CONFIDENTIAL PROTOCOL

A Randomized, Multiple-Dose, Blinded, Placebo-Controlled, Parallel-Design, Multiple-Center, Clinical Study to Evaluate the Therapeutic Equivalence of Fluticasone Propionate and Salmeterol Inhalation Powder, 100 mcg/50 mcg (Supplied by Teva Pharmaceuticals Ireland) to ADVAIR DISKUS® 100/50 (fluticasone propionate/salmeterol) Inhalation Powder, (GlaxoSmithKline) in Subjects With Asthma

1.0 TITLE PAGE

Drug Product	Fluticasone Propionate and Salmeterol Inhalation Powder, 100 mcg/50 mcg
Population	Males and non-pregnant females, ≥ 12 years and ≤ 75 years of age, with asthma.
Study Design	A randomized, multiple-dose, blinded, placebo-controlled, parallel-group, multiple-center bioequivalence study with pharmacodynamic endpoints
Sponsor	Teva Pharmaceuticals
Protocol Number	71736001
[redacted]	71736001
Protocol Date	03Jan2019 Final Version 1

[redacted]

2.0 KEY STUDY PERSONNEL AND FACILITIES

Sponsor: Teva Pharmaceuticals
400 Interpace Parkway
Parsippany NJ, 07054, US

CRO: [redacted]

Sponsor's Representative: [redacted]

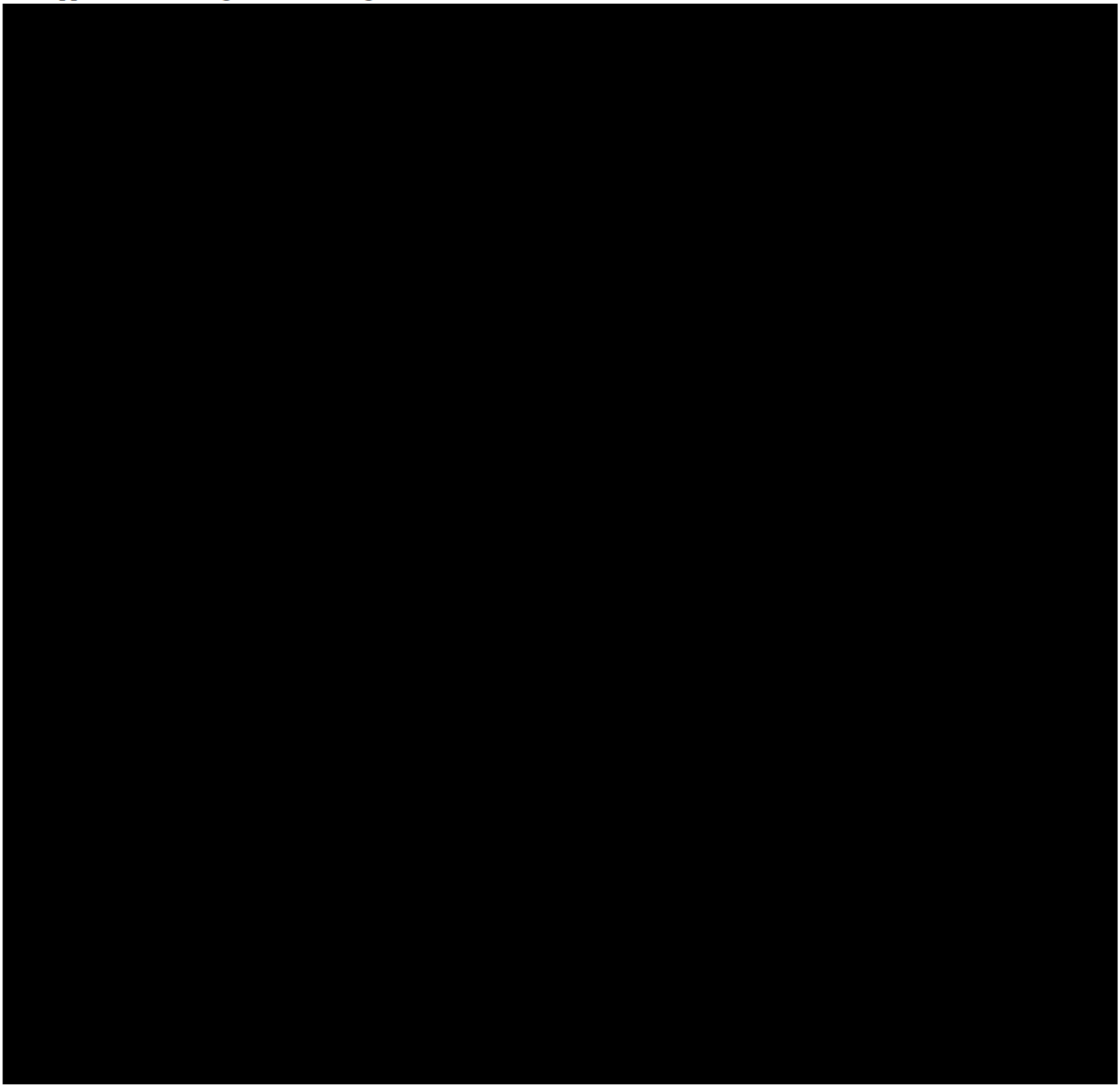
CRO Representative: [redacted]

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.



PRINCIPAL INVESTIGATOR'S SIGNATURE

I _____, agree to conduct protocol 71736001 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 (Teva Pharmaceuticals) or [redacted], the company managing the study.

_____ _____

Principal Investigator Date

4.0 TABLE OF CONTENTS

5.0 SYNOPSIS

Protocol Number	71736001
Title	A Randomized, Multiple-Dose, Blinded, Placebo-Controlled, Parallel-Design, Multiple-Center, Clinical Study to Evaluate the Therapeutic Equivalence of Fluticasone Propionate and Salmeterol Inhalation Powder, 100 mcg/50 mcg (Supplied by Teva Pharmaceuticals Ireland) to ADVAIR DISKUS® 100/50 (fluticasone propionate and salmeterol) Inhalation Powder, (GlaxoSmithKline) in Subjects With Asthma.
Objectives	The objectives of this study are to: 1. Evaluate the therapeutic equivalence of a generic Fluticasone Propionate and Salmeterol Inhalation Powder, 100 mcg/50 mcg (Supplied by Teva Pharmaceuticals Ireland) to ADVAIR DISKUS® 100/50 (fluticasone propionate and salmeterol) Inhalation Powder, (GlaxoSmithKline) in subjects with asthma. 2. Demonstrate the superiority of the Test and Reference (active) treatments over Placebo treatment in subjects with asthma.
Sponsor	Teva Pharmaceuticals
Study Products	1. **Test**: Fluticasone Propionate and Salmeterol Inhalation Powder, 100 mcg/50 mcg (Supplied by Teva Pharmaceuticals Ireland) 2. **Reference**: ADVAIR DISKUS® 100/50 (fluticasone propionate and salmeterol) Inhalation Powder, (GlaxoSmithKline) 3. **Placebo**: Fluticasone Propionate and Salmeterol Inhalation Powder Placebo (FS DPI Placebo; Supplied by Teva Pharmaceuticals Ireland)
Dosage Regimen	Subjects will be instructed to administer one inhalation of the study product twice daily for 28 ± 2 days. Subjects will administer the first inhalation on the morning of Visit 2 (Day 1). The last dose should be administered on the evening **before** Visit 3. Each subject is expected to receive up to 60 doses of the study product.
Study Design	A randomized, multiple-dose, blinded, placebo-controlled, parallel-group, multiple-center bioequivalence study with pharmacodynamic endpoints
Study Population	Approximately [redacted] males and non-pregnant females, ≥ 12 years and ≤ 75 years of age, diagnosed with asthma (as defined by the National Asthma Education and Prevention Program) will be enrolled in the placebo run-in period to allow for approximately [redacted] subjects to be randomized to study products to obtain [redacted] subjects in the per-protocol (PP) population.
Confinement	Subjects will remain confined to clinic for approximately 13 hours during Visit 2 (Day 1).

Study Conduct	Eligible subjects will complete the clinic visits as follows: • Visit 1: Screening o Visit 1a: General Screening ([redacted] o Visit 1b: Screening (Day -21 to -14). [redacted] Following completion of Screening procedures, qualified subjects will enter into Placebo Run-in: (14-21 days prior to Day 1). [redacted] • Visit 2: Randomization (Day 1) • Visit 3: End of Study (Day 29 ± 2)/Early Termination <u>Screening</u> Screening evaluations will be performed in accordance with the study schematic. Safety assessments will include: vital sign measurement, height, weight, physical examination, serum pregnancy test (for all women of childbearing potential), drug, alcohol, and cotinine testing, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations. Clinical assessments will include Forced Expiratory Volume in 1 second (FEV_1) taken at each visit. [redacted]. Forced Volume Vital Capacity (FVC) and FEV_1/FVC ratio [(FEV_1/FVC) x 100] will be recorded with FEV_1 measurements at each visit. Pre-bronchodilator FEV_1 at Screening must be 40%-85% (including these values) of predicted value. Once a qualifying FEV_1 is obtained, [redacted] puffs [redacted]) of albuterol inhalation will be administered (at each inhalation, the breath is held for 5-10 second before the subject exhales; four separate doses are delivered at approximate 30 seconds intervals) and spirometry will be repeated starting approximately 15 minutes from the last inhalation. The subject must demonstrate at least 15% reversibility of FEV_1 within 30 minutes after albuterol administration to qualify for inclusion in the study. Post-

	bronchodilator vital signs will be obtained. [redacted] Following completion of Screening procedures, qualified subjects will enter into Placebo Run-in: (14-21 days prior to Day 1). Enrollment Eligible subjects will be enrolled in a placebo run-in period for 14-21 days to establish baseline FEV_1 values. [redacted]. Subjects will be dispensed an inhaler containing Placebo product to be administered twice daily. Subjects must administer at least [redacted] of the required doses during the run-in period to be eligible for randomization. Eligible subjects will also receive an albuterol inhaler to be used as a rescue medication throughout the study. Randomization Subjects who meet all inclusion/exclusion and randomization criteria at Visit 2 will be randomized to study product in a [redacted] ratio (Test: Reference: Placebo). Serial pulmonary function tests will be performed over 12 hours at Visit 2. FEV_1 should be measured at approximately [redacted] before the first dose of study product and approximately 30 minutes, 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose. The second dose of study product will be administered after the 12-hour FEV_1 is collected. [redacted] The average of the acceptable FEV_1 measurements will be used to determine the baseline FEV_1, which must be $\geq$ 40% and $\leq$ 85% of predicted normal value and may not vary by more **than** [redacted] from the qualifying Screening visit FEV_1 value at Visit 2 for the subject to be eligible for inclusion in the study. Placebo compliance during the Run-in Period should be at least [redacted]%. Subjects will measure twice-daily (morning and evening) peak expiratory flow (PEF; air flow in and out of the lungs) at home using a hand held

	spirometry device. End of Study The final three pre-dose FEV_1 measurements will be collected at Visit 3. The first FEV_1 should take place at the same time of day as the [redacted] pre-dose measurement, respectively, collected at Visit 2 (± 2 hours). The remaining FEV_1 measurements should be collected at [redacted] following the preceding measurement. [redacted]. Subjects will be instructed not to dose within 6 hours before FEV_1 measurements at Visit 3. The last dose of study product should be administered on the evening **before** Visit 3. Subjects should not administer the rescue medication within 6 hours before any study visit.
Inclusion Criteria	1. Male or non-pregnant, non-lactating female, ≥ 12 years and ≤ 75 years of age. 2. Signed informed consent form that meets all criteria of current Food and Drug Administration (FDA) regulations. For subjects who are considered minors in the state the study is being conducted (< 18 years in most states), the parent or legal guardian should sign the consent form and the child will be required to sign a subject "assent" form. 3. Body mass index (BMI) between 18 kg/m^2 and 39 kg/m^2, inclusive, for subjects > 18 years old. For subjects 12 to 18 years old, BMI between 15 kg/m^2 and 35 kg/m^2, inclusive. 4. Female subjects who are of non-childbearing potential must meet one of the following criteria: • surgically sterile (e.g., bilateral oophorectomy, tubal ligation, hysterectomy or permanent sterilization procedures), with the procedure performed at least 3 months before initial dosing • naturally postmenopausal (no menses) for at least 1 year before initial dosing and/or has a documented FSH level ≥ 40 mIU/mL at screening • pre-menarchal 5. Females of childbearing potential must not be pregnant or lactating at Screening or Randomization as confirmed by a negative serum pregnancy test with a sensitivity of 25 mIU/mL of human chorionic gonadotropin at Screening, and a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL at all other visits. [redacted]

	[redacted].
	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.
	6. Diagnosis of asthma (based on National Asthma Education and Prevention Program [NAEPP] guidelines) at least 12 weeks before Screening.
	7. Pre-bronchodilator $FEV_1 \geq 40\%$ and $\leq 85\%$ of predicted at Screening and Randomization.
	8. Airway reversibility $\geq 15\%$ of FEV_1 within 30 minutes after receiving [redacted] puffs of albuterol inhalation [redacted], pressurized metered-dose inhaler) at Screening.
	9. Able to discontinue use of their asthma medications during the run-in period and for the remainder of the study.
	10. Able to replace current short-acting beta-agonists [SABAs] with the study supplied salbutamol/albuterol rescue inhaler for use as needed for the duration of the study. Subjects must be able to withhold all SABAs for at least 6 hours before lung function assessments on study visits.
	11. Able to continue on stable regimen of theophylline for the duration of the study and able to withhold theophylline as judged by the Investigator for the required time intervals before study visits. See Section 10.2.4 for required washouts.
	12. Able to discontinue oral corticosteroids, parenteral corticosteroids and oral SABAs for the time intervals before study visits as specified in Section 10.2.4.
	13. Able to perform valid and reproducible pulmonary function tests as per ATS American Thoracic Society including no evidence of spirometry effort-induced bronchoconstriction.
	14. Currently non-smoking (including vapor cigarettes), no use of any tobacco products within 1 year prior to Screening and has ≤ 10 pack-years smoking of historical use (i.e., one pack per day for 10 years).
	15. Ability to use the inhalation products correctly.

Exclusion Criteria	1. Life-threatening asthma, defined as a history of asthma episode(s) requiring intubation, and/or associated with hypercapnoea; respiratory arrest or hypoxic seizures, asthma related syncopal episode(s), or asthma-related hospitalizations within one year before Screening or during the run-in period. 2. Allergy or significant history of hypersensitivity, idiosyncratic reactions, or intolerance to any sympathomimetic drug (e.g., salmeterol or albuterol), or any inhaled, intranasal, or systemic corticosteroid therapy, or milk proteins. 3. History of cystic fibrosis, bronchiectasis, or co-morbid respiratory or sinus diseases, including chronic obstructive pulmonary disease, 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. 4. Evidence of viral or bacterial upper or lower respiratory tract infections (e.g., pneumonia, viral bronchitis, sinobronchitis, etc.), sinus infection, or middle ear infection within four weeks before Screening or during the run-in period. 5. Current evidence or history of cardiovascular disorders, including uncontrolled hypertension, uncontrolled coronary artery disease, known aortic or cerebral aneurysm, myocardial infarction or stroke, and/or current coronary insufficiency that, in the opinion of the Investigator, would compromise subject safety or interfere with the evaluations. 6. Cardiac arrhythmia or 12-lead ECG abnormalities that, in the opinion of the Investigator, would compromise subject safety or interfere with the evaluations; or a [redacted] for females using Fredericia formula. 7. Subjects receiving or who may require during the study non-potassium sparing diuretics or medications with the potential to affect the course of asthma or to interact with sympathomimetic amines within 30 days before Screening. Examples include but not limited to beta blockers, oral decongestants, benzodiazepines, digitalis, phenothiazines, polycyclic antidepressants, monoamine oxidase inhibitors. 8. History of posterior subcapsular cataracts or glaucoma that, in the opinion of the Investigator, would compromise subject safety. 9. Any clinically significant finding on physical exam or clinical labs that, in the opinion of the Investigator, would compromise subject's safety or

	data integrity. 10. History or current evidence of significant renal, hepatic, cardiovascular (including ECG with evidence of ischemic heart disease, congestive heart failure, and cardiac dysrhythmia), neurologic, hematologic, endocrine, psychiatric dysfunction, or any other significant medical illness or disorder in the opinion of the Investigator, would compromise subject safety or interfere with the evaluations. 11. History of convulsive disorders. 12. History within the past 6 months or current evidence of hyperthyroidism. 13. History within the past 6 months or current evidence of uncontrolled diabetes. 14. History of paradoxical bronchospasm. 15. Use of inhaled SABAs within 6 hours before Screening or use of rescue medication within 6 hours before Randomization. 16. Use of oral SABAs within [redacted] before Screening. 17. Use of oral or parenteral corticosteroids within [redacted] before Screening. 18. Use of muscarinic beta$_2$-agonists (MABAs), ipratropium bromide, or ipratropium bromide with albuterol within [redacted] before Screening. 19. Use of cromolyn sodium within [redacted] before Screening. 20. Use of antihistamines (other than cetirizine, desloratadine, or diphenhydramine), including fexofenadine and loratadine, [redacted] before Screening or Randomization. 21. Use of cetirizine within [redacted] before Screening or Randomization. 22. Use of desloratadine [redacted] before Screening or Randomization. 23. Use of diphenhydramine [redacted] before Screening or Randomization. 24. Use of inhaled long-acting beta$_2$-agonists (LABAs) (e.g., salmeterol, formoterol) or combination products containing bronchodilators (e.g., Symbicort) [redacted] before Screening. 25. Use of tiotropium within [redacted] before Screening. 26. Exercise within [redacted] before Screening. 27. Use of leukotriene modifiers within [redacted] before Screening. 28. Any surgery within 6 months before Screening that, in the opinion of

	the Investigator, would compromise subject safety or integrity of the study data. 29. Biological treatment for asthma, approved or investigational [redacted] before Screening and throughout the study. 30. Receipt of any drug as part of a research study within 30 days before Screening. 31. Positive test results for drugs of abuse, alcohol or cotinine at Screening. [redacted]. 32. Employees of the Investigator or research center or their immediate family members. 33. Previous participation in this study. 34. Inability to understand the requirements of the study and the relative information and are unable or not willing to comply with the study protocol.
Randomization Inclusion/Exclusion	At the end of the Run-in period subjects will be randomized to treatment if they continue to meet all of the general inclusions criteria and do not meet any of the general exclusion criteria. In addition, they must also meet all following inclusion criteria and do not meet any of the following exclusion criteria. Randomization inclusion criteria: 1. Compliance with the Run-in placebo treatment dosing [redacted] as evaluated via the diary entries. 2. Minimum of 2 acceptable, as determined by ERT spirometry as meeting all ATS criteria, pre-dose FEV_1 measurements needed to establish baseline. 3. Calculated baseline FEV_1 must be $\geq 40\%$ and $\leq 85\%$ of predicted normal value. The baseline FEV_1 will be calculated by the Principal Investigator (or designee) at the respective clinical site. Randomization exclusion criteria: 1. Occurrence of clinically significant asthma exacerbations according to the pre-defined criteria (see Section 10.2.6). 2. Viral or bacterial, U/LRTI or sinus or middle ear infection during the Run in Period, or on the first day of treatment. 3. Use of prohibited medications during the placebo run in period (see Washout Table in Section 10.2.4).

	4. Change of [redacted] FEV_1 value from baseline compared to qualifying Screening FEV_1. [redacted] 5. Coexisting of all occurrences liver injury that meets Hy's law criteria, defined as: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation of > 3x the upper limit of normal (ULN), total bilirubin elevation of > 2x ULN, and the absence of initial findings of cholestasis (i.e. no substantial increase of alkaline phosphatase [ALP]).
Route of Administration	Oral inhalation
Efficacy Endpoints	The two co-primary efficacy endpoints are (1) the baseline-adjusted area under the serial FEV_1-time curve calculated from time zero to 12 hours (AUC_{0-12h}) on Day 1 of treatment (Visit 2), and (2) the baseline-adjusted pre-dose FEV_1 measured in the morning of Day 29 ± 2 (Visit 3), after the last dose in the prior evening. Baseline FEV_1 is defined as the average of at least two acceptable pre-dose FEV_1 values on Day 1. [redacted]
Statistical Analysis	The Baseline FEV_1 will be subtracted from post-dose FEV_1 values to obtain the baseline-corrected values on Day 1. Baseline-adjusted area under the serial FEV_1-time curve from time zero to 12 hours (AUC_{0-12h}) will be calculated by the linear trapezoidal method. The statistical analyses will involve Analysis of Covariance (ANCOVA) with terms for [redacted] as fixed effects and using [redacted] as a covariate in the model. **<u>Therapeutic Equivalence</u>** Therapeutic equivalence will be evaluated for the primary endpoint in the PP population. [redacted], the adjusted 90% confidence interval will be calculated for the Test/Reference ratio of the mean baseline-adjusted AUC_{0-12h} on Day 1 and for the Test/Reference ratio of the mean baseline-adjusted morning pre-dose FEV_1 on Day 29 ± 2 using an iterative procedure similar to Fieller's method. The mean baseline value for use in the iterative procedure will be determined from the Baseline FEV_1 of all subjects receiving active treatment in the PP population, without regard to the treatment received. If the adjusted 90% confidence intervals for the least-squares mean Test/Reference ratios are

	within 80.00-125.00% for both co-primary endpoints, then therapeutic equivalence of the Test to Reference product will be considered to have been demonstrated. **Superiority to Placebo** The superiority of the Test and Reference products over Placebo is concluded if the values for mean baseline-adjusted AUC_{0-12h} and mean baseline-adjusted morning pre-dose FEV_1 on Day 29 ± 2 for the active treatments are statistically superior to those respective values of the Placebo at the 5% significance level ($p < 0.05$, two-sided). The superiority of Test and Reference treatments over the Placebo will be evaluated in the same ANCOVA model for Test vs. Placebo and Reference vs. Placebo. [redacted]
Safety Analysis	There will be two Safety populations: • [redacted] [redacted] All study subjects who were randomized and used the study product on at least one occasion will be included in the comparative safety analysis. Adverse events (AEs) will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 21.1 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. Concomitant medication used during the study will be tabulated by treatment by subject.
Sample Size Determination	[redacted]

6.0 STUDY SCHEMATIC

Procedures	[redacted]
Informed Consent	
Medical History and Baseline Demographics	
Vital Signs	
Height and Weight	
Physical Exam	
Drug, Cotinine, and Alcohol Testing	
Serum Pregnancy Test**	
Urine Pregnancy Test**	
12-Lead ECG	
Clinical Laboratory Testing	
Concomitant Medication	
Spirometry (FEV_1 and FVC) §	
Reversibility Test§	
Pulse Oximetry	
Inclusion/Exclusion Criteria Review	
Dispense Randomized Study Product and Instructions	
Dispense Run-In Product and Instructions	
Dispense Rescue Medication (as applicable)	
Dosing¶	
Adverse Events	
Provide Diaries	
Collect/Review Diaries	
Collect Placebo from Run-in Period	
Collect Rescue Medication	

Procedures	[redacted]
Collect Study Product	
Schedule next visit	

*Vital signs will be measured before and after reversibility assessment

**Female subjects of childbearing potential.

†Required for randomized subjects only. Subjects who fail randomization will be discharged from the study following completion of appropriate Visit 2 procedures.

[redacted]

¶Subjects will dose at the clinical site at Visit 1b and Visit 2.

#[redacted]

7.0 LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATS	American Thoracic Society
BE	Bioequivalence
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
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
IND	Investigational New Drug
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LABA	Long-acting $Beta_2$-Agonist
MABA	Muscarinic-Acting $Beta_2$-Agonist
mcg	Microgram
MDMA	Ecstasy
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
mL	Milliliter
NAEPP	National Asthma Education and Prevention Program
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-Protocol
RR	Respiratory Rate
SABA	Short-Acting $Beta_2$-Agonist

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SPE	Safety Population Enrolled
SPR	Safety Population Randomized
THC	Tetrahydrocannabinol
US	United States

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.[1-3] 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.[1,3,4]

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.[5-7] Exacerbation of symptoms may be triggered by a variety of factors including infections, allergens, exercise, inhaled irritants, or emotional episodes.[1,8]

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. 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).[6]

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.[9,10]

8.2 Availability and Efficacy of Already Approved Therapies

There are two types of therapies currently available for the treatment of asthma: quick relief medications and long-term control medications.[11,12] Quick relief medications or SABAs, for example, 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 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.

Inhaled corticosteroids have been shown to be the most effective long-term treatment of persistent asthma.[13] Long-acting beta$_2$-agonists (LABAs) are taken daily to relax the muscles lining the airways that carry air to the lungs. This allows the tubes to remain open, making breathing easier. Current recommendations are for LABAs to be used only with inhaled corticosteroids. Combination medications include fluticasone and salmeterol (ADVAIR DISKUS®, ADVAIR HFA®), budesonide and formoterol (Symbicort®), and mometasone and formoterol (Dulera®).[14]

8.3 Scientific and Statistical Considerations

The overall bioequivalence (BE) recommendations for this product are *in vitro* and *in vivo* (pharmacokinetic [PK] and pharmacodynamic [PD]) studies. Bioequivalence assessment of dry powder inhalers is complicated because delivery to the sites of action in the lung does not occur primarily after systemic absorption. As such, this locally-acting product is intended to produce its effect upon delivery to sites in the lung without relying on systemic absorption, though systemic absorption may contribute to its clinical effect. For these reasons, *in vitro* studies coupled with a PK and PD study are required to determine the delivery of drug substance to sites of action in the lung. This study satisfies the PD regulatory requirements of the clinical studies.

8.4 Justification for Use of Placebo

The FDA Draft Guidance on fluticasone propionate; salmeterol xinafoate powder/inhalation product recommends that all subjects participate in a placebo run-in period to wash out any pre-study corticosteroids/LABAs and establish baseline FEV_1 values.[15]

A Placebo group is included in the active treatment period of the study to confirm the sensitivity of the study and minimize the possibility of a false positive result of therapeutic equivalence. Therefore, in addition to demonstrating therapeutic equivalence between Test and Reference products, both active products must show statistical superiority to the Placebo.[16,17] Eligible subjects will have an [redacted] chance of being randomized to Placebo ([redacted] randomization scheme of Test: Reference: Placebo).

All subjects will be dispensed a rescue inhaler to treat sudden asthma symptoms during the placebo run-in and active treatment periods of the study.

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 US 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.[18]

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

The objectives of this study are to:

1. Evaluate the therapeutic equivalence of a generic Fluticasone Propionate and Salmeterol Inhalation Powder, 100 mcg/50 mcg (Supplied by Teva Pharmaceuticals Ireland) to ADVAIR DISKUS® 100/50 (fluticasone propionate and salmeterol) Inhalation Powder, (GlaxoSmithKline) in subjects with asthma.
2. Demonstrate the superiority of the Test and Reference (active) treatments over Placebo treatment in subjects with asthma.

10.0 INVESTIGATIONAL PLAN

Study Design and Plan Description

This randomized, multiple-dose, blinded, placebo-controlled, parallel-design, multiple-center, clinical endpoint study has been designed to evaluate the clinical (therapeutic) effect of generic Fluticasone Propionate and Salmeterol Inhalation Powder, 100 mcg/50 mcg (Supplied by Teva Pharmaceuticals Ireland) to ADVAIR DISKUS® 100/50 (fluticasone propionate and salmeterol) Inhalation Powder, (GlaxoSmithKline) in subjects with asthma.

Following a 14-21 day placebo run-in period, subjects who continue to meet inclusion/exclusion criteria will be randomized in a [redacted] ratio (Test: Reference: Placebo) for 28 ± 2 days of treatment. Approximately [redacted] subjects will enter the run-in period to randomize approximately [redacted] subjects to the active treatment period of the study. To qualify for inclusion in the study, subjects must be ≥ 12 years and ≤ 75 years of age, with a diagnosis of asthma as defined by the National Asthma Education and Prevention Program (NAEPP) guidelines at least 12 weeks before Screening.[19]

Before any study-specific procedures are performed, all subjects will read and sign the IRB-approved informed consent form (ICF) or assent, as applicable.

Eligible subjects will complete the clinic visits as follows:

- Visit 1: Screening
  - Visit 1a: General Screening [redacted]
  - Visit 1b: Screening (Day -21 to -14).

[redacted].

Following completion of Screening procedures, qualified subjects will enter into Placebo Run-in: (14-21 days prior to Day 1). [redacted].

- Visit 2: Randomization (Day 1)
- Visit 3: End of Study (Day 29 ± 2)/Early Termination

Screening

Screening evaluations will be performed in accordance with the study schematic. Safety assessments will include: vital sign measurement, height, weight, physical examination, serum pregnancy test (for all women of childbearing potential), drug, alcohol, and cotinine testing, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations. Clinical assessments will include FEV_1 taken at each visit. [redacted] orced Volume Vital Capacity (FVC) and FEV_1/FVC ratio [(FEV_1/FVC) x 100] will be recorded with FEV_1 measurements at each visit. Pre-bronchodilator FEV1 at Screening must be 40%-85% (including these values) of predicted value. Once a qualifying FEV_1 is obtained, [redacted] puffs [redacted]; 90 mcg per puff, pressurized metered-dose inhaler) of albuterol inhalation will be administered (at each inhalation, the breath is held for 5-10 second before the subject exhales; four separate doses are delivered at approximate 30 seconds intervals) and spirometry will be repeated starting approximately 15 minutes from the last inhalation. The subject must demonstrate at least 15% reversibility of FEV_1 within 30 minutes after albuterol administration to qualify for inclusion in the study. Post bronchodilator vital signs will be obtained.

[redacted]

Following completion of Screening procedures, qualified subjects will enter into Placebo Run-in: (14-21 days prior to Day 1). [redacted].

Enrollment

Eligible subjects will be enrolled in a placebo run-in period for 14-21 days to establish baseline FEV_1 values. Subjects will be dispensed an inhaler containing Placebo product to be administered twice daily. Subjects must administer at least [redacted] of the required doses during the run-in period to be eligible for randomization. Subjects will also receive an albuterol inhaler to be used as a rescue medication throughout the study.

Randomization

Subjects who meet all inclusion/exclusion and randomization criteria at Visit 2 will be randomized to study product in a [redacted] ratio (Test: Reference: Placebo). Serial pulmonary function tests will be performed over 12 hours at Visit 2. FEV_1 should be measured at approximately [redacted]) before the first dose of study product and approximately 30 minutes, 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose. The second dose of study product will be administered after the 12-hour FEV_1 is collected. At least two of the pre-dose FEV_1 measurements must meet ATS criteria for quality to be acceptable. The average of the acceptable FEV_1 measurements will be used to determine the baseline FEV_1, which must be $\geq$ 40% and $\leq$ 85% of predicted normal value and may not vary by more [redacted] from the qualifying Screening visit FEV_1 value at Visit 2 for the subject to be eligible for inclusion in the study.

End of Study

The final three FEV_1 measurements will be collected at Visit 3. The first FEV_1 should take place at the same time of day as the [redacted] pre-dose measurement, respectively, collected at Visit 2 (± 2 hours). The remaining FEV_1 measurements should be collected within [redacted]) following the preceding measurement. [redacted] pre-dose FEV_1 measurements must meet ATS criteria for quality to be acceptable. The last dose of study product should be administered on the evening **before** Visit 3.

Subjects should not administer the rescue medication, or study product within 6 hours before any study visit.

10.1 Selection of Study Design

The study was designed based on the FDA Draft Guidance on fluticasone propionate; salmeterol xinafoate powder/inhalation product, and generally accepted standards for the conduct of bioavailability and bioequivalence studies.[15]

10.2 Selection of Study Population

10.2.1 Inclusion Criteria

1. Male or non-pregnant, non-lactating female, $\geq$ 12 years and $\leq$ 75 years of age.
2. Signed informed consent form that meets all criteria of current Food and Drug Administration (FDA) regulations. For subjects who are considered minors in the state the study is being conducted (< 18 years in most states), the parent or legal guardian should sign the consent form and the child will be required to sign a subject "assent" form.
3. Body mass index (BMI) between 18 kg/m^2 and 39 kg/m^2, inclusive, for subjects > 18 years old. For subjects 12 to 18 years old, BMI between 15 kg/m^2 and 35 kg/m^2, inclusive.
4. Female subjects who are of non-childbearing potential must meet one of the following criteria:

- surgically sterile (e.g., bilateral oophorectomy, tubal ligation, hysterectomy or permanent sterilization procedures), with the procedure performed at least 3 months before initial dosing
- naturally postmenopausal (no menses) for at least 1 year before initial dosing and/or has a documented FSH level ≥ 40 mIU/mL at screening
- pre-menarchal

5. Females of childbearing potential must not be pregnant or lactating at Screening or Randomization as confirmed by a negative serum pregnancy test with a sensitivity of 25 mIU/mL of human chorionic gonadotropin at Screening and a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL at all other visits. [redacted]

   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.
6. Diagnosis of asthma (based on National Asthma Education and Prevention Program [NAEPP] guidelines) at least 12 weeks before Screening.
7. Pre-bronchodilator $FEV_1 \geq 40\%$ and $\leq 85\%$ of predicted at Screening and Randomization.
8. Airway reversibility ≥ 15% of FEV_1 within 30 minutes after receiving [redacted] puffs of albuterol inhalation ([redacted], pressurized metered-dose inhaler) at Screening.
9. Able to discontinue use of their asthma medications during the run-in period and for the remainder of the study.
10. Able to replace current short-acting beta-agonists [SABAs] with the study supplied salbutamol/albuterol rescue inhaler for use as needed for the duration of the study. Subjects must be able to withhold all SABAs for at least 6 hours before lung function assessments on study visits.
11. Able to continue on stable regimen of theophylline for the duration of the study and able to withhold theophylline as judged by the Investigator for the required time intervals before study visits. See Section 10.2.4 for required washouts.
12. Able to discontinue oral corticosteroids, parenteral corticosteroids and oral SABAs for the time intervals before study visits as specified in Section 10.2.4.

13. Able to perform valid and reproducible pulmonary function tests as per ATS (American Thoracic Society) including no evidence of spirometry effort-induced bronchoconstriction.
14. Currently non-smoking (including vapor cigarettes), no use of any tobacco products within 1 year prior Screening and has ≤ 10 pack-years smoking of historical use (i.e., one pack per day for 10 years).
15. Ability to use the inhalation products correctly.

10.2.2 Exclusion Criteria

1. Life-threatening asthma, defined as a history of asthma episode(s) requiring intubation, and/or associated with hypercapnoea; respiratory arrest or hypoxic seizures, asthma related syncopal episode(s), or asthma-related hospitalizations within one year before Screening or during the run-in period.
2. Allergy or significant history of hypersensitivity, idiosyncratic reactions, or intolerance to any sympathomimetic drug (e.g., salmeterol or albuterol), or any inhaled, intranasal, or systemic corticosteroid therapy, or milk proteins.
3. History of cystic fibrosis, bronchiectasis, or co-morbid respiratory or sinus diseases, including chronic obstructive pulmonary disease, 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.
4. Evidence of viral or bacterial upper or lower respiratory tract infections (e.g., pneumonia, viral bronchitis, sinobronchitis, etc.), sinus infection, or middle ear infection within four weeks before Screening or during the run-in period.
5. Current evidence or history of cardiovascular disorders, including uncontrolled hypertension, uncontrolled coronary artery disease, known aortic or cerebral aneurysm, myocardial infarction or stroke, and/or current coronary insufficiency that, in the opinion of the Investigator, would compromise subject safety or interfere with the evaluations.
6. Cardiac arrhythmia or 12-lead ECG abnormalities that, in the opinion of the Investigator, would compromise subject safety or interfere with the evaluations; or a [redacted]
7. Subjects receiving or who may require during the study non-potassium sparing diuretics or medications with the potential to affect the course of asthma or to interact with sympathomimetic amines within 30 days before Screening. Examples include but not limited to beta blockers, oral decongestants, benzodiazepines, digitalis, phenothiazines, polycyclic antidepressants, monoamine oxidase inhibitors.
8. History of posterior subcapsular cataracts or glaucoma that, in the opinion of the Investigator, would compromise subject safety.

9. Any clinically significant finding on physical exam or clinical labs that, in the opinion of the Investigator, would compromise subject's safety or data integrity.
10. History or current evidence of significant renal, hepatic, cardiovascular (including ECG with evidence of ischemic heart disease, congestive heart failure, and cardiac dysrhythmia), neurologic, hematologic, endocrine, psychiatric dysfunction, or any other significant medical illness or disorder in the opinion of the Investigator, would compromise subject safety or interfere with the evaluations.
11. History of convulsive disorders.
12. History within the past 6 months, or current evidence of hyperthyroidism.
13. History within the past 6 months, or current evidence of uncontrolled diabetes.
14. History of paradoxical bronchospasm.
15. Use of inhaled SABAs within 6 hours before Screening or use of rescue medication within 6 hours before Randomization.
16. Use of oral SABAs within [redacted] before Screening.
17. Use of oral or parenteral corticosteroids within [redacted] before Screening.
18. Use of muscarinic beta$_2$-agonists (MABAs), ipratropium bromide, or ipratropium bromide with albuterol within [redacted] before Screening.
19. Use of cromolyn sodium within [redacted] before Screening.
20. Use of antihistamines (other than cetirizine, desloratadine, or diphenhydramine), including fexofenadine and loratadine, within [redacted] before Screening or Randomization.
21. Use of cetirizine within [redacted] before Screening or Randomization.
22. Use of desloratadine within [redacted] before Screening or Randomization.
23. Use of diphenhydramine within [redacted] before Screening or Randomization.
24. Use of inhaled long-acting beta$_2$-agonists (LABAs) (e.g., salmeterol, formoterol) or combination products containing bronchodilators (e.g., Symbicort) within [redacted] before Screening.
25. Use of tiotropium within [redacted] before Screening.
26. Exercise within [redacted] before Screening.
27. Use of leukotriene modifiers within [redacted] before Screening.
28. Any surgery within 6 months before Screening that, in the opinion of the Investigator, would compromise subject safety or integrity of the study data.

29. Biological treatment for asthma, approved or investigational [redacted] before Screening and throughout the study.
30. Receipt of any drug as part of a research study within 30 days before Screening.
31. Positive test results for drugs of abuse, alcohol or cotinine at screening. [redacted]
32. Employees of the Investigator or research center or their immediate family members.
33. Previous participation in this study.
34. Inability to understand the requirements of the study and the relative information and are unable or not willing to comply with the study protocol.

10.2.3 Randomization Inclusion/Exclusion

At the end of the Run-in period subjects will be randomized to treatment if they continue to meet all of the general inclusions criteria and do not meet any of the general exclusion criteria. In addition, they must also meet all following inclusion criteria and do not meet any of the following exclusion criteria.

Randomization inclusion criteria:

1. Compliance with the Run-in placebo treatment dosing [redacted] as evaluated via the diary entries.
2. Minimum of 2 acceptable, as determined by ERT spirometry as meeting all ATS criteria, pre-dose FEV_1 measurements needed to establish baseline.
3. Calculated baseline FEV_1 must be $\geq$ 40% and $\leq$ 85% of predicted normal value. [redacted].

Randomization exclusion criteria:

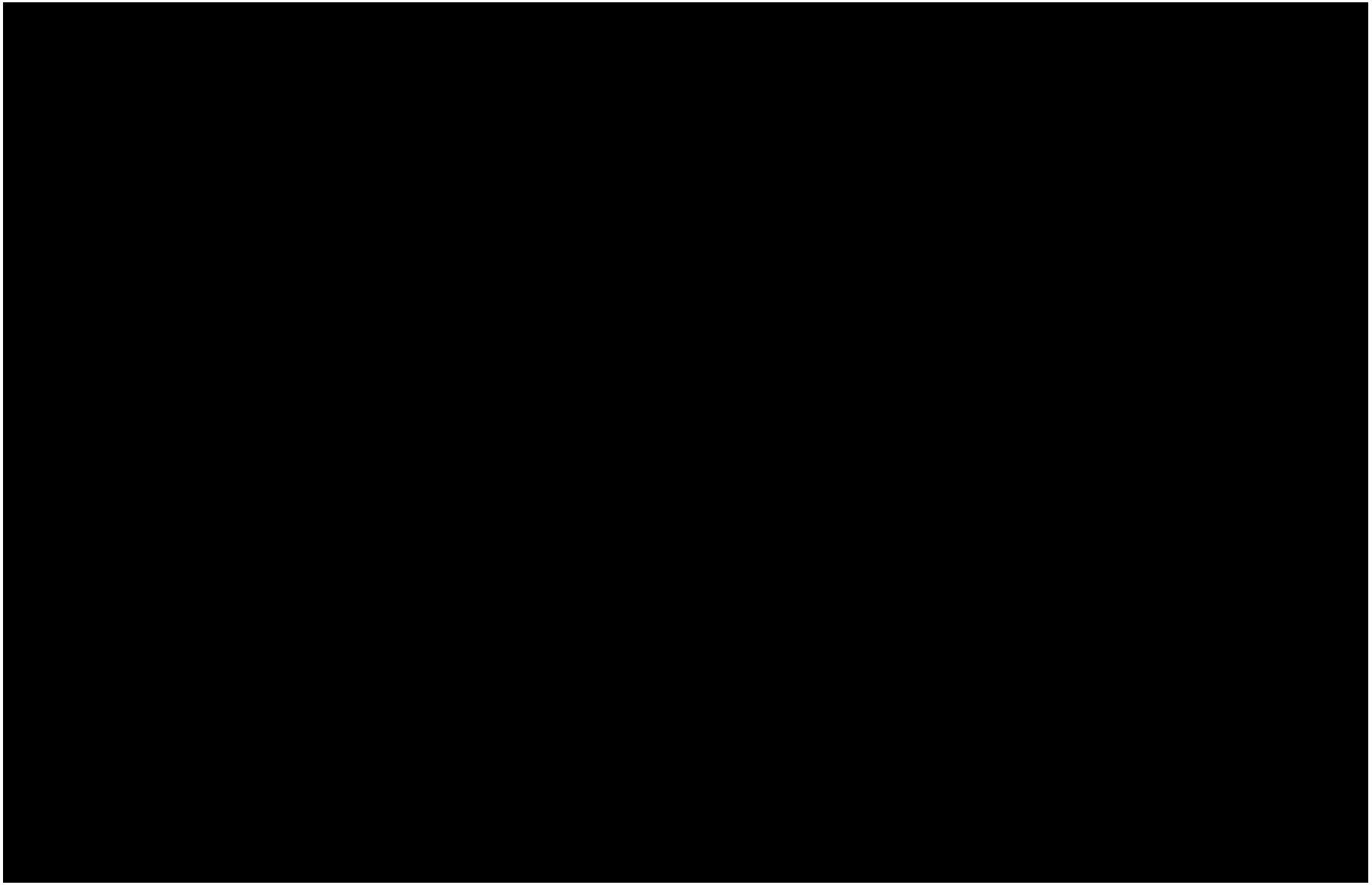
1. Occurrence of clinically significant asthma exacerbations according to the pre-defined criteria (see Section 10.2.6).
2. Viral or bacterial, U/LRTI or sinus or middle ear infection during the Run in Period, or on the first day of treatment.
3. Use of prohibited medications during the placebo run-in period (see Washout Table in Section 10.2.4).
4. Change of [redacted] in calculated average FEV_1 value from baseline compared to Screening qualifying FEV_1. [redacted].
5. Coexisting of all occurrences liver injury that meets Hy's law criteria, defined as: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation of > 3x the upper

limit of normal (ULN), total bilirubin elevation of > 2x ULN, and the absence of initial findings of cholestasis (i.e. no substantial increase of alkaline phosphatase [ALP]).

10.2.4 Restrictions During the Study

The following medications will not be allowed prior to Screening for the respective time intervals through the run-in period and for the duration of the study (see details and exceptions where applicable):

[redacted]



Subjects should not exercise within [redacted] of any study visit.

Subjects will be requested to refrain from consuming caffeine containing products such as coffee, tea, cola drinks, energy drinks, or chocolate within [redacted] of any study visit, if possible. On Visit 2, subjects will also be requested to refrain from consuming caffeine-containing products until the last point of the spirometry at Visit 2, if possible.

[redacted]

10.2.5 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.

If a randomized subject terminates from the study early, all efforts will be made to complete their next scheduled visit to perform all required End of Study/ Early termination visit activities except spirometry that does 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.
- Serious AE, regardless of relationship to study medication.
- 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, defined as a clinically significant exacerbation (see Section 10.2.6) that requires emergency intervention, treatment with restricted medications or hospitalization. Withdrawal of the subject from the study is based on Investigator judgment if he or she believes it is in the best interest of the subject to withdraw from the study and provided alternative treatment.
- Excessive use of rescue albuterol during the study. See Section 10.2.6.

- Subject requires the use of rescue medication during serial spirometry at Visit 2.
- Participant enrolls in another clinical trial, or is found to have previously enrolled in this clinical trial.

10.2.6 Exacerbation of Asthma

The definition of a clinically significant asthma exacerbation for this clinical trial is based on the official statement from ATS/ERS Task Force on Asthma Control and Exacerbations.[20]

An asthma exacerbation will include at least one of the following:

[redacted].

Asthma exacerbations meeting the pre-defined criteria above must be recorded as AEs. If they meet the definition of an SAE, they should be recorded as such. Any subject who reports the occurrence of an asthma exacerbation meeting the definition above during the Run-in period will be excluded from randomization. [redacted]

Subjects may also be withdrawn from the study in case of clinically significant worsening of the condition and/or at PI discretion. Clinically meaningful worsening of asthma may be indicated by a significant decrease of FEV_1 and/or PEF at scheduled or unscheduled study visits or during study monitoring; excessive use of rescue medication (i.e., [redacted]; emergency hospitalization or emergency medical attention related to asthma aggravation/exacerbation; necessary use of additional, excluded medication for the control of asthma exacerbation or its further prevention.

10.3 Treatments

10.3.1 Treatment Administration

During the placebo run-in period, subjects will be instructed to administer one inhalation of the Placebo run-in product twice daily (approximately 12 hours apart) for 14-21 days. [redacted] Subjects will be instructed on proper oral inhalation technique and self-administer the first dose of Placebo under the supervision of the Independent Dispenser at Visit 1. The last dose should be administered on the evening before Visit 2.

Prior to entering in the Placebo run-in period, rescue medication will be dispensed to subjects at Visit 1. Subjects will be instructed on proper dosing technique and to use rescue medication if asthma symptoms arise during the study.

During the active treatment period of the study, subjects will be instructed to administer one inhalation of the study product with proper technique twice daily (approximately 12 hours apart) for 28 ± 2 days. After each inhalation, subjects should rinse his/her mouth with water without swallowing to reduce the risk of oropharyngeal candidiasis. Subjects will self-administer the morning dose of study product under supervision of the Independent Dispenser at Visit 2. Subjects should administer the last dose on the evening before their final visit. Subjects will be instructed not to dose within approximately [redacted] before any study visit.

Identity of Investigational Product

The following products will be used in the study:

- **Test**: Fluticasone Propionate and Salmeterol Inhalation Powder, 100 mcg/50 mcg (Supplied by Teva Pharmaceuticals Ireland)
- **Reference**: ADVAIR DISKUS® 100/50 (fluticasone propionate and salmeterol) Inhalation Powder (GlaxoSmithKline)
- **Placebo**: Fluticasone Propionate and Salmeterol Inhalation Powder Placebo (FS DPI Placebo; Supplied by Teva Pharmaceuticals Ireland)

10.3.2 Study Product Shipment, Storage, and Retention

The study product will be shipped to each Investigator's site from the Drug Depot. One individual study product inhaler (i.e., Test, Reference or Placebo) will be packaged, as a subject kit. For Placebo Run-In, each subject will be assigned to one subject kit. [redacted]. Each kit will have a unique six-digit randomization number. The study product will be blinded, packaged and delivered to the site in bulk. 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 medication will be maintained in accordance with federal regulations.

For every study product shipment received at the investigative site, the Investigator (or designee) will randomly select study product kits for retention. The selection process will ensure a sufficient amount of retention samples are retained as per Sponsor requirement. These kits will be affixed with a label by independent dispenser/investigator to be clearly marked as retention samples and are not to be used for dispensing to study subjects. The selected retention samples will be retained at a third party storage facility [redacted] under FDA regulations as study retention samples.[21]

At the investigative site all study product will be stored at controlled room temperature between 20° and 25°C (68° and 77°F) with excursions permitted from 15° to 30°C (59° and 86°F), away from direct heat or sunlight in a secure, dry place with access by authorized individuals only. Any excursions from the permitted range of 15–30ºC (59º–86ºF) will require prompt notification to [redacted], and thereafter [redacted] will notify the Sponsor Designee. 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 the Sponsor.

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 will be returned to the Sponsor or designee. 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 product must be retained for all the sites participating in the study, at the designated third party storage facility, to meet the sample retention requirements as outlined by the FDA.[21]

An Investigational Product Plan will be provided to clarify study product details and will take precedence over what is outlined in the protocol, if differences are noted.

10.3.3 Method of Assigning Subjects to Treatment Groups

Enrollment

At Visit 1, using [redacted] (IWRS), all subjects who have read and signed the ICF will be assigned a Subject number. Eligible subjects will be dispensed a blinded Placebo inhaler for the placebo run-in period from the bulk supply provided to each site. Subject numbers will consist of a three-digit site number and a three-digit individual subject number. The three-digit subject numbers will be assigned automatically in ascending order beginning with 101 at each study site.

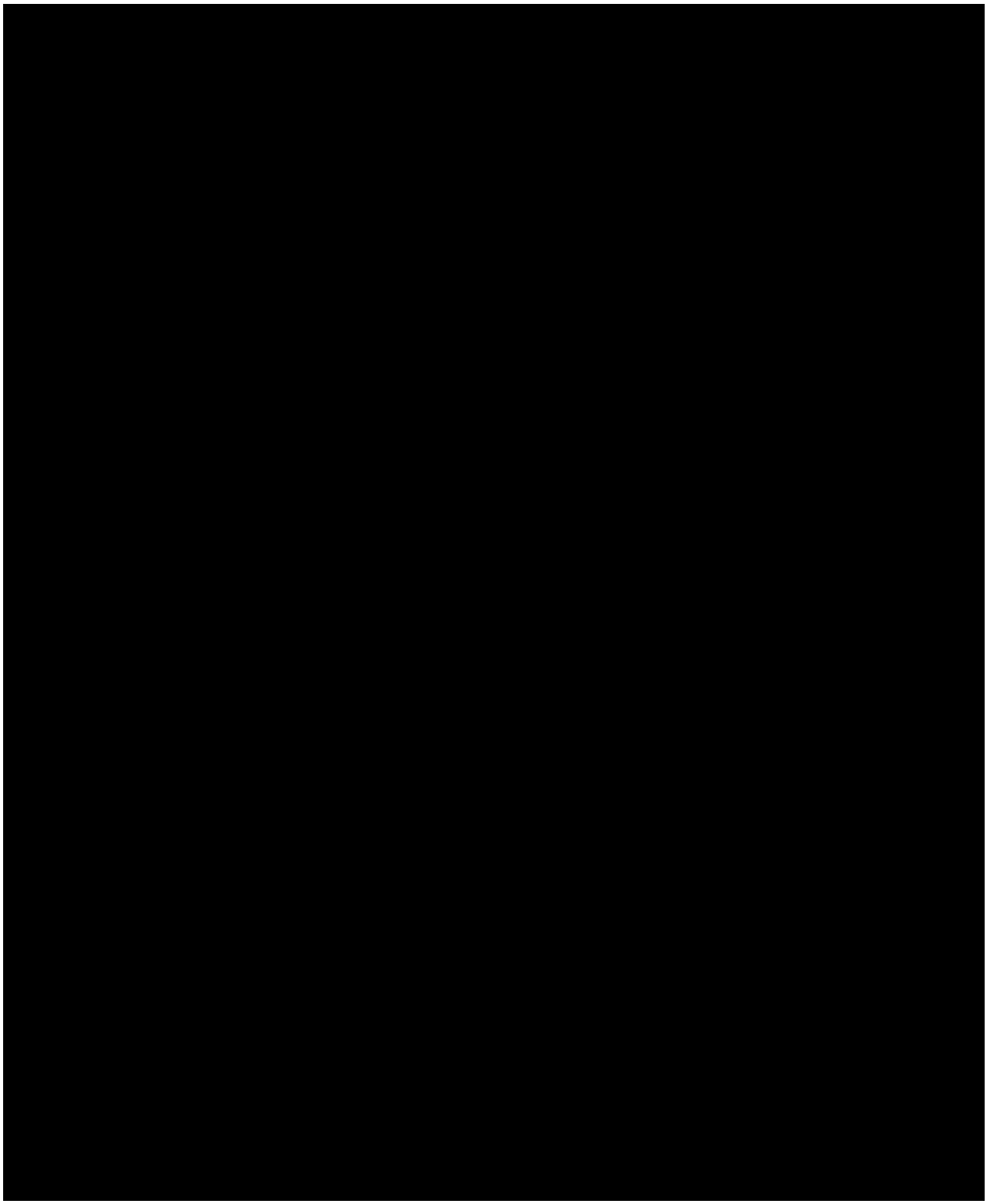
Randomization

The study product will be packaged and blinded by the Drug Depot. Randomization will be pre-planned according to a computer-generated randomization schedule using [redacted] The system will also assign study product kit numbers (based on the randomization schedule created by an independent biostatistician). The study product kit number is the identifying number listed on the study product dispensed to eligible patients. The study product kit number is a [redacted].

At the end of the study, after all the clinical data have been entered and the study database has been locked, a copy of the randomization schedule will be sent to the statistician.

10.3.4 Study Blind

[redacted]



10.3.5 Compliance

10.3.5.1 Placebo Run-In

Subjects will be provided with a diary to record the time and date of dosing, any missed doses, other concomitant medications, and any AEs. Subject will enter into a 14-21 day, [redacted], Placebo run-in period following completion of screening procedures. Subjects must administer at least [redacted] of the intended doses during the placebo run-in period to be eligible for randomization. Compliance criteria for the placebo are as outlined in the table below:

Study Design			Compliance Criteria
Study Period	Treatment Duration	Scheduled Doses	Not less than [redacted])
Placebo Run-in	14-21 days	28-42	[redacted]

10.3.5.2 Treatment

Subjects taking fewer than [redacted] the required doses over the 28 ± 2 days will be considered non-compliant with dosing and excluded from the per-protocol (PP) population. Compliance with number of doses will be verified by the use of the diaries. Compliance criteria for the active treatment period of the study are as outlined in the table below:

Study Design			Compliance Criteria	
Study Period	Treatment Duration	Scheduled Doses	Not more than	Not less than
Randomized Treatment	[redacted]	[redacted]	[redacted]	[redacted]

10.4 Study Conduct

10.4.1 Screening Visit

A signed and dated written ICF must be obtained before undergoing any study related activities, including, but not limited to, Principal Investigator directed discontinuation of prohibited medications or for blood work. All study spirometry should be initiated approximately between the hours of [redacted]

10.4.2 Visit 1a: General Screening

Visit 1a for Informed Consent may be conducted up to [redacted]

1. **Informed Consent**: Subjects who are willing to comply with study procedures will read, understand, and sign an IRB-approved ICF. Subjects who are considered minors in the state in which the study is being conducted will read and sign the assent to participate form, and their parent or legal guardian must sign the ICF.
2. **Medical History and Baseline Demographics**: Collect the subject's medical history and demographic information.
3. **Concomitant Medications**: Review the subject's use of concomitant medication within the last [redacted] (confirming washouts).
4. **Dispense Rescue Medication**: An inhaler (to be later used at Visit 1b for the reversibility assessment, if applicable) will be dispensed to be used as rescue medication during the wash-out period.

10.4.3 Visit 1b: Screening (Day -21 to Day -14)

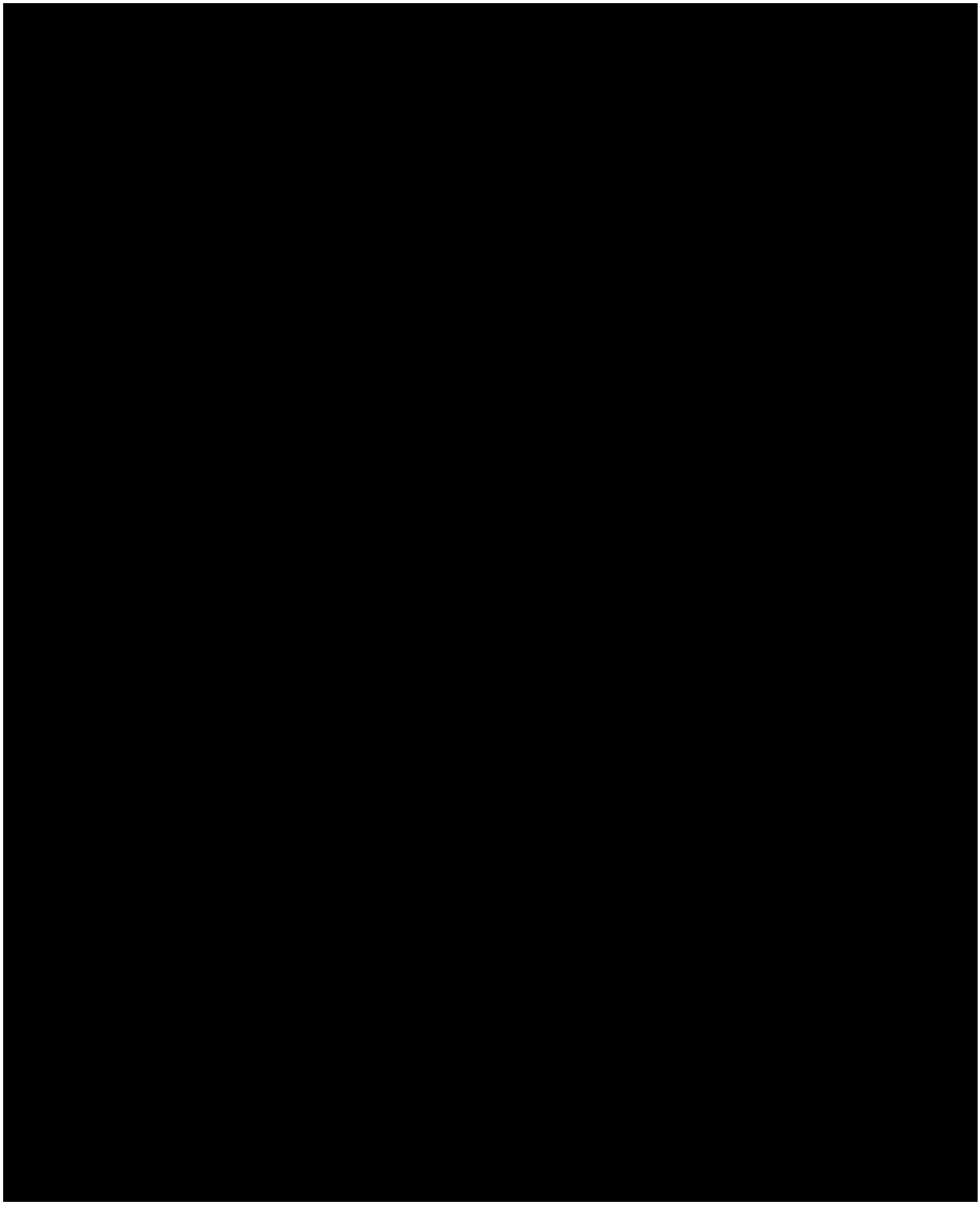
The following tests, evaluations, and procedures will be performed and documented for each subject:

1. **Concomitant Medications**: Review the subject's use of concomitant medication within the last [redacted] (confirming washouts).
2. **Physical Exam**: Perform an examination that includes at a minimum general appearance, head, ear, eyes, nose, and throat (HEENT), cardiovascular, lungs and thorax, neurological, and musculoskeletal.
3. **Height and Weight**: Height and weight will be collected.
4. **Pregnancy Test**: All females of childbearing potential will have a serum pregnancy test performed. The test must be negative for the subject to be eligible for randomization in the study. Inconclusive pregnancy tests should be repeated and confirmed negative before continued study participation. [redacted].
5. **Saliva alcohol test and urine drug/cotinine test**: All subjects will have a saliva alcohol test and a urine drug (amphetamines [stimulants], MDMA [ecstasy], barbiturates, benzodiazepines, cannabinoids/tetrahydrocannabinol (THC)/marijuana, cocaine, opiates) and cotinine test performed. All tests must be negative for the subject to be eligible for enrollment in the study. [redacted]
6. **Clinical Laboratory Testing:** All subjects will have a blood sample taken for hematology and clinical chemistry testing and a urine sample for urinalysis. [redacted]

[redacted].

7. **12-Lead ECG**: Subjects will undergo a 12-lead ECG to screen for significant abnormal cardiothoracic findings.
8. **Spirometry**: FEV_1, FVC and FEV_1/FVC ratio [(FEV_1/FVC) x 100] will be recorded. A pre-treatment evaluation will be done. Pre-bronchodilator FEV_1 at Screening must be 40%-85% of predicted value. Another spirometry assessment will be performed within 30 minutes after albuterol administration. [redacted]
9. **Vital Signs**: Blood pressure (BP), heart rate (HR), respiratory rate (RR) and temperature will be collected before and after reversibility assessment.
10. **Reversibility Assessment**: After qualifying FEV_1 (40%-85% of predicted value) is obtained; [redacted] puffs [redacted] mcg; 90 mcg per puff) of albuterol will be administered to the subject through an inhaler. The subject must demonstrate at least 15% reversibility of FEV_1 within 30 minutes after albuterol administration to qualify for inclusion in the study. [redacted]
11. **Pulse Oximetry**: Pulse oximetry will be measured during the spirometry testing.
12. **Inclusion/Exclusion Criteria Review**: Review and confirm that subject fulfills all inclusion/exclusion criteria for study eligibility.
13. **Dispense Rescue Medication, Placebo Product, and Instructions** [redacted] The inhaler used for the reversibility assessment will be re-dispensed to eligible subjects to be used as rescue medication. A new inhaler may be dispensed if needed. Subjects will also receive one inhaler of Placebo product with instructions for dose administration.
14. **Dosing (**[redacted] After pre-dose spirometry assessments are complete, subjects will self-administer study treatment (one puff from the inhaler) with the Independent Dispenser observing. The time of actuation will be recorded, as well as the adequacy of inhaler technique.
15. **Adverse Events**: Subjects will be questioned about any AEs that occurred during the visit.
16. **Provide Diary (if repeat visit is not needed)**: Subjects will receive a diary to record dosing dates and times, AEs, concomitant medications, and rescue medication use.

[redacted]



10.4.5 Visit 2: Randomization (Day 1)

Subjects, who at Visit 2 no longer meet the inclusion/exclusion or randomization inclusion/exclusion criteria, or who in the Investigator's opinion are not suitable for continued participation will not be randomized and will be discontinued from the study after completion of appropriate Visit 2 procedures.

1. **Collect Study Product**: Placebo product inhalers will be collected.
2. **Vital Signs**: BP, HR, RR, and temperature will be collected.
3. **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 randomization in the study.
4. **12-Lead ECG**: Subjects may undergo a 12-lead ECG to screen for significant abnormal cardiothoracic findings at the discretion of the Investigator.
5. **Collect and Review Diary**: Diaries will be collected and reviewed for compliance with protocol requirements.
6. **Concomitant Medications**: Subjects will be questioned about any changes in concomitant medication use since the last visit. The subjects will also be questioned regarding washout of drugs prior to lung function testing.
7. **Adverse Events**: Subjects will be questioned about AEs since the last visit.
8. **Spirometry**: Serial spirometry will be performed over 12 hours. FEV_1 should be measured approximately [redacted] before the first dose of study product and approximately 30 minutes, 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose. At least two of the pre-dose FEV_1 measurements must meet ATS criteria for quality to be acceptable. The average of the acceptable FEV_1 measurements will be used to determine the baseline FEV_1, which must be $\geq$ 40% and $\leq$ 85% of predicted normal value and may not vary by more **than** [redacted] from the qualifying Screening visit FEV_1 value.
9. **Placebo Compliance:** During the Run-in Period, should be at leas [redacted]
10. **Pulse Oximetry**: Pulse oximetry will be measured during the spirometry testing.
11. **Inclusion/Exclusion Criteria Review**: Review and confirm that subject continues to fulfill all inclusion/exclusion criteria for study eligibility.
12. **Randomization Inclusion/Exclusion Criteria Review**: Review and confirm that subject fulfills all randomization inclusion/exclusion criteria for study eligibility.
13. **Dispense Study Product and Instructions**: [redacted]. A review of inhaler dosing technique will be performed.

14. **Dispense Rescue Medication**: The inhaler used for the reversibility assessment will be dispensed to eligible patients to be used as rescue medication, if needed.
15. **Dosing**: After pre-dose spirometry assessments are complete, subjects will self-administer study treatment (one puff from the inhaler) with the [redacted] The time of actuation will be recorded, as well as the adequacy of inhaler technique.
16. **Provide Diary**: Subjects will receive a diary to record dosing dates and times, AEs, concomitant medications, and rescue medication use.
17. **Schedule Visit 3**. Remind the subjects of the requirements to follow before coming to Visit 3.

10.4.6 Visit 3: End of Study (Day 29 ± 2)/Early Termination

1. **Vital Signs**: BP, HR, RR, and temperature will be collected.
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.
4. **Clinical Laboratory Testing:** All subjects will have a blood sample taken for hematology and clinical chemistry testing and a urine sample for urinalysis.
5. **12-Lead ECG**: Subjects will undergo a 12-lead ECG to screen for significant changes in cardiothoracic findings.
6. **Collect and Review Diary**: Diaries will be collected and reviewed for compliance with protocol requirements.
7. **Concomitant Medications**: Subjects will be questioned about any changes in concomitant medication use since the last visit. The subjects will also be questioned regarding washout of drugs prior to lung function testing.
8. **Adverse Events**: Subjects will be questioned about AEs since the last visit.
9. **Spirometry**: The final [redacted] FEV_1 measurements will be collected. The first FEV_1 should occur at the same time of day as the [redacted] pre-dose measurement, respectively, collected at Visit 2 (± 2 hours). The remaining FEV_1 measurements should be collected at [redacted] following the preceding measurement. [redacted]
10. **Pulse Oximetry**: Pulse oximetry will be measured during the spirometry testing.
11. **Collect Study Product/Rescue Medication**: All study product and rescue medication inhalers will be collected.

10.5 Study Procedures

10.5.1 Informed Consent

At Visit 1, before performing any study-related procedures all subjects will read and sign an IRB-approved ICF. In addition, subjects who are considered minors in the state the study is being conducted (< 18 years of age in most states) must have a signed parental/guardian ICF, indicating approval to participate, as well as a signed assent to participate form. No subject will be entered into the study without reading, understanding and signing an ICF/assent. A copy of the ICF will be provided to the subject. If the ICF/assent is required in any language besides English, translation will be performed by a certified translator and then approved by the IRB.

10.5.2 Medical History and Baseline Demographics

At Visit 1, subjects will be questioned about medical history, including smoking history, acute and chronic medical history, and medical history relevant to their asthma.

Each subject will also be required to provide basic demographic information (i.e., date of birth, sex, ethnicity, and race).

10.5.3 Vital Signs

The subject's vital signs will be recorded (BP, HR, RR, and temperature) at each clinic visit.

10.5.4 Height and Weight

Height and weight will be collected at Visit 1.

10.5.5 Physical Exam

At Visits 1 and 3, 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.

10.5.6 Clinical Laboratory Testing

As part of the Screening procedures (Visit 1) and at Visit 3 (or early termination for randomized subjects only), subjects will have a blood sample taken for hematology and clinical chemistry testing and a urine sample for urinalysis. Any clinically significant findings will be noted. [redacted]

10.5.7 Pregnancy Testing

A serum pregnancy test on women of childbearing potential will be performed at Screening (Visit 1). Urine pregnancy tests on women of childbearing potential will be performed the repeat screening visit, if applicable, and at Visits 2 and 3. The test(s) must be negative for the subject to be eligible for inclusion in the study. [redacted]

[redacted] Inconclusive tests must be repeated and confirmed negative prior to continuation 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.

Any subject who becomes pregnant during the study must be discontinued and End of Study procedures completed. The outcome of the pregnancy will be followed by the Investigator to birth or early termination as appropriate. The pregnancy will be reported as an AE (see Section 12.2.8).

10.5.8 12-Lead ECG

Subjects will undergo a 12-lead ECG at Screening and End of Study. An ECG may be performed at Visit 2 at the discretion of the Investigator. Any clinically significant findings will be noted.

10.5.9 Concomitant Medication Use

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

10.5.10 Adverse Events

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

10.5.11 Spirometry Testing

[redacted] FVC and FEV_1/FVC ratio [(FEV_1/FVC) x 100] will also be recorded along with FEV_1 measurements at each visit. Pre-bronchodilator FEV_1 at Screening must be 40%-85% of predicted value. [redacted]. Once qualifying FEV_1 is obtained, albuterol inhalation [redacted], pressurized metered-dose inhaler) will be administered and another spirometry assessment will be performed.

Serial pulmonary function tests will be performed over 12 hours at Visit 2. FEV_1 should be measured approximately[redacted] before the first dose of study product and approximately 30 minutes, 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose. At least two of the pre-dose FEV_1 measurements must meet ATS criteria for quality to be acceptable. The average of the acceptable FEV_1 measurements will be used to determine the baseline FEV_1, which must be $\geq$ 40% and $\leq$ 85% of predicted normal value at Visit 2 for the subject to be eligible for inclusion in the study.

The final[redacted] FEV_1 measurements will be collected at Visit 3. The first FEV_1 should occur at the same time of day as the [redacted] pre-dose measurements, respectively, collected at Visit 2

(± 2 hours). The remaining FEV_1 measurements should be collected at [redacted] following the preceding measurement. [redacted]

10.5.12 Reversibility Assessment

Once qualifying FEV_1 is obtained at Screening, [redacted] puffs ([redacted] mcg; 90 mcg per puff, pressurized metered-dose inhaler) of albuterol inhalation will be administered and spirometry will be performed. The subject must demonstrate at least 15% reversibility of FEV_1 within 30 minutes after albuterol administration to qualify for inclusion in the study. [redacted]

10.5.13 Pulse Oximetry

Pulse oximetry will be measured during spirometry assessments.

10.5.14 Peak Flow Measurements

Subjects will measure twice-daily (morning and evening) peak expiratory flow (PEF; air flow in and out of the lungs) using a home spirometer/eDiary device. The subject will be dispensed the device upon entrance into the placebo run-in period. The same device will be used for the subject throughout their participation in the study. Subjects will be trained on the use of the device and PEF procedures at the Screening visit. At home PEF measurements are collected for interim safety monitoring only, and will not be included in statistical analyses.

10.5.15 Inclusion/Exclusion Criteria Review

At Visits 1 and 2, inclusion/exclusion criteria will be reviewed to ensure subjects' eligibility for participation in the study.

10.5.16 Dispense Rescue Medication, Placebo Product, and Instructions

At Visit 1 and Visit 2 (if needed), eligible subjects will be dispensed albuterol to be used as a rescue medication during the study. Subjects will be dispensed the same albuterol inhaler used for the reversibility assessment. Prior to use for reversibility assessments, the rescue medication inhaler should be re-primed as appropriate, in an area away from subjects. At Visit 1, subjects will also receive one inhaler of Placebo product with instructions for dose administration. Subjects must administer at least [redacted] of the required doses to be eligible for randomization.

10.5.17 Dispense Study Product and Instructions

[redacted] will dispense randomized study product to eligible subjects at Visit 2, along with a set of dosing instructions. A review of inhaler dosing technique will be performed. The subjects will be reminded about the blinding requirements of this study.

10.5.18 Dosing

Subjects will dose at the clinical site at Visits 1, and 2. The first dose of Placebo product will be administered at Visit 1 after completion of spirometry and reversibility assessments. The first dose of randomized study product will be administered at Visit 2 after completion of pre-dose spirometry assessments.

10.5.19 Collect Study Product/Rescue Medications

Placebo product inhalers will be collected at Visit 2. Study product inhalers will be collected at Visit 3. Rescue medications will be collected at Visit 3 or any other visit where an additional inhaler was dispensed.

10.5.20 Provide, Review, and Collect Diary

Subjects will be provided with diaries and trained on their use (eDiary [redacted]) including instructions to record dosing dates and times, AEs, concomitant medications, and rescue medication use throughout the study. The diaries will be reviewed at each visit by the study staff and completed diaries will be collected at the end of the study. [redacted]

10.6 Adverse Events

Subjects will be encouraged to report signs, symptoms, and any changes in health to the clinic staff. Severity of each AE will be determined based on observation and questioning of the subject. The Investigator will judge the severity and relationship of the event to the study products.

10.6.1 Adverse Event Definition

An AE is any untoward medical occurrence in a subject, regardless of whether it has a causal relationship with this treatment.

In this study, any AE occurring after the subject has signed the ICF/assent until the end of follow-up period should be recorded and reported as an AE.

An AE can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study product. A new condition or the worsening of a pre-existing condition will be considered an AE. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered AEs.

Accordingly, an AE can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication

- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the subject from the study, are associated with clinical signs and symptoms or a serious adverse event (SAE), or require medical treatment or further diagnostic work up, or are considered by the Investigator to be clinically significant [redacted]
- A treatment-emergent AE is any AE that occurs after initiation of study product, or any event already present that worsens in either intensity or frequency following exposure to study product.

10.6.2 Serious Adverse Events

An SAE is an AE, regardless of the relationship to study product, and at any dose, that results in any of the following outcomes or actions:

- Death
- A life-threatening AE (i.e., the subject was at immediate risk of death from the event as it occurred; does not include an event that, had it occurred in a more severe form, might have caused death)
- Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an AE, or that they occurred as a consequence of the event. Hospitalizations scheduled prior to study entry will not be considered SAEs, unless there was worsening of the pre-existing condition during the subject's participation in this study
- Persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- An important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the subject and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An AE that does not meet any of the criteria for seriousness listed above will be regarded as a non-serious AE.

All occurrences of possible drug induced liver injury that meets Hy's law criteria, defined as all of the below, must be reported by the investigator to the sponsor as a serious adverse event:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation of > 3x the upper limit of normal (ULN)
- total bilirubin elevation of > 2x ULN
- absence of initial findings of cholestasis (i.e., no substantial increase of alkaline phosphatase [ALP])

10.6.3 Other Significant Adverse Events

When tested, marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as SAEs should be collected in the electronic case report form (eCRF) and summarized in the clinical study report.

10.6.4 Severity

The severity of each AE must be recorded as one of the choices on the following scales:

- Mild: No limitation of usual activities
- Moderate: Some limitation of usual activities
- Severe: Inability to carry out usual activities

10.6.5 Relationship of an Adverse Event to the Study Drug

Adverse events will be assessed for the relationship to the study product (causality) according to the following scale:

TERM	DEFINITION	CLARIFICATION
No Reasonable Possibility (not related)	This category applies to those AEs which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to those AEs, which after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug.	An adverse experience may be considered No Reasonable Possibility if it is clearly due to extraneous causes or when (must have two): It does not follow a reasonable temporal sequence from the administration of the test drug. It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. It does not follow a known pattern of response to the test drug.

TERM	DEFINITION	CLARIFICATION
		It does not reappear or worsen when the drug is re-administered.
Reasonable Possibility (related)	This category applies to those AE for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty or felt with a high degree of certainty to be related to the test drug.	An adverse experience may be considered Reasonable Possibility related if or when (at least two of the following): It follows a reasonable temporal sequence from administration of the drug. It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. It disappears or decreases on cessation or reduction in dose. There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. It follows a known pattern of response to the test drug.

10.6.6 Expectedness

An AE that is not included in the AE section of the relevant Safety Information Reference by its specificity, severity, outcome, or frequency is considered an unexpected AE.

The Reference safety information for this study, ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder) Product Insert, to be used as reference for safety information can be found in Appendix B.

The Sponsor's Pharmacovigilance Department will determine the expectedness for all SAEs. Neither the contract research organization (CRO) nor the Investigators will determine the expectedness.

10.6.7 Recording and Reporting of Adverse Events

In this study, safety will be assessed by qualified study personnel by evaluating reported AEs, ECGs, physical examination, pulse oximetry, vital signs measurements, and use of concomitant medication.

For AE recording, the study period is defined for each subject as that time period from signature of the ICF through the end of the study (including any follow-up period) (see Sections 10.4.1 and 12.2.12).

All AEs that occur during the defined study period must be recorded on the source documentation, regardless of the severity of the event or judged relationship to the study product. For SAEs, the SAE form must also be completed and the SAE must be reported immediately (see Section 10.6.8). The Investigator does not need to actively monitor subjects for AEs once the study has ended. However, SAEs occurring in a subject after the treatment of that subject has ended should be reported to the Sponsor if the Investigator becomes aware of them.

At each contact with the subject, the Investigator or designee must question the subject about AEs by asking an open ended question such as, "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe." All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings may be recorded collectively as a single diagnosis on the eCRF and, if it is an SAE, on the SAE form.

The onset and end dates and times, action taken regarding study product, treatment administered, and outcome for each AE must be recorded on the source documentation.

The relationship of each AE to study product treatment and study procedures, and the severity and seriousness of each AE, as judged by the Investigator, must be recorded as described above.

The clinical course of each AE will be monitored at suitable intervals until resolved or stabilized or returned to baseline, until the subject is referred for continued care to a health care professional or until a determination of a cause unrelated to the study product or study procedure is made.

Adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1 or higher and reported with respect to severity, duration, relationship to study medication(s), seriousness, and action taken.

10.6.8 Reporting of Serious Adverse Events

To satisfy regulatory requirements, all SAEs (as described in Section 10.6.2) that occur during the study period (including any protocol-defined follow-up period), regardless of judged relationship to treatment with the study product, must be reported to the CRO by the Investigator. The event must be reported within 24 hours of when the Investigator learns about it. Completing the SAE form and reporting the event must not be delayed, even if not all the information is available.

A Safety Plan will be provided to clarify details of collecting, recording and reporting of adverse events and other safety assessments, as deemed necessary, and will take precedence over what is outlined in the protocol, if differences are noted.

PLEASE NOTE THAT EMAIL IS THE PREFERRED MEANS OF COMMUNICATION.

The CRO should inform the Sponsor's Pharmacovigilance Department if the whole study is discontinued early because of safety reasons.

For studies conducted in US: It is the responsibility of the CRO to report an SAE to the FDA within proper time constraints as per the Guidance for Industry and Investigators Safety Reporting Requirements for Investigational New Drugs (INDs) and BA/BE Studies- December 2012. Confirmation of submission of this report must then be provided to Teva's study representative as well as their Pharmacovigilance department (contact info below).

Sites outside of the US will be responsible for reporting the SAE to [redacted] and local regulatory authorities, as appropriate.

The timeliness for submission of expedite reports should be 15 days or 7 days (death cases) or as otherwise specified in local regulations.

Any serious or unexpected AEs should be reported to [redacted] within 24 hours. Following is the contact information:

[redacted]

All SAEs, whether or not drug-related, will be immediately (within one business day) reported by [redacted] to the following Sponsor contact by email and followed by a written report within five (5) working days:

US Pharmacovigilance Unit

Email: [redacted]
Fax: [redacted]

Sponsor's Contact person for this Biostudy (copy of the SAE details for information purposes only):

Amanda Valente
Associate Director, Global Clinical Endpoint
Teva Pharmaceuticals
Tel: [redacted]
Mobile: [redacted]

Email: [redacted]

These SAE reports must contain the following information, preferably using the template provided by the Sponsor:

A. Study name/number

B. Study Product

C. Investigator details (name, site information, phone)

D. Subject Number

E. Subject Initials when appropriate

F. Subject Demographics

G. Relevant Medical History and Concomitant Disease

H. Suspect Medication Information

I. Clinical Event (i.e., Drug-Event Information and Case Narrative)

1) Description (Seriousness Criteria, Intensity/Severity, Outcome)
2) Date of onset and end date (if available)
3) Treatment (drug, dose, dosage form, dechallenge/rechallenge)
4) AE Relationship to study product
5) Action taken regarding study product in direct relationship to the AE

J. If the AE was Fatal:

1) Date and cause of death (whether or not the death was related to study drug)
2) Autopsy findings (if available)

K. Concomitant Medication Information

L. Relevant Laboratory/Diagnostic Information

The SAE form and supportive documents should be filled/written in English. The SAE form completion and reporting must not be delayed even if all of the information is not available at the time of the initial contact. Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded within 24 hours of the information becoming available to the same address as the initial report. Subjects who have had an SAE during the treatment period must be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained.

Each report of an SAE will be reviewed and evaluated by the Investigator and the Sponsor's Pharmacovigilance Department to assess the nature of the event and the relationship of the event to the study product, study procedures, and to underlying disease.

10.6.9 Submission of SAEs

Any SAE will be reported to competent authority and ethics committee according to the country specific requirements and the responsibilities defined in Section 10.6.8. All AEs will be reported in the clinical study report with the complete information named above according to the requirements of the Note for Guidance on Structure and Content of Clinical Study Reports (CPMP/ICH/137/95).

11.0 STATISTICAL METHODS

11.1 Statistical Plan

A statistical analysis plan (SAP), detailing the study populations, intended statistical analysis, and reporting 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 SAP. The SAP will take precedence over what is outlined in the protocol, if differences are noted.

All statistical analysis will be conducted using SAS®, Version 9.4 or higher. Datasets will be prepared using headings from Clinical Data Standards Interchange Consortium (CDISC) Study Data Tabulation Model implementation for human clinical trials and Analysis Dataset Model.

11.2 Determination of Sample Size

[redacted]

[redacted]

11.3 Study Populations

11.3.1 PP Population

[redacted]

11.3.2 mITT Population

[redacted]

11.3.3 Safety Populations

[redacted]

[redacted]

11.4 Baseline Comparability

The following subject demographic characteristics will be summarized separately in the PP, mITT, and SPR 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)
- Number of years subject has suffered from symptoms caused by asthma
- Baseline FEV_1

Summary tables by treatment group will be presented. Continuous variables will be summarized using descriptive statistics (number of observations, median, minimum, maximum, mean, and SD). Categorical variables will be summarized using frequencies and percentage. Baseline treatment comparisons will be presented using Chi-Square or Cochran-Mantel-Haenszel tests for the categorical variables, and Analysis of Variance (ANOVA) for the continuous variables.

All data will be listed by treatment and subject.

11.5 Efficacy Endpoints

The two co-primary efficacy endpoints are (1) the baseline-adjusted area under the serial FEV_1-time curve calculated from time zero to 12 hours ($AUC_{0\text{-}12h}$) on Day 1 of treatment (Visit 2), and (2) the baseline-adjusted pre-dose FEV_1 measured in the morning of Day 29 ± 2 (Visit 3), after the last dose in the prior evening.

[redacted]

11.6 Primary Endpoint Analyses

The Baseline FEV_1 will be subtracted from post-dose FEV_1 values to obtain the baseline-corrected values. Baseline-adjusted area under the serial FEV_1-time curve from time zero to 12 hours ($AUC_{0\text{-}12h}$) will be calculated by the linear trapezoidal method.. The statistical analyses will involve Analysis of Covariance (ANCOVA) with terms for [redacted] as fixed effects and using [redacted] as a covariate in the model.

Therapeutic Equivalence

Therapeutic equivalence will be evaluated for the primary endpoint in each PP population. Under the assumptions of normally distributed data, the adjusted 90% confidence interval will be calculated for the Test/Reference ratio of the mean baseline-adjusted $AUC_{0\text{-}12h}$ on Day 1 [redacted] and for the Test/Reference ratio of the mean baseline-adjusted morning pre-dose FEV_1 on Day 29 ± 2 [redacted] using an iterative procedure similar to Fieller's method. The mean baseline value for use in the iterative procedure will be determined from the Baseline FEV_1 of all subjects receiving active treatment in the PP population, without regard to the treatment received. If the adjusted 90% confidence intervals for the least-squares mean Test/Reference ratios are within 80.00-125.00% for both co-primary endpoints, then therapeutic equivalence of the Test to Reference product will be considered to have been demonstrated.

Superiority to Placebo

The superiority of the Test and Reference products over Placebo is concluded if the values for mean baseline-adjusted $AUC_{0\text{-}12h}$ and the mean baseline-adjusted morning pre-dose FEV_1 on Day 29 ± 2 for the active treatments are statistically superior to those respective values of the Placebo at the 5% significance level ($p < 0.05$, two-sided). The superiority of Test and Reference treatments over the Placebo will be evaluated in the same ANCOVA model for Test vs. Placebo and Reference vs. Placebo. [redacted].

11.7 Safety Analysis

All study subjects who were randomized and used the study product on at least one occasion will be included in the comparative safety analysis. Adverse events will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 21.1 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.

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, United States (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.[23-26] 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 FDA Form 1572 will act as the Principal Investigator at each study site. Protocols will be noted as approved by placement of the [redacted] Representative's signature on the cover page. The Sponsor of the study will also approve the protocol by having a study-responsible individual sign the protocol cover 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. In addition, subjects who are considered minors in the state the study is being conducted (< 18 years of age in most states) must have a signed parental/guardian ICF, indicating approval to participate, as well as a signed assent to participate form. 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 or assent, as appropriate. The Investigator or designee will also sign and date the form, along with a staff member who will sign the ICF as a witness to verify that the subject has indeed received information. If any other language is required, translation will be performed by a certified translator. A copy of the ICF and/or assent will be provided to the subject.

12.2.3 Protocol and Informed Consent Changes

Sponsor approved changes to the protocol or the ICFs will be implemented as revisions to the original documents and will require additional review and approval by the IRB. Revisions to the original protocol will be documented in amendments, incorporated as a preface to the new version. 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. 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 Case Report Forms

All subjects will be identified by initials, date of birth, and a unique subject number. Source documents will be used to record all study-related data. Source document entries will be used to complete 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 3 (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 (i.e., at the site's close-out visit) all used and unused study product will be returned to Sponsor or designee.

12.2.6 Drug Storage

All study product will be stored at controlled room temperature between 20° and 25°C (68° and 77°F) with excursions permitted from 15° to 30°C (59° and 86°F), away from direct heat or sunlight in a secure, dry place with access by authorized individuals only. Any excursions from the permitted range of 15–30ºC (59º–86ºF) will require prompt notification to [redacted], and thereafter [redacted] will notify the Sponsor Designee. 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 Sponsor or designee.

12.2.7 Retention of Reserve Samples

For every study product shipment received at the Investigator's site, the Investigator (or designee) will randomly select study product kits for retention. The selection process will ensure a sufficient amount of retention samples are retained as per Sponsor requirement. The number of each subject kit kept for retention will be noted on the drug accountability form as a retention sample, in addition to the retention sample log. These retention samples should be stored under the appropriate storage conditions for a minimum of 5 years following the application approval or, if not approved, at least 5 years after the completion of the study. Retention samples should not be returned to Sponsor/CRO/packaging group at any time. The retention samples will be shipped to a third party storage facility:

[redacted]

[redacted]

12.2.8 Pregnancies

If following initiation of study treatment, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study product exposure; the study product will be permanently discontinued. The Principal Investigator or designee must immediately notify the Medical Monitor of this event. Reporting timelines and [redacted] contact will be consistent with SAE reporting guidelines (see Section 10.6.8 of the protocol), i.e., pregnancies will be reported to the [redacted] within 24 hours to the contacts listed in Section 10.6.8.

All subjects who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous or voluntary termination). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after termination from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy does not continue to term, one of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion not due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.

12.2.9 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.[27]

12.2.10 Record Retention

All drug accountability records, eCRFs, source data, and related regulatory documents must be retained according to 21 CFR 312.62(c) for a period of 2 years following the date the marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

12.2.11 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.

12.2.12 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.

12.2.13 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.[28] Abbreviated New Drug Application 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.

12.2.14 Termination of the Study

The Sponsor reserves the right to terminate the study at any time for administrative reasons. The study may also be terminated by regulatory authorities. An investigator has the right to discontinue his/her site's participation at any time following consultation with the Sponsor. Following a decision to discontinue the trial, the investigator will immediately inform both the study subjects and the IEC responsible for this trial within 10 working days, stating the reasons for discontinuation of the study and, furthermore, advise them in writing of any potential risks to the health of study subjects or other persons. It is Sponsor's responsibility to report the premature termination of the study to the regulatory agencies within 15 days providing them with the reasons for the trial discontinuation and advising them in writing of any potential risks to the health of study subjects or other persons. The CRO may notify the regulatory agency on behalf of the Sponsor.

13.0 REFERENCES

[redacted]

14.0 APPENDICES

14.1 APPENDIX A - NAEPP Guidelines for Asthma Severity Classification. National Asthma Education and Prevention Program Expert Panel Report 3

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 - ADVAIR DISKUS® 100/50 (fluticasone propionate/salmeterol) Inhalation Powder Package Insert

14.3 APPENDIX C – Clinical Laboratory Testing

As part of the Screening procedures and at Visit 3 (or early termination for randomized subjects only), subjects will have a blood sample taken for hematology and clinical chemistry testing and a urine sample for urinalysis. The testing panel should include as a minimum the following tests:

Hematology

- Hematocrit
- White blood cell count
- Platelets
- Hemoglobin
- Red blood cell count
- Red cell distribution width
- Differential white cell count
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration

Chemistry

- Alkaline phosphatase
- Total bilirubin
- Alanine transaminase
- Creatinine
- Aspartate transaminase
- Glucose
- Blood urea nitrogen
- Bicarbonate
- Calcium
- Potassium
- Sodium
- Total Protein
- Albumin

Urinalysis

- Protein
- Glucose
- Specific gravity
- Ketone
- Bilirubin
- pH
- blood

Clinical Laboratory Testing will be performed at a central laboratory.

14.4 APPENDIX D- Amendments to the Protocol

Amendment	Date	
1	12/20/2018	

The following revisions were made to the protocol dated 11/13/2018:

- [redacted]
- [redacted]
- [redacted]
- [redacted].