects meeting post-saline FEV_1 criteria will undergo methacholine bronchoprovocation challenge with progressively increasing concentrations to determine the subject's baseline provocation concentration of inhaled methacholine required to reduce FEV_1 by 20% (PC_{20}) relative to the post-saline value. The maximum concentration of methacholine to be administered in this step will be 8 mg/mL. Subjects who do not respond to methacholine doses at or below 8 mg/mL will not be eligible for enrollment in the study.

Once the methacholine challenge test is completed, rescue albuterol will be administered and spirometry will be performed approximately 15 minutes later until the subject's FEV_1 returns to within 90% of the best post-saline FEV_1 or until the Principal Investigator determines that the FEV_1 has stabilized and it is safe to allow the subject to leave the site. Vital signs will also be repeated.

Dosing Visits

Eligible subjects will return for four treatment visits. The first dosing visit will occur no more than 14 days after Screening procedures and the interval (washout period) between dosing visits should be at least 24 hours. At each treatment visit, the following will be performed before dosing:

- Vital sign measurement
- 12-lead electrocardiogram (ECG) as the discretion of the Investigator after the initial Screening visit

- Pulse oximetry (during methacholine bronchoprovocation challenges)
- Concomitant medication update (confirming washouts)
- Adverse Events (AE) review
- Urine pregnancy test for all women of childbearing potential

A pre-treatment evaluation will be performed. This will confirm that pre-challenge FEV_1 is ≥ 80% of predicted and within 88 and 112% of qualifying spirometry value at Screening visit. After the first inhalation of saline control is administered, the FEV_1 should not drop more than 10% compared to pre-challenge value and should be ≥ 70% of the predicted value. If the subject fails to meet any of these requirements, the procedures must be stopped, albuterol administered, and the visit should be rescheduled. Subjects who fail three consecutive visits should be dropped from the study.

Subsequently, review of inhaler dosing technique, priming and preparation of inhalers will be performed. The subject will receive one of the four randomized study treatments. The time of last actuation will be recorded, as well as the adequacy of inhaler technique. Approximately 15 minutes after the last inhalation of study treatment, a methacholine bronchoprovocation challenge will be given with progressive concentrations to determine the PC_{20}. The 20% reduction in FEV_1 will be determined relative to the post-saline FEV_1. After the procedures have been completed, albuterol will be administered to reverse airway obstruction and subjects will be followed until FEV_1 returns to within 90% of the best FEV_1 captured during the saline stage on that study day or until the Principal Investigator determines that the FEV_1 has stabilized and it is safe to allow the subject to leave the site.

Subjects who withdraw prematurely will be evaluated at a final visit, but spirometry, chest x-rays, and methacholine administration do not need to be performed.

The spirometry procedures and the methacholine bronchoprovocation challenges in this study are to be performed in accordance with the ATS Guidelines for Methacholine and Exercise Challenge Testing.[17] The maximum methacholine dose administered will be 8 mg/mL at Screening and 128 mg/mL for treatment visits.

10.2 Selection of Study Design

The study was designed based on the FDA Draft Guidance on albuterol sulfate metered/inhalation products, and generally accepted standards for the conduct of bioavailability and bioequivalence studies.[18]

To minimize any possibility of a carry-over effect, a washout period of at least 48 hours was selected for this study based on the FDA guidance.

10.3 Selection of Study Population

10.3.1 Inclusion Criteria

1. Men or non-pregnant women 18 to 65 years of age.
2. Signed informed consent form that meets all criteria of current FDA regulations.

3. Females of childbearing potential must not be pregnant or lactating (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin). Women of childbearing potential must agree to the use of a reliable method of contraception (e.g., total abstinence, intrauterine device, a double-barrier method, oral, transdermal, injected or implanted non- or hormonal contraceptive), throughout the study. A sterile sexual partner is not considered an adequate form of birth control. Subjects on hormonal contraceptives must have been on the same hormonal contraceptive for at least one month before the Screening and continue throughout the duration of the study.
4. Male subjects who are considered potent must be willing to avoid passage of semen to their partner and use an acceptable barrier method of contraception throughout the duration of the study. Each man will be considered potent unless surgically sterilized (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
5. Subjects with diagnosis of stable, mild asthma (based on NAEPP guidelines), confirmed by prior medical records, for at least 6 months before Screening.

   The subjects should fulfill the following NAEPP criteria:

   a. **Symptoms**: > 2 days per week but not daily
   b. **Nighttime awakenings**: 3-4 times per month
   c. **Short-acting beta$_2$-agonist (SABA) use for symptom control (other than for EIB)**: > 2 days per week but not daily AND no more than one time on any day.
   d. **Interference with Normal Activity**: Minor limitation
6. $FEV_1 \geq 80\%$ of predicted at Screening day and no more than 10% drop in FEV_1 and no less than 70% of predicted post-saline control.
7. Airway responsiveness to methacholine demonstrated by a pre-albuterol dose $PC_{20} \leq 8$ mg/mL at Screening.
8. Able to perform valid and reproducible pulmonary function tests including no evidence of spirometry effort-induced bronchoconstriction.
9. Non-smoker for at least 6 months before Screening and a maximum smoking history of five pack-years (i.e., one pack per day for five years).
10. Ability to use inhalation aerosol correctly.

10.3.2 Exclusion Criteria

1. Allergy or significant history of hypersensitivity or idiosyncratic reactions or intolerance to albuterol sulfate, beta$_2$ receptor-agonist drug, HFA and/or any related compounds.
2. Need for daily oral corticosteroids in the past three months.
3. History of seasonal asthma exacerbations, in which case the subject should be studied outside of the relevant allergen season.

4. History of cystic fibrosis, bronchiectasis, or co-morbid respiratory or sinus diseases, including COPD, chronic bronchitis, emphysema, tuberculosis, pulmonary carcinoma, pulmonary fibrosis, pulmonary hypertension that, in the opinion of the Investigator, would compromise subject safety or interfere with the evaluations.
5. Evidence of conditions that could alter airway reactivity to methacholine, including upper or lower respiratory tract infections (e.g., pneumonia, viral bronchitis, allergic rhinitis, sinobronchitis, etc.) within 6 weeks before Screening.
6. Treatment in emergency room or hospitalization for acute asthmatic symptoms within 3 months before Screening.
7. Current cardiovascular disorders, including uncontrolled hypertension, known aortic or cerebral aneurysm, myocardial infarction or stroke in the last 6 months, and/or current coronary insufficiency that, in the opinion of the Investigator, would compromise subject safety or interfere with the evaluations.
8. Cardiac arrhythmia or 12-lead electrocardiogram (ECG) abnormalities, that in the opinion of the Investigator would compromise subject safety or interfere with the evaluations, or a QTc > 440 ms for males and > 460 ms for females using Fredericia formula.
9. Subjects receiving beta blocker via any route or who may require beta blockers during the study.
10. History of narrow angle glaucoma.
11. Any clinically significant finding on physical exam, ECG, or chest x-ray (to be performed at Investigator's discretion) that, in the opinion of the Investigator, would compromise subject's safety or data integrity.
12. History of significant renal, hepatic, cardiovascular (including ECG with evidence of ischemic heart disease, congestive heart failure), neurologic, endocrine dysfunction, or any other significant medical illness or disorder in the opinion of the Investigator, would compromise subject safety or interfere with the evaluations.
13. History of convulsive disorders or hyperthyroidism.
14. History of uncontrolled diabetes.
15. History of paradoxical bronchospasm.
16. SABAs use within 8 hours before Screening.
17. Use of muscarinic $beta_2$-agonists (MABAs), ipratropium bromide, or ipratropium bromide with albuterol within 24 hours before Screening.
18. Use of cromolyn sodium within 8 hours before Screening.
19. Use of nedocromil within 48 hours before Screening

20. Use of antihistamines (hydroxyzine, cetirizine, etc.) within 24 hours before Screening.
21. Use of long-acting $beta_2$-agonists (LABAs) (e.g., salmeterol, formoterol) or combination products containing bronchodilators (e.g., Symbicort) within 48 hours before Screening.
22. Use of tiotropium within one week before Screening.
23. Inhalation corticosteroids must have remained at a constant dosage for the previous 4 weeks; their withholding is at discretion of the Investigator.
24. Use of theophylline medications within 24 hours before Screening.
25. Consumption of caffeine containing products such as coffee, tea, cola drinks, energy drinks or chocolate on the day of Screening.
26. Exercise within 6 hours before Screening.
27. Use of beta blockers, non-potassium sparing diuretics, digoxin, monoamine oxidase inhibitors, cholinesterase inhibitors or tri-cyclic anti-depressants within 30 days before Screening.
28. Use of leukotriene modifiers within 24 hours before Screening.
29. Any surgery within 6 months before Screening that, in the opinion of the Investigator, would compromise subject safety or integrity of the study data.
30. Receipt of any drug as part of a research study within 30 days before Screening.
31. Employees of the Investigator or research center or their immediate family members.
32. Previous participation in this study.
33. Inability to understand the requirements of the study and the relative information and are unable or not willing to comply with the study protocol.

10.3.3 Restrictions During the Study

The following medications will not be allowed when subjects are enrolled in the study:

- Beta blockers
- Non-potassium sparing diuretics
- Digoxin
- Monoamine oxidase inhibitors
- Cholinesterase inhibitors
- Tri-cyclic anti-depressants
- MABAs within 24 hours before any study visit.
- SABAs within 8 hours before any study visit.

- Ipratropium bromide or ipratropium bromide with albuterol within 24 hours before any study visit.
- Cromolyn sodium within 8 hours before any study visit.
- LABAs (e.g., salmeterol, formoterol) or combination products containing bronchodilators (e.g., Symbicort) within 48 hours before any study visit.
- Tiotropium within one week before any study visit.
- Theophylline medications within 24 hours before any study visit.
- Leukotriene modifiers within 24 hours before any study visit.
- Nedocromil within 48 hours before any study visit.
- Antihistamines within 24 hours before any study visit.

Inhalation corticosteroids must have remained at a constant dosage for the previous 4 weeks; their withholding is at discretion of the Investigator. Subjects should not consume caffeine containing products such as coffee, tea, cola drinks, energy drinks or chocolate on the day of any study visit. Subjects should not exercise within 6 hours of any study visit.

10.3.4 Removal of Subjects from the Study

Subjects will be advised that they are free to withdraw from the study at any time for any reason or, if necessary, the Investigator may withdraw a subject from the study to protect the health of that subject. A subject may also be withdrawn for not complying with study procedures. The clinical report will include all reasons for early withdrawals.

All subjects who receive randomized treatment will be included in the safety analysis. If a subject terminates from the study early, all efforts will be made to complete their next visit study procedures, but spirometry chest x-rays, and methacholine administration do not need to be performed. In case of early termination the Investigator will fully document the reason for early termination. Reasons for early termination may include the following:

- Subject withdrew consent.
- Significant AE that led the Investigator or subject to withdraw for safety reasons.
- Non-compliance with protocol requirements (e.g., use of restricted medication, not following dosing procedures, failure to make scheduled study visits in a timely fashion).
- Pregnancy
- Significant worsening of asthma such that the Investigator and/or subject believes it is in the best interest of the subject to withdraw from the study and be provided alternative treatment.
- Participant enrolls in another clinical trial, or is found to have previously enrolled in this clinical trial.

10.4 Treatments

10.4.1 Treatments Administration

The Independent Dispenser will prime each inhaler of study product before using for the first time by shaking well for 5 seconds, then releasing 3 test sprays into the air, away from the face, until a uniform spray is obtained. The Independent Dispenser will dispense 4 study inhalers containing randomized study product, according to treatments listed in table above, to each eligible subject, along with a set of dosing instructions. Subjects will administer one puff (oral inhalation) from each of the provided inhalers with a spacer at 1 minute intervals, in accordance with dosing instructions, with the Independent Dispenser observing. The date and time of dose will be recorded. Treatments will be as follows:

Treatment A: Zero-dose Two different Reference Placebo inhalers and two different Test Placebo inhalers	1 puff Inhaler 1 1 puff Inhaler 2 1 puff Inhaler 3 1 puff Inhaler 4
Treatment B: 90 mcg of Reference One Reference inhaler, one Reference Placebo inhaler, and two different Test Placebo inhalers	1 puff Inhaler 1 1 puff Inhaler 2 1 puff Inhaler 3 1 puff Inhaler 4
Treatment C: 180 mcg of Reference Two different Reference inhalers and two different Test Placebo inhalers	1 puff Inhaler 1 1 puff Inhaler 2 1 puff Inhaler 3 1 puff Inhaler 4
Treatment D: 90 mcg of Test One Test inhaler, one Test Placebo inhaler, and two different Reference Placebo inhalers	1 puff Inhaler 1 1 puff Inhaler 2 1 puff Inhaler 3 1 puff Inhaler 4

10.4.2 Identity of Investigational Product

The following products will be used in the study:

- **Test (T active)**: Albuterol Sulfate Inhalation Aerosol, eq 90 mcg base per inhalation (Sun Pharmaceuticals Industries Limited)
- **Reference (R active)**: PROAIR® HFA (albuterol sulfate) Inhalation Aerosol, eq 90 mcg base per inhalation (Teva Respiratory, LLC)
- **Test Placebo (T Placebo)**: Placebo for Albuterol Sulfate Inhalation Aerosol (i.e., vehicle canister with T active actuator [Sun Pharmaceuticals Industries Limited])
- **Reference Placebo (R Placebo)**: Placebo for Albuterol Sulfate Inhalation Aerosol (i.e., vehicle canister with R active actuator [Sun Pharmaceuticals Industries Limited])

The Reference product, PROAIR ® HFA (albuterol sulfate) inhalation aerosol, is supplied as an 8.5 g pressurized aluminum canister in a box. Each canister contains 200 metered actuations and is supplied with a red plastic actuator (or mouthpiece) and a white mouthpiece cap. Each actuation delivers 120 mcg of albuterol sulfate from the canister valve and 108 mcg of albuterol sulfate from the actuator mouthpiece (equivalent to 90 mcg of albuterol base).

10.4.3 Study Product Shipment, Storage and Retention

The study product will be shipped to each Investigator's site from a centralized pharmacy. The Principal Investigator at each site is responsible for ensuring that all study products are stored in a locked, secure location, with access limited to the Investigator and his/her designee(s). An accurate inventory of the study product will be maintained in accordance with federal regulations. Randomization of treatments will be generated in blocks. Four patient kits, each containing the four treatments (A, B, C and D), will constitute a block. Retention samples will be kept aside by study site to comply the applicable regulatory requirement. For any re-supply shipments of randomized study product retention samples will be kept aside by the study site. These samples should not be used for dispensing to study subjects and will be retained at the site under FDA regulations as study retention samples.[17]

All study product will be stored at controlled room temperature between 15° and 25°C (59° and 77°F), away from direct sunlight (or freezing temperatures) in a secure place with access by authorized individuals only. Any excursions from the permitted range of 15–25ºC (59º–77ºF) will require prompt notification to [redacted] and thereafter [redacted] will notify the Sponsor Designee. The inhalers are to be stored with actuators 'down'. The Investigator will be responsible for maintaining accurate records of drug receipt, dispensing, and return. At the end of the study, all partially used and unused study products will be returned to [redacted]

Once the site has been notified that they may do so, all unused study product and empty or partially used study product, other than that randomly selected for retention samples may be returned to [redacted] It is important that retention samples not be returned to [redacted] the Sponsor or the packaging company during or at the end of the study. Sufficient study medication must be retained among the sites participating in the study to meet the sample retention requirements in accordance with FDA regulations (21 CFR 320.38 and 21 CFR 320.63.).

10.4.4 Method of Assigning Subjects to Treatment Groups

At Visit 1 eligible subjects will be enrolled in the study, and scheduled for Visit 2. At Visit 2, eligible subjects will be randomized to one of the four sequences as shown below. Treatments will be administered according to a four-treatment, four-period, four-sequence design. The randomization will be generated in blocks of four with each sequence occurring once in each block.

Sequence	Period 1	Period 2	Period 3	Period 4
1	A	B	C	D

2	D	C	B	A
3	C	A	D	B
4	B	D	A	C

Each subject will receive a 'Treatment Box' containing four inhalers (contained in small boxes) of study product, corresponding to one of the four treatments (A, B, C or D) assigned to the study period as demonstrated in the table above.

Subjects will be randomized to a treatment regimen in a blinded fashion by assigning randomization numbers in ascending sequential order starting with the lowest available randomization number at each site. All subjects randomized will be identified by initials, date of birth, and a unique seven-digit subject number. The first two-digits will identify the Investigator site where the subject was enrolled and the last five will correspond with the randomization number of study product 'Treatment Box' assigned to the subject. A perforated or two-part label will be attached to each of the small boxes containing individual inhalers. Both pieces of the label should include the following information: Protocol number, randomization number, space for subject's initials, statement that the study product is for Investigational Use only, space for dispensing date and the Sponsor's name. In addition all subjects will be provided with written instructions on how to use the study medication. One part of the label will remain attached to the box. The other part will be removed before dispensing and attached to the study product log.

10.4.5 Study Blind

The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the subject assignment. The subject will be requested not to discuss the appearance of the study product canister with the Investigator or study staff outside of the Independent Dispenser.

Each study site will have at least one Independent Dispenser. The role of the Independent Dispenser is to dispense and collect all study product inhalers from the subjects, observe subject dosing in the office and to ensure the study product logs are reported correctly. They should not be involved in collecting any efficacy or safety data in the study thus ensuring the integrity of the study blind. This will allow the study to be conducted under double-dummy conditions.

To ensure that information that could potentially bias handling of data is not disclosed, the clinical packaging company will hold the randomization scheme until database lock. For each subject an unblinding card contained within a sealed envelope will be provided, to be opened in case of medical emergency only. The unblinding cards should be stored in a secure location at all times.

The treatment code may be revealed on an individual basis in the case of a serious adverse event (SAE) for which the Investigator must know the identity of the study product to initiate appropriate treatment.

All SAEs will be evaluated for expectedness and causality by the Investigator or designee. Unblinding of sponsor's designated Pharmacovigilance personnel will be done for subjects

experiencing an SAE if it is required by FDA for regulatory reporting purposes. This unblinding is only for reporting purposes and all other study personnel from the Sponsor, [redacted] and the study site will continue to be blinded to the treatment allocation.

Where possible, the Sponsor and [redacted] Medical Monitor should be contacted before breaking the blind for any subject. In the event the blind is broken for any reason Sponsor and [redacted] will be notified as soon as possible in writing of the details of the occurrence.

All randomized bottles will be checked for any evidence of tampering. Any subject who has the blind broken during the study, or whose randomized bottle shows any evidence of tampering will only be eligible for inclusion in the safety analysis.

At the conclusion of the study, after the database has been locked, each site will be sent a sealed envelope containing the full study randomization scheme that should be retained with the study documents in the event of an FDA Inspection.

All study products are similar in size, shape and color. A standard label overlay will be used and there is no difference in odor of the products. Therefore, all three products are indistinguishable. This will allow the study to be conducted under double-blind conditions, such that neither the subject nor the Investigator or study staff members will know the identity of each subject's treatment.

10.4.6 Compliance

Subjects will self-administer study treatments in the clinic during each of the Visits 2-5, as per dosing instructions provided, and with the Independent Dispenser observing. Subjects who fail to administer study product per instructions, or attempt to tamper blinding labels will be considered non-compliant.

10.5 Study Conduct

10.5.1 Visit 1 (Day -14 to Day -1): Screening

1. **Informed Consent**: Subjects who are willing to comply with study procedures will read, understand and sign an informed consent.
2. **Baseline Demographics**: Collect the subject's demographic information.
3. **Medical History**: Collect the subject's medical history. Subject must have a documented diagnosis of stable, mild asthma as confirmed by prior medical records.
4. **Vital Signs**: Blood pressure (BP), heart rate (HR), respiratory rate (RR) and temperature will be collected before and after methacholine procedures.
5. **Height and Weight**: Height and weight will be collected.
6. **Physical Exam**: Perform an examination of head, ear, eyes, nose, throat and lungs.
7. **Urine Pregnancy Test**: All females of childbearing potential will have a urine pregnancy test performed. The test must be negative for the subject to be eligible for inclusion in the study.

8. **12-Lead ECG**: Subjects may undergo a 12-lead ECG to screen for significant abnormal cardio-thoracic findings.
9. **Chest X-ray**: Chest x-ray may be performed at the discretion of the Investigator.
10. **Concomitant Medications**: Review the subject's use of concomitant medication within the last 6 months.
11. **Spirometry**: FEV_1, FVC and FEV_1/FVC ratio [(FEV_1/FVC) x 100] will be recorded before and after saline administration. Once the methacholine test is completed, rescue albuterol will be administered and spirometry will be performed approximately 15 minutes later until the subject's FEV_1 returns to within 90% of the best post-saline FEV_1 or until the Investigator determines that the FEV_1 has stabilized and it is safe to allow the subject to leave the site.
12. **Saline Control Administration**: Once Qualifying FEV_1 is obtained, a saline control will be administered to the subject through a nebulizer.
13. **Methacholine Challenge**: Subjects meeting post-saline FEV_1 criteria will undergo methacholine bronchoprovocation challenge with progressively increasing concentrations to determine the subject's baseline provocation concentration of inhaled methacholine required to reduce FEV_1 by 20% (PC_{20}) relative to the post-saline value. The maximum concentration of methacholine be administered in this step will be 8 mg/mL. Methacholine should be diluted per the ATS recommendations and recorded when PC_{20} is reached.
14. **Pulse Oximetry**: Pulse oximetry will be measured during the methacholine challenge.
15. **Inclusion/Exclusion Criteria Review**: Review and confirm that subject fulfills all inclusion/exclusion criteria for study eligibility.
16. **Provide Diary**: Subjects will receive a diary to record AEs or concomitant medications.
17. **Adverse Events**: Patients will be questioned about any AEs that occurred during the visit.
18. Schedule Visit 2

10.5.2 Visit 2: Period 1 Dosing and Clinical Assessment

1. **Vital Signs**: BP, HR, RR and temperature will be collected before and after methacholine procedures.
2. **Urine Pregnancy Test**: All females of childbearing potential will have a urine pregnancy test performed before dosing. The test must be negative for the subject to be eligible for continuation in the study.
3. **12-Lead ECG**: Subjects may undergo a 12-lead ECG to screen for significant abnormal cardio-thoracic findings at the discretion of the Investigator.
4. **Concomitant Medications**: Subjects will be questioned about any changes in concomitant medication use since the last visit.

5. **Spirometry**: FEV_1, FVC and FEV_1/FVC ratio [(FEV_1/FVC) x 100] will be recorded before and after saline administration. A pre-treatment evaluation will confirm that pre-challenge FEV_1 is $\geq$ 80% of predicted and within 88 and 112% of qualifying spirometry value at Screening visit. Spirometry will be performed following the saline administration. Post-saline FEV_1 should not drop more than 10% from pre-saline (Qualifying) FEV_1 and should be $\geq$ 70% of predicted value. Spirometry procedures will be performed after the administration of methacholine and will be repeated until PC_{20} is found. Once the methacholine test is completed, rescue albuterol will be administered and spirometry will be performed approximately 15 minutes later until the subject's FEV_1 returns to within 90% of the best post-saline FEV_1 or until the Investigator determines that the FEV_1 has stabilized and it is safe to allow the subject to leave the site.
6. **Saline Control Administration**: Once Qualifying FEV_1 is obtained, a saline control will be administered to the subject through a nebulizer.
7. **Prime and Dispense Study Product and Instructions**: An Independent Dispenser will prime and dispense randomized treatment (a set of four inhalers) to subject, along with a set of dosing instructions. Subjects will be assigned a randomization number. A review of inhaler dosing technique, priming and preparation of inhalers will be performed.
8. **Dosing**: Before the methacholine challenge, subjects will self-administer study treatment (one puff from each of the four inhalers) with the Independent Dispenser observing. The time of last actuation will be recorded, as well as the adequacy of inhaler technique.
9. **Methacholine Challenge**: Approximately 15 minutes after the last inhalation of study product, subjects will undergo methacholine bronchoprovocation challenge with progressive concentrations to determine the subject's PC_{20}. The 20% reduction in FEV_1 will be determined relative to the post-saline FEV_1. Methacholine should be diluted per the ATS recommendations.
10. **Pulse Oximetry**: Pulse oximetry will be measured during the methacholine challenge and recorded when PC_{20} is reached.
11. **Assessment of Compliance**: The site staff/Independent Dispenser will record any non-compliance to dosing instructions.
12. **Provide Diary**: Subjects will receive a diary to record AEs or concomitant medications.
13. **Collect/Review Diary**: Diaries will be collected and reviewed for compliance with the protocol.
14. **Adverse Events**: Subjects will be questioned about AEs since the last visit.
15. Schedule next visit.

10.5.3 Visit 3: Period 2 Dosing and Clinical Assessment

The interval between Visit 2 dosing and Visit 3 dosing should be at least 48 hours

1. **Vital Signs**: BP, HR, RR and temperature will be collected before and after methacholine procedures.
2. **Urine Pregnancy Test**: All females of childbearing potential will have a urine pregnancy test performed before dosing. The test must be negative for the subject to be eligible for continuation in the study.
3. **12-Lead ECG**: Subjects may undergo a 12-lead ECG to screen for significant abnormal cardio-thoracic findings at the discretion of the Investigator.
4. **Concomitant Medications**: Subjects will be questioned about any changes in concomitant medication use since the last visit.
5. **Spirometry**: FEV_1, FVC and FEV_1/FVC ratio [(FEV_1/FVC) x 100] will be recorded before and after saline administration. A pre-treatment evaluation will confirm that pre-challenge FEV_1 is $\geq$ 80% of predicted and within 88 and 112% of qualifying spirometry value at Screening visit. Spirometry will be performed following the saline administration. Post-saline FEV_1 should not drop more than 10% from pre-saline (Qualifying) FEV_1 and should be $\geq$ 70% of predicted value. Spirometry procedures will be performed after the administration of methacholine and will be repeated until PC_{20} is found. Once the methacholine test is completed, albuterol will be administered and spirometry will be performed approximately 15 minutes later until the subject's FEV_1 returns to within 90% of the best post-saline FEV_1 or until the Investigator determines that the FEV_1 has stabilized and it is safe to allow the subject to leave the site.
6. **Saline Control Administration**: Once Qualifying FEV_1 is obtained, a saline control will be administered to the subject through a nebulizer.
7. **Prime and Dispense Study Product and Instructions**: An Independent Dispenser will prime and dispense randomized treatment (a set of four inhalers) to subject, along with a set of dosing instructions. A review of inhaler dosing technique, priming and preparation of inhalers will be performed.
8. **Dosing**: Before the methacholine challenge, subjects will self-administer study treatment (one puff from each of the four inhalers) with the Independent Dispenser observing. The time of last actuation will be recorded, as well as the adequacy of inhaler technique.
9. **Methacholine Challenge**: Approximately 15 minutes after the last inhalation of study product, subjects will undergo methacholine bronchoprovocation challenge with progressive concentrations to determine the subject's PC_{20}. The 20% reduction in FEV_1 will be determined relative to the post-saline FEV_1. Methacholine should be diluted per the ATS recommendations.
10. **Pulse Oximetry**: Pulse oximetry will be measured during the methacholine challenge and recorded when PC_{20} is reached.

11. **Assessment of Compliance**: The site staff/Independent Dispenser will record any non-compliance to dosing instructions.
12. **Provide Diary**: Subjects will receive a diary to record AEs or concomitant medications.
13. **Collect/Review Diary**: Diaries will be collected and reviewed for compliance with the protocol.
14. **Adverse Events**: Subjects will be questioned about AEs since the last visit.
15. Schedule next visit

10.5.4 Visit 4: Period 3 Dosing and Clinical Assessment

The interval between Visit 3 dosing and Visit 4 dosing should be at least 48 hours

1. **Vital Signs**: BP, HR, RR and temperature will be collected before and after methacholine procedures.
2. **Urine Pregnancy Test**: All females of childbearing potential will have a urine pregnancy test performed before dosing. The test must be negative for the subject to be eligible for continuation in the study.
3. **12-Lead ECG**: Subjects may undergo a 12-lead ECG to screen for significant abnormal cardio-thoracic findings at the discretion of the Investigator.
4. **Concomitant Medications**: Subjects will be questioned about any changes in concomitant medication use since the last visit.
5. **Spirometry**: FEV_1, FVC and FEV_1/FVC ratio [(FEV_1/FVC) x 100] will be recorded before and after saline administration. A pre-treatment evaluation will confirm that pre-challenge FEV_1 is $\geq$ 80% of predicted and within 88 and 112% of qualifying spirometry value at Screening visit. Spirometry will be performed following the saline administration. Post-saline FEV_1 should not drop more than 10% from pre-saline (Qualifying) FEV_1 and should be $\geq$ 70% of predicted value. Spirometry procedures will be performed after the administration of methacholine and will be repeated until PC_{20} is found. Once the methacholine test is completed, albuterol will be administered and spirometry will be performed approximately 15 minutes later until the subject's FEV_1 returns to within 90% of the best post-saline FEV_1 or until the Investigator determines that the FEV_1 has stabilized and it is safe to allow the subject to leave the site.
6. **Saline Control Administration**: Once Qualifying FEV_1 is obtained, a saline control will be administered to the subject through a nebulizer.
7. **Prime and Dispense Study Product and Instructions**: An Independent Dispenser will prime and dispense randomized treatment (a set of four inhalers) to subject, along with a set of dosing instructions. A review of inhaler dosing technique, priming and preparation of inhalers will be performed.

8. **Dosing**: Subjects will self-administer study treatment (one puff from each of the four inhalers) with the Independent Dispenser observing. The time of last actuation will be recorded, as well as the adequacy of inhaler technique.
9. **Methacholine Challenge**: Approximately 15 minutes after the last inhalation of study product, subjects will undergo methacholine bronchoprovocation challenge with progressive concentrations to determine the subject's PC_{20}. The 20% reduction in FEV_1 will be determined relative to the post-saline FEV_1. Methacholine should be diluted per the ATS recommendations.
10. **Pulse Oximetry**: Pulse oximetry will be measured during the methacholine challenge and recorded when PC_{20} is reached.
11. **Assessment of Compliance**: The site staff/Independent Dispenser will record any non-compliance to dosing instructions.
12. **Provide Diary**: Subjects will receive a diary to record AEs or concomitant medications throughout the study.
13. **Adverse Events**: Subjects will be questioned about AEs since the last visit.
14. **Collect/Review Diary**: Diaries will be collected and reviewed for compliance with the protocol.
15. Schedule next visit

10.5.5 Visit 5: Period 4 Dosing and Clinical Assessment, End of Study

The interval between Visit 4 dosing and Visit 5 dosing should be at least 48 hours

1. **Vital Signs**: BP, HR, RR and temperature will be collected before and after methacholine procedures.
2. **Physical Exam**: Perform an examination of head, ear, eyes, nose, throat and lungs.
3. **Urine Pregnancy Test**: All females of childbearing potential will have a urine pregnancy test performed before dosing. The test must be negative for the subject to be eligible for continuation in the study.
4. **12-Lead ECG**: Subjects will undergo a 12-lead ECG to screen for significant abnormal cardio-thoracic findings at the discretion of the Investigator.
5. **Concomitant Medications**: Subjects will be questioned about any changes in concomitant medication use since the last visit.
6. **Spirometry**: FEV_1, FVC and FEV_1/FVC ratio [(FEV_1/FVC) x 100] will be recorded before and after saline administration. A pre-treatment evaluation will confirm that pre-challenge FEV_1 is ≥ 80% of predicted and within 88 and 112% of qualifying spirometry value at Screening visit. Spirometry will be performed following the saline administration. Post-saline FEV_1 should not drop more than 10% from pre-saline (Qualifying) FEV_1 and should be ≥

70% of predicted value. Spirometry procedures will be performed after the administration of methacholine and will be repeated until PC_{20} is found. Once the methacholine test is completed, albuterol will be administered and spirometry will be performed approximately 15 minutes later until the subject's FEV_1 returns to within 90% of the best post-saline FEV_1 or until the Investigator determines that the FEV_1 has stabilized and it is safe to allow the subject to leave the site.

7. **Saline Control Administration**: Once Qualifying FEV_1 is obtained, a saline control will be administered to the subject through a nebulizer.
8. **Prime and Dispense Study Product and Instructions**: An Independent Dispenser will prime and dispense randomized treatment (a set of four inhalers) to subject, along with a set of dosing instructions. A review of inhaler dosing technique, priming and preparation of inhalers will be performed.
9. **Dosing**: Before the methacholine challenge, subjects will self-administer study treatment (one puff from each of the four inhalers) with the Independent Dispenser observing. The time of last actuation will be recorded, as well as the adequacy of inhaler technique.
10. **Methacholine Challenge**: Approximately 15 minutes after the last inhalation of study product, subjects will undergo methacholine bronchoprovocation challenge with progressive concentrations to determine the subject's PC_{20}. The 20% reduction in FEV_1 will be determined relative to the post-saline FEV_1. Methacholine should be diluted per the ATS recommendations.
11. **Pulse Oximetry**: Pulse oximetry will be measured during the methacholine challenge and recorded when PC_{20} is reached.
12. **Assessment of Compliance**: The site staff/Independent Dispenser will record any non-compliance to dosing instructions.
13. **Adverse Events**: Subjects will be questioned about AEs since the last visit.
14. **Collect/Review Diary**: Completed diaries will be collected and reviewed for compliance with the protocol.
15. Exit patient from the study

10.6 Study Procedures

10.6.1 Informed Consent

At Visit 1, before performing any study-related procedures the study subject must sign the IRB-approved ICF. The ICF will be reviewed and approved by an IRB before study commencement. No subject will be entered into the study without reading, understanding and signing an ICF. If the ICF is required in any language besides English, translation will be performed by a certified translator and then approved by the IRB.

10.6.2 Baseline Demographics

At Visit 1, each subject will be required to provide basic demographic information (i.e., date of birth, sex, ethnicity, and race and tobacco use/smoking history).

10.6.3 Medical History

At Visit 1, subjects will be questioned about medical history, including acute and chronic medical history and medical history relevant to their asthma. Subject must have a documented diagnosis of stable, mild asthma as confirmed by prior medical records.

10.6.4 Vital Signs

The subject's vital signs will be recorded (pulse, BP, temperature and respiration rate) before and after methacholine procedures at each clinic visit.

10.6.5 Height and Weight

Height and weight will be collected at Visit 1.

10.6.6 Physical Exam

At Visits 1 and 5, the Investigator will perform a general physical exam for each qualified subject and any significant findings will be noted. The physical exam at a minimum must include a head, ear, eyes, nose, lungs and throat examination.

10.6.7 Urine Pregnancy Test

Urine pregnancy tests on women of childbearing potential will be performed at each clinic visit. The test must be negative for the subject to be eligible for inclusion in the study. If the subject is of non-childbearing potential, the source document must list the reason why she is of non-childbearing potential.

Subjects with a positive pregnancy test during Screening will not be enrolled in the study. Subjects who report they have become pregnant or who have a positive pregnancy test at the end of study visit will be followed to completion of the pregnancy. The pregnancy will be reported as an AE.

10.6.8 12-Lead ECG

Subjects will undergo a 12-lead ECG at Screening. An ECG may be performed at subsequent visits at the discretion of the Investigator. Any clinically significant findings will be noted.

10.6.9 Chest X-Ray

A chest x-ray may be performed at Visit 1 at the discretion of the Investigator.

10.6.10 Concomitant Medication Use

At Visit 1, subjects will be questioned about current and concomitant medication use over the previous 6 months. At all subsequent visits, subjects will be questioned about ongoing or new concomitant medication use.

10.6.11 Adverse Events

At the end of Visit 1, patients will be questioned about any AEs that occurred during the visit. At Visits 2, 3, 4, and 5 patients will be questioned regarding any changes in their medical status since their previous visit. Any significant changes observed after ICF signing will be reported as AEs.

10.6.12 Spirometry Testing

FEV_1 and FVC measurements will be performed using the KoKo® Pulmonary Function Testing Spirometer with built-in dosimeter (Koko® Digidoser, Item# 323205) or the KoKo Dosimeter (Item # 414400-A) in accordance with the ATS Guidelines for Methacholine and Exercise Challenge Testing.[17] Instructions and demonstration of use will be provided to subjects at the time of receipt of randomized treatment.

FEV_1 measurement is reported in liters, and data are digitally displayed on the KoKo Dosimeter device monitor for recording. Normal values for FEV_1 vary according to age, sex, height, mass and ethnicity. To account for such variations, FEV_1 % predicted will be calculated. FEV_1 % predicted is defined as subject's FEV_1 value expressed as a percentage of the reference average FEV_1 for a person of similar age, sex and body composition.

FEV_1, FVC and FEV_1/FVC ratio [(FEV_1/FVC) x 100] will be recorded before and after saline administration at each visit. Qualifying FEV_1 at Screening must be $\geq$ 80% of predicted value. Spirometry will be performed before and after the saline administration. Post-saline FEV_1 should not drop more than 10% from pre-saline (Qualifying) FEV_1 and should be $\geq$ 70% of predicted value. If the subject fails to meet either requirement, the challenge must be stopped, rescue albuterol administered and the visit should be rescheduled. Subjects who fail three consecutive visits should be dropped from the study.

Pre-treatment evaluations will be completed at each dosing visit. This evaluation will confirm that pre-challenge FEV_1 is $\geq$ 80% of predicted and within 88 and 112% of qualifying spirometry value at Screening visit. After the first inhalation of saline control is administered, the FEV_1 should not drop more than 10% compared to pre-challenge value. If the subject fails to meet either requirement, the challenge must be stopped, albuterol administered and the visit should be rescheduled. Subjects who fail three consecutive visits should be dropped from the study.

Spirometry procedures will be performed after the administration of methacholine and will be repeated until PC_{20} is found. After the procedures have been completed, albuterol will be administered to reverse airway obstruction and subjects will be followed until FEV_1 returns to within 90% of the best FEV_1 captured during the saline stage on that day or until the Principal Investigator determines that the FEV_1 has stabilized and it is safe to allow the subject to leave the site.

10.6.13 Saline Control Administration

Once Qualifying FEV_1 is obtained, a saline control will be administered to the subject through a nebulizer.

10.6.14 Methacholine Challenge

The spirometry procedures and the methacholine bronchoprovocation challenges in this study are to be performed in accordance with the ATS Guidelines for Methacholine and Exercise Challenge Testing.

Screening

Subjects meeting FEV_1 criteria will undergo methacholine bronchoprovocation challenge with progressively increasing concentrations to determine the subject's baseline provocation concentration of inhaled methacholine required to reduce FEV_1 by 20% (PC_{20}) relative to the post-saline value.

Methacholine should be prepared in doubling concentrations as recommended by the ATS for the two-minute tidal breathing dosing protocol.[17]

Saline (0.0 mg/mL), 0.03 mg/mL, 0.06 mg/mL, 0.125 mg/mL, 0.25 mg/mL, 0.50 mg/mL, 1 mg/mL, 2 mg/mL, 4 mg/mL, 8 mg/mL

The maximum concentration of methacholine be administered in this step will be 8 mg/mL. Subjects who do not respond to methacholine doses at or below 8 mg/mL will not be eligible for enrollment in the study.

Dosing Visit

Approximately 15 minutes after the last inhalation of study product, a methacholine bronchoprovocation challenge will be given with progressive concentrations in order to determine the PC_{20}. The 20% reduction in FEV_1 will be determined relative to the post-saline FEV_1.

Methacholine should be prepared in the following concentrations:

Saline (0.0 mg/mL), 0.03 mg/mL, 0.06 mg/mL, 0.125 mg/mL, 0.25 mg/mL, 0.50 mg/mL, 1 mg/mL, 2 mg/mL, 4 mg/mL, 8 mg/mL, 16 mg/mL, 32 mg/mL, 64 mg/mL, 128 mg/mL

The maximum methacholine dose at each dosing visit will be 128 mg/mL.

10.6.15 Pulse Oximetry

Pulse oximetry will be monitored during the methacholine challenge and recorded when PC_{20} is reached.

10.6.16 Prime and Dispense Study Product and Instructions

Before dispensing the study product, the Independent Dispenser will prime the inhaler of study product immediately before using for the first time by releasing 3 test sprays into the air, shaking well for 5 seconds before each spray, until a uniform spray is obtained. Priming of randomized study product should occur in a separate area, away from subjects. The Independent Dispenser will dispense 4 inhalers of randomized study product to each eligible subject, along with a set of dosing instructions. Subjects will be asked to dose in clinic with Independent Dispenser observing.

10.6.17 Collecting Study Product

Study product inhalers will be collected at each visit following dosing.

10.6.18 Provide, Collect, and Review Diary

Subjects will be provided dosing instructions to facilitate consistent dosing before pharmacodynamic (PD) recordings at each clinic visit.

Subjects will be provided with a diary, with instructions, to record AEs and concomitant medications throughout the study. The diary will be collected and reviewed for compliance with the protocol at Visits 2-5 by the study staff.

10.7 Adverse Events

The subjects will be monitored throughout the study for any AEs. Adverse events will be collected through both solicited and unsolicited means and subsequently coded in tabular form using the MedDRA (Version 21.0 or higher) Adverse Event Dictionary. The subjects will be encouraged to report signs, symptoms, and any changes in health to the clinic staff. Severity of each AE will be determined by the clinic staff based on observation and questioning of the subjects. The Investigator will judge the relationship of the event to the study product. Adverse events should be followed up until end of study visit or last dose of study product administration..

10.7.1 Definitions

Adverse Event

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavorable and unintended sign, symptom or disease, temporally associated with the use of a medicinal (investigational) product, whether or not related to this product. This includes events not seen at baseline, or worsened even if present at baseline.

Action taken with study product:

- Drug Withdrawn
- Dose not changed
- Not Applicable

Outcome:

- Recovered/ Resolved
- Recovering/ Resolving
- Recovered/ resolved with sequelae
- Not Recovered/ Not Resolved

- Fatal
- Unknown

10.7.2 Events Not to Be Considered Adverse Events

Medical baseline or pre-dosing conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are not to be considered AEs.

10.7.3 Severity of Adverse Events

Severity of AE

The severity of the AE will be graded by the Investigator using the following criteria as guidelines:

- MILD: Awareness of symptom but does not interfere with routine activities.
- MODERATE: Discomfort sufficient to interfere with routine activities.
- SEVERE: Impossible to perform routine activities.

10.7.4 Relationship of Adverse Events

Relationship to the Study Product

TERM	DEFINITION	CLARIFICATION
Unrelated	Those AEs which, after careful consideration, are clearly due to extraneous causes (medical history, demography details, disease, environment, etc.)	
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.	1. It does not follow a reasonable temporal sequence (Improbable temporal relationship) from administration of the drug. 2. It could also be explained by patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals including food-drug interactions
Possibly	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.	1. It follows a reasonable temporal sequence from administration of the drug. 2. It could also be explained by patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals (including food-drug interactions). 3. There is no information or uncertainty with regard to what has happened after stopping the drug.
Probably	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug,	1. It follows a reasonable temporal sequence from administration of the drug. 2. It could not be readily explained (unlikely) by the

TERM	DEFINITION	CLARIFICATION
	unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.	patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals including food-drug interactions. 3. It disappears or decreases in severity on cessation or reduction in dose or on administration of a specific antagonist wherever possible. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists. 4. No re-challenge information is available or possible.
Certainly	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.	1. It follows a plausible time sequence to drug intake, this means that there is a positive argument in sufficient detail to support the view that the drug is causally involved, pharmacologically or pathologically e.g., pharmacokinetics and type of reaction. 2. It could not be explained by patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals including food-drug interactions (i.e., no alternative causes). 3. It disappears or decreases in severity on cessation or reduction in dose or on administration of a specific antagonist wherever possible. 4. It is an objective and specific medical disorder or a recognized pharmacological phenomenon for instance 'grey baby syndrome' and chloramphenicol or anaphylaxis immediately after the administration of a drug that had been given previously. This means that any other event is automatically excluded and can never qualify for 'Certain' (even in the case of a positive re-challenge observation). 5. It reappears on re-administration of the drug (only if ethically correct i.e., in case of non-serious, and easily treatable AEs).

10.7.5 Expectedness Assessment

The sponsor's designated Pharmacovigilance personnel will be responsible for determining expectedness.

The most recent version of the albuterol sulfate Investigator's Brochure will serve as Reference Safety Information for determination of expectedness.

The package insert of PROAIR® HFA (albuterol sulfate) Inhalation Aerosol will be used for assessment of expectedness of SAEs occurring in patients treated with PROAIR® HFA.

10.8 Serious Adverse Events

10.8.1 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose :

- Results in death: includes all deaths, even those that appear to be completely unrelated to study treatment (e.g., car accident where subject is a passenger).
- Is life-threatening: in the view of the Investigator, the subject is at immediate risk of death at the time of the event.
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life).
- Requires insubject hospitalization or prolongation of existing hospitalization.
- Causes congenital anomaly or birth defect.an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require medical or surgical intervention to prevent one of the serious outcomes listed above (e.g., intensive treatment in an emergency room, convulsions that do not result in hospitalizations). Emergency Room visits that require medical or surgical intervention to prevent one of the other serious outcomes listed above are considered an SAE.

10.8.2 Events That Do Not Meet the Definition of a Serious Adverse Event

Elective hospitalizations to administer, or to simplify study treatment or study procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs).

10.8.3 Serious Adverse Event Reporting

Any SAE, whether deemed drug-related or not, must be reported by the Investigator to [redacted] and sponsor's designated Pharmacovigilance personnel by email/fax within 24 hours after the Principal Investigator or Study Coordinator becomes aware of its occurrence. The Principal Investigator or the Principal Investigator's designee must complete an SAE Form and email/fax it to [redacted] and [redacted] within 24 hours of notification of the event.

Any SAEs should be reported to [redacted] and [redacted] within 24 hours. Following is the contact information:

[redacted]

The US FDA shall be initially notified by an expedited safety report of any SAE by the Sponsor, no later than 15 calendar days from the “date learned” of the event. The US FDA will be initially notified within 7 calendar days of any fatal or life-threatening SAEIf the safety report submitted within 7 calendar days is complete, an additional submission within 15 days from ”day 0” is not required.

Sponsor’s designeewill inform other investigators involved in the study within 15 days of becoming aware of the occurrence of the SAE or as per regulation.

All AEs encountered during the study will be reported on the appropriate form and summarized in the final report.

10.9 Definition of the Adverse Event Reporting Period:

The AE/SAE reporting period for safety surveillance begins after the patient has signed ICF and continues until end of study visit or early termination visit.

10.10 Monitoring of Subjects with Adverse Events

Adverse events will be recorded and assessed continuously throughout the study and will be assessed for final outcome at the End of Study visit. All AE/SAEs ongoing at the End of Study visit must be monitored and followed up by the Investigator until stabilization/resolution or until the outcome is known as per medical judgment of Investigator, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

Any AE/SAE that occurs after the End of Study visit or early termination visit will be reported if it is considered related to study product by Investigator.

10.11 Pregnancy

A pregnancy test will be performed at Screening and at all visits specified in the protocol. Subjects with a positive test at Screening will be excluded from study. If a subject becomes pregnant during the study, the pregnancy will be recorded as a significant medical event and reported per SAE reporting procedure and the subject will be withdrawn from the study immediately. Women of childbearing potential will be instructed to practice an acceptable method of birth control for the duration of the study. Similarly, male subjects enrolled to the study will be instructed not to father a child and avoid passage of semen to their partner by using an acceptable contraceptive method discussed by the Investigator during their enrollment into the study. If a female partner of the male subject becomes pregnant during the study, the pregnancy will be recorded appropriately. The pregnancy reporting form will be completed and submitted to sponsor's designated Pharmacovigilance personnel within timelines defined in protocol for SAE reporting. All pregnancies (female subject and female partner of male subject) shall be followed every three months until its outcome and one month post-delivery. If there are abnormalities present at delivery, the newborn will be followed for an appropriate period, up to three months, to assess the functional and health status. If there is an SAE in association with pregnancy or delivery, the SAE will be followed until resolution or stabilization.

11.0 STATISTICAL METHODS

11.1 Statistical Plan

A statistical analysis plan, detailing the intended statistical analysis of the study data, will be prepared as a separate document and finalized before database lock. Any deviation from the original statistical plan will be described and justified in the final report, as appropriate. The procedure for accounting for missing, unused and spurious data will be included in the statistical analysis plan.

All statistical analysis will be conducted using SAS®, Version 9.4. A dose-scale pharmacodynamic (PD) analysis will be conducted using NONMEM®. Datasets will be prepared using headings from Clinical Data Standards Interchange Consortium (CDISC) Study Data Tabulation Model (SDTM) implementation for human clinical trials and Analysis Dataset Model (ADaM).

11.2 Determination of Sample Size

The sample size estimation for this study was based on data from the study by Newhouse et al. that reported the bronchoprotective effect of inhaled salbutamol (albuterol) on methacholine $PC_{20}FEV_1$.[2]

The highest within-subject coefficient of variability (COV) value for ln-transformed PC_{20} was estimated as 0.846 from the mean ratio and SD values for the PC_{20} at the 200 and 100 mcg doses (Table 1 in reference 2). Based on this COV, 98 evaluable subjects would be required in the PD population to demonstrate pharmacodynamic equivalence (i.e., 90% confidence interval on relative bioavailability [F] is within the bioequivalence limits of 0.67 to 1.50) with 90% power for a crossover study, assuming a true ratio of F = 1.1. To allow for approximately 20% of subjects that may discontinue from the study or have major protocol violations, and therefore not qualify for the PD population, up to 123 subjects will be randomized in the study.

11.3 Study Populations

11.3.1 Per-Protocol (PP) Population

The PP population will include all subjects who:

- Completed all four randomized treatment periods.
- Were compliant with study treatment dosing procedures.
- Did not use any restricted concomitant medications.
- Did not have any other significant protocol deviations.

11.3.2 Pharmacodynamic (PD) Population

The PD population used in the dose-scale analyses will include patients who:

- Completed at least one of the four randomized treatment periods.
- Were compliant with study treatment dosing procedures.
- Did not use any restricted concomitant medications.
- Did not have any other significant protocol deviations.

11.3.3 Safety Populations

The Safety population will include all subjects who administered at least one actuation of any of the study products.

11.4 Subject Characteristics

The following subject demographic characteristics will be summarized separately in the PP, PD and Safety populations.

- Age (years)
- Sex (male/female)
- Ethnicity (Hispanic/non-Hispanic)
- Race (White, Black/African American, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native)
- Tobacco use (yes/no)
- Number of years subject has suffered from symptoms caused by asthma
- Qualifying spirometry
- $PC_{20}FEV_1$

11.5 Primary Pharmacodynamic Endpoint

The primary pharmacodynamic endpoint will be the post-dose PC_{20}, which is the provocative concentration of the methacholine challenge agent required to reduce the FEV_1 by 20% following administration of differing doses of albuterol (or placebo) by inhalation. The 20% reduction in FEV_1 will be determined relative to the post-saline FEV_1 measure before the placebo or albuterol administration.

11.6 Pharmacodynamic Equivalence

The primary bioequivalence evaluation using the dose-scale analysis will be performed using the PD population; NONMEM allows for the use of all available data, without biasing the F estimation. This bioequivalence test will be conducted at the 0.05 significance level. If bioequivalence is achieved for the PD population, the same test will also be conducted on the PP population at the same significance level. If bioequivalence is not achieved for the PD population then no test will be conducted on the PP. As a result of this step-down approach, no adjustment is necessary on the significance levels for either test.

Pharmacodynamic equivalence between Test and Reference products will be based on the Dose-Scale method of analysis of the post-dose $PC_{20}FEV_1$ (mg/mL) data using non-linear E_{max} modeling, as outlined in the FDA Draft Guidance on Orlistat capsule.[1] Alternative models may be tested if warranted by the data, and these models as well as the specific criteria related to their use, will be described in the statistical analysis plan. The methacholine $PC_{20}FEV_1$ will be calculated by linear interpolation from the observed data relating the % decrease in FEV_1 from the post-saline FEV_1 to the concentration of methacholine that provokes at least a 20% decrease in FEV_1. This interpolation will be based on log transformed methacholine concentrations. In the event that subjects receiving the maximum concentration of methacholine (128 mg/mL) at any treatment visit (Visits 2-5) do not achieve at least a 20% fall in FEV_1, then they will have their $PC_{20}FEV_1$ data interpolated as though

they had achieved positivity at 128 mg/mL (i.e., $PC_{20}FEV_1$ will be imputed as 128 mg/mL) and will be included in the PP population. The $PC_{20}FEV_1$ data will be log-transformed if they are log-normally distributed.

If the 90% confidence interval for F falls within 67.00-150.00% then pharmacodynamic equivalence will be considered to have been demonstrated. F is the potency ratio of the doses of Test and Reference formulations that produce an equivalent pharmacodynamic response at the ED_{50} of the Reference dose-response E_{max} curve. The 90% confidence interval for F will be estimated by a bootstrap procedure using Efron's bias-corrected and accelerated (BCA) method.

11.6 Safety Analysis

All study subjects who receive at least one actuation of any of the study products will be included in the comparative safety analysis. Adverse events will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 21.0 or higher and presented by treatment group. Summary tables listing the type, date of onset, date of resolution, incidence, severity, outcome, action taken, and Investigator's opinion of relationship to the study product will be presented by treatment group for AEs reported after randomization.

Signs and symptoms of asthma will not be considered AEs, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/subject considers that it is in the subject's best interest to be dropped from continued participation in the study and given alternative therapy for their condition. If sufficient data exist, then AEs frequencies will be compared among treatments using Fisher's exact test.

Concomitant medication used during the study will be tabulated by treatment by subject.

12.0 REGULATORY OBLIGATIONS

12.1 Institutional Review Board

The study protocol, ICF, product label (as applicable) and any specific advertising will be submitted to, and approved by, an IRB before the start of the study. A form must be signed by the chairman or designee of the IRB noting the approvals. This notification of the board's approval along with a description by profession and gender of the board's composition will be provided to the Sponsor and/or Sponsor Representative.

12.2 Study Documentation

This study will be conducted in compliance with the protocol; Good Clinical Practices and all applicable regulations, including the Federal Food, Drug and Cosmetics Act, US applicable Code of Federal Regulations (title 21), parts 50, 56, 312, 320, and any IRB requirements relative to clinical studies; and the Declaration of Helsinki, June 1964, as modified by the 64th World Medical Association General Assembly, October 2013.[19-22]The Investigator will permit trial-related monitoring, audits, IRB review and regulatory inspections providing direct access to source data/documents.

12.2.1 Protocol

The Investigator indicated on Form FDA 1572 will act as the Principal Investigator at each study site. Protocols will be noted as approved by placement of the [redacted] signature on the signature page. The Sponsor of the study will also approve the protocol by having a study-responsible individuals sign the protocol signature page.

12.2.2 Informed Consent

An ICF that includes all of the relevant elements currently required by FDA and local state regulations will be provided to each prospective study subject at Screening, before enrollment into the study. The type and method of study, tests to be administered, any potential or possible hazards, and the subject's right to withdraw from the study at any time will be explained to the subjects by the Investigator or designee. Once the Investigator or designee is assured that an individual candidate understands the implications of participating in this study, the subject will be asked to give consent by signing and dating in the appropriate areas of the ICF. The person obtaining consent will also sign and date the form, along with the Investigator who will sign the ICF to verify that the subject has indeed received information. A copy of the ICF will be provided to the subject.

12.2.3 Protocol and Informed Consent Changes

Revisions to the original protocol will be documented in amendments, incorporated as a preface to the new version and approved by the IRB. Any revision that substantially alters the study design or increases potential risk to the subject requires the subject’s consent to continue in the study. Revisions to the original ICF will also be approved by the IRB. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and ICF amendments/revisions, along with letters noting IRB approval, will be submitted to the Sponsor.

12.2.4 Source Documents and Electronic Case Report Forms

All subjects will be identified by initials, and a unique subject number. Source documents will be used to record all study-related data. Source document entries will be used to complete electronic case report forms (eCRFs). All data and eCRFs will be reviewed, evaluated and signed by the Investigator, as required.

The original source documents and a copy of the corresponding eCRFs will be retained by the Investigator. Subjects who terminate early from the study will have the Visit 4 (end of study) source/eCRF completed.

12.2.5 Drug Accountability

All study product receipt, inventory, dispensing, dosing and reconciliation records will be maintained in compliance with federal regulations. The study product will be dispensed to qualified study subjects according to established procedures. At the end of the study (after the database has been locked) all used and unused study product, other than that which has been randomly selected for retention samples, will be returned to Sponsor or designee.

12.2.6 Drug Storage

All study product will be stored at controlled room temperature between 15° and 25°C (59° and 77°F), away from direct sunlight (or freezing temperatures) in a secure place with access by authorized individuals only. Any excursions from the permitted range of 15–25ºC (59º–77ºF) will require prompt notification to [redacted] and thereafter [redacted] will notify the Sponsor. The inhalers are to be stored with actuators 'down'. The Investigator will be responsible for maintaining accurate records of drug receipt, dispensing, and return. At the end of the study, all partially used and unused study product will be returned to [redacted]

12.2.7 Reporting Safety Information to the IRB

The Investigator must promptly report to the Investigator's IRB all unanticipated problems involving risks to subjects. This includes death from any cause and all SAEs occurring during the study, regardless of the assessed causality.[23]

12.2.8 Record Retention

All drug accountability records, CRFs, source data and related regulatory documents must be retained for at least two years following completion of the study or for two years after the Test product has been approved for marketing by the FDA, if applicable.

12.2.9 Study Monitoring and Auditing

[redacted] will be responsible for monitoring the study according to Good Clinical Practice and applicable regulations. Monitoring visits are for the purpose of confirming adherence to the protocol and to verify complete and accurate data collection. The clinical site will make all records associated with the study available to [redacted] representative during such visits and audits.

Medical advisors and clinical research associates or assistants may request to witness subject evaluations occurring as part of this protocol. The study may be subject to audit by the Sponsor, Sponsor Representative or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to required subject records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation.

12.2.10 End of the Trial

The end of the trial is defined as the time at which the last subject has completed their last visit in the study. Upon completion of the study, the study product will no longer be available to the subject but the Investigator can, at their discretion, discuss alternative treatments with the subject.

12.2.11 Clinical Study Report

At the end of the study a full report per requirements of Sponsor and regulatory authorities will be prepared which will include a narrative of the clinical conduct and results of the study, a statistical report including a description of the analysis performed, and other documentation as may be appropriate. The report will be in electronic format according to the electronic Common

Technical Document (eCTD) and International Conference on Harmonisation (ICH) formatting standards and guidelines.[24] Abbreviated New Drug application (ANDA) summary tables will also be generated. Data sets will be provided in SAS® transport (.xpt) format with appropriate description (Read Me) files as required by FDA.

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14.0 APPENDICES

14.1 APPENDIX A – NAEPP Guidelines for Asthma Severity Classification

FIGURE 14. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN YOUTHS 12 YEARS OF AGE AND ADULTS

Assessing severity and initiating treatment for patients who are not currently taking long-term control medications

Components of Severity		Classification of Asthma Severity ≥12 years of age			
		Intermittent	Persistent: Mild	Persistent: Moderate	Persistent: Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
Normal FEV$_1$/FVC: 8–19 yr 85%; 20–39 yr 80%; 40–59 yr 75%; 60–80 yr 70%	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV$_1$ between exacerbations • FEV$_1$ >80% predicted • FEV$_1$/FVC normal	• FEV$_1$ >80% predicted • FEV$_1$/FVC normal	• FEV$_1$ >60% but <80% predicted • FEV$_1$/FVC reduced 5%	• FEV$_1$ <60% predicted • FEV$_1$/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.			
		Relative annual risk of exacerbations may be related to FEV$_1$.			
Recommended Step for Initiating Treatment (See "Stepwise Approach for Managing Asthma" for treatment steps.)		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Key: EIB, exercise-induced bronchospasm, FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

14.2 APPENDIX B – PROAIR® HFA (albuterol sulfate) Inhalation Aerosol Package Insert

14.3 APPENDIX C – Albuterol Sulfate Inhalation Aerosol Investigator's Brochure

14.4 APPENDIX D – Amendments to the Protocol

Amendment	Date	
1	09/06/2017	

The following revisions were made to the protocol dated 06/01/2017.

- Revision Date: Title page and Footer
- Added to Screening Section-*All clinical assessments except height and weight will be performed at each rescheduled visit.* Pg 9 and 22
- Inclusion Criteria Deleted from # 3 - *such as condom plus diaphragm with spermicide*
- Study schematic updated
- Added: *Scientific and statistical considerations corrected to read interpolated not extrapolated; clarification on FEV1 imputation was added.* Pg 20 and pg 45
- Added: *Screening updated to match synopsis ("rescue" added to albuterol administration and added repeated vital signs)*. Page 22
- Added AE assessment to procedures in 10.5.1. Page 32:
- Added to Methacholine Challenge throughout all visits
  - *meeting post-saline FEV_1 criteria*
  - *Methacholine should be diluted per the ATS recommendations and recorded when PC_{20} is reached.*
- Added to Urine Pregnancy Test throughout all visits
  - *before dosing.*
- Added to Pulse Oximetry throughout all visits
  - *and recorded when PC20 is reached.*
- Added collect/review diary to visits 2-5
- Corrected for consistency to say "through a nebulizer". Section 10.5.3 point # 6
- Changed through out to comply with the guidance
  - *Gender to Sex*
- Corrected Section 10.6.8
- Added to Section 10.6.11, Adverse Events:
  - *At the end of Visit 1, patients will be questioned about any AEs that occurred during the visit. At Visits 2, 3, 4, and 5 patients will be questioned regarding any changes in their medical status since their previous visit. Any significant changes observed after ICF signing will be reported as AEs*
- Added to Section 10.6.12:
  - *If the subject fails to meet either requirement, the challenge must be stopped, rescue albuterol administered and the visit should be rescheduled. Subjects who fail three*

consecutive visits should be dropped from the study.

- Added to Section 10.6.14:
  - *Methacholine should be prepared in doubling concentrations as recommended by the ATS for the two-minute tidal breathing dosing protocol.17*

    Saline (0.0 mg/mL), 0.03 mg/mL, 0.06 mg/mL, 0.125 mg/mL, 0.25 mg/mL, 0.50 mg/mL, 1 mg/mL, 2 mg/mL, 4 mg/mL, 8 mg/mL
  - *Methacholine should be prepared in the following concentrations:*

    Saline (0.0 mg/mL), 0.03 mg/mL, 0.06 mg/mL, 0.125 mg/mL, 0.25 mg/mL, 0.50 mg/mL, 1 mg/mL, 2 mg/mL, 4 mg/mL, 8 mg/mL, 16 mg/mL, 32 mg/mL, 64 mg/mL, 128 mg/mL
- Corrected Section 10.6.15: *Pulse oximetry will be monitored during the methacholine challenge and recorded when PC_{20} is reached.*
- Corrected title of 10.6.18 (previously 10.6.16) and corrected the text to match the procedures described in 10.5.

Amendment	Date	
2	10/06/2017	

- Updated AE, SAE, and pregnancy collection and reporting information.
- Added procedures for breaking the blind in the event of an SAE/SUSAR.

Amendment	Date	
3	04/05/2018	

The following revisions were made to the protocol dated 10/06/2017:

- Updated Inclusion/Exclusion criteria.
- Revised procedures for selection of retention samples.
- Removed mITT population and replaced with PD population.
- Revised PD analysis text throughout.
- Removed "Other" from the list of Race options.
- Updated MedDRA version.
- Revised AE/SAE reporting procedures.
- Added expectedness assessment.
- Added Investigator's Brochure and Product Insert to protocol appendices.