Clinical Research Protocol
FLUNISOLIDE HFA IN CHILDREN WITH SMALL AIRWAY DISEASE

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Investigational Product:	Flunisolide HFA
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Approval:

Principal Investigator Sponsor Signature *Date*

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 14.1024

Protocol Title: Flunisolide HFA in Children with Small Airway Disease

Protocol Date: 6/15/15

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Investigator Signature *Date*

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Print Name and Title

Site # _____

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List of Abbreviations

AE	adverse experience
CFR	Code of Federal Regulations
CF	cystic fibrosis
CRF	case report form
FDA	Food and Drug Administration
FEF_{25-75}	Forced expiratory flow between the 25^{th} and 75^{th} percent of vital capacity
FEV_1	forced expiratory volume in one second
FRC	Functional residual capacity
FVC	forced vital capacity
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IOS	Impulse Oscillometry
IRB	Institutional Review Board
MDI	Metered Dose Inhaler
PI	Principal Investigator
SAE	serious adverse experience

PROTOCOL SYNOPSIS

TITLE	Flunisolide HFA in Children with Small Airway Disease
FUNDING AGENCY	MEDA Pharmaceuticals
PRINCIPAL INVESTIGATORS	Nemr Eid, MD University of Louisville Louisville, KY Scott Bickel, MD University of Louisville Louisville, KY
PRINCIPAL INVESTIGATOR SPONSOR	MEDA Pharmaceuticals
DATA COORDINATING CENTER	University of Louisville Physicians – Pediatric Pulmonology (Academic Office)
NUMBER OF SITES	One
STUDY DESIGN	Prospective, randomized, parallel, open label study
OBJECTIVE	To assess whether there is a dose-related difference with flunisolide HFA in pediatric patients with small airway obstruction based on pulmonary function parameters specifically designed to measure changes in small airway function.
NUMBER OF SUBJECTS	50

SUBJECT ELIGIBILITY CRITERIA	**Inclusion Criteria:** 1. Diagnosis of asthma by pediatrician or asthma specialist 2. Informed consent by parent or legal guardian 3. 6 years to 21 years of age at Screening Visit 4. Ability to comply with medication use, study visits and study procedures as judged by the site investigator 5. $FEF_{25-75\%} < 65\%$ of predicted as a marker for small airway disease **Exclusion Criteria:** 1. Acute wheezing at Screening visit or at Baseline visit 2. Acute intercurrent respiratory infection, defined as an increase in cough, wheezing, or respiratory rate with onset in 1 week preceding Screening visit or 3 weeks preceding Baseline visit 3. Oxygen saturation < 94% at Screening visit or at Baseline visit 4. Clinically significant upper airway obstruction as determined by the Site Investigator (e.g. severe laryngomalacia, markedly enlarged tonsils, significant snoring, diagnosed obstructive sleep apnea) 5. Severe gastroesophageal reflux, defined as persistent frequent emesis despite anti-reflux therapy 6. Physical findings that would compromise the safety of the subject or the quality of the study data as determined by site investigator 7. ICS use within 7 days of Baseline visit, systemic steroid use within 30 days of Baseline visit 8. CF, ILD, history of severe BPD or other underlying significant respiratory disease apart from asthma 9. Patients who are pregnant may not enroll in this study
TEST DRUG, DOSE AND MODE OF ADMINISTRATION	Flunisolide HFA (Aerospan™, MEDA Pharmaceuticals, Somerset, NJ) 1 or 2 inhalations administered via MDI twice daily for 6 weeks.

DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Study visits will occur at screening, baseline, and 6 weeks (± 1 week). Total duration of subject participation will be up to 8 weeks. As enrollment will occur over approximately 12 months, total duration of the study is expected to be up to 14 months (12 months enrollment plus about 2 months for the last subjects to complete treatment).
Screening, enrollment, randomization and treatment	*Screening*: At the Screening visit, a focused, standardized history and physical exam will be conducted by one of the physicians on the research team. Patients will also undergo pre and post bronchodilator spirometry. Spirometry values prior to the administration of bronchodilator will be used to assess patient's enrollment status. *Enrollment and Randomization:* At the Baseline visit, patients will undergo a repeat focused, standardized history and physical exam. Spirometry and IOS will both be undertaken pre and post bronchodilator (in this order: IOS, spirometry, bronchodilator, IOS, spirometry). *Treatment*: Subjects will receive treatments twice per day for 6 ± 3 days.
CONCOMITANT MEDICATIONS	Allowed: All standard therapies Prohibited: Other forms of ICS, LABAs
Efficacy Evaluations	Physiologic effects (change in lung function between baseline and end of treatment) and Clinical Effects (number of asthma exacerbations, asthma control scores) will be compared between subjects randomized to flunisolide HFA 1 inhalation BID and to flunisolide HFA 2 inhalations BID.
Primary endpoint	The average change in FEV1, FEF25-75% , R5, R5-R20, AX, Fres and X5 measured by spirometry and IOS during from baseline to end of treatment (6 ± 3 days) between subjects randomized to flunisolide HFA 1 inhalation BID and to flunisolide HFA 2 inhalations BID.
SECONDARY	The number of protocol-defined asthma exacerbations requiring

ENDPOINTS	treatment with oral steroids between subjects randomized to flunisolide HFA 1 inhalation BID and to flunisolide HFA 2 inhalations BID.
SAFETY EVALUATIONS	Rates of adverse events, withdrawal, adherence to treatment, rate of asthma exacerbations will be monitored.
SAFETY MONITORING	As this is an FDA approved drug being used in approved populations at approved doses, the elements listed under "safety evaluations" as above will be tracked by the PIs but no formal data safety review board will be in place.
STATISTICS **Primary Analysis Plan**	The primary aim is to compare the average change in spirometric values (FEV1 and $FEF_{25-75\%}$) and IOS values (R5, R5-R20, AX, Fres) from baseline to Week 6 from participants randomized flunisolide HFA 1 inhalation BID and to flunisolide HFA 2 inhalations BID. The change in scores from baseline to six-week follow-up will initially be compared using paired t-tests and Chi-squared tests for trend. Repeated measurements will be analyzed using generalized linear mixed-effects regression modeling (GLMM) techniques. For continuous outcomes (e.g., FEV1, $FEF_{25-75\%}$, Fres, X5, AX, R5-R20.) the identity link function and normal distribution will be used. For count data (e.g., use of Beta-agonists, episodes of coughing, episodes of wheezing, etc.) the log link function and the Poisson distribution will be used. If we dichotomize outcomes (e.g., a Beta-agonist was used, coughing occurred, etc.) the logit link function and Bernoulli distribution will be used. Statistical analyses will be performed using SAS® Version 9.3 (SAS Institute Inc., Cary, NC).
Rationale for Number of Subjects	Based on our preliminary studies, we anticipate that 10% of all potential participants will not be eligible and/or willing to participant; and that 10% of the eligible/willing participants will be lost to follow-up. Therefore, we will recruit a total of n=50 individuals for the current study. This is a feasible sample size for the research team to recruit and enroll in the current study. Power calculations were based

	on the anticipated total sample size (n=40) that will be available for complete analysis. We will develop separate mixed-effects general linear models for each of the continuous outcomes. From the anticipated sample size (n=40) the study has 86% power to detect a 10% main effect of each treatment for each outcome, our anticipated effect size given preliminary studies. When using count data the study has 94% power to detect a 10% decrease in the rate of outcomes (coughing, wheezing, etc.), our anticipated change in the rate. Using the dichotomized version of some outcomes, this study has 80% power to detect on odds ratio of 1.32 with a two sided α=0.05 (n=40). Therefore, we have more than sufficient numbers of participants in each comparison group.

1 BACKGROUND

Flunisolide HFA is an inhaled corticosteroid that is a reformulated version of the older CFC preparation. The CFC formulation was approved in 1981 and had been in use as an asthma controller since with good results.1 The HFA formulation, which is in solution as opposed to suspension, has superior lung deposition when compared to its CFC counterpart (68% versus 20%).[1] Studies have demonstrated flunisolide HFA's effectiveness with regards to controlling airway inflammation and improving lung function[2,3] while maintaining an excellent side effect profile, including no measurable effect on growth over one year.[4] These attributes make it ideal for use in pediatric patients in whom growth suppression is a common concern. In addition, the current device used for delivery has a built-in spacer to ensure optimal lung deposition.

It is known that flunisolide HFA is uniformly distributed throughout all airways, with deposition approaching 68% and less drug being deposited in the oral cavity than larger molecule inhaled corticosteroids. Fluticasone, for example, has a larger particle size and results in about 20% lung deposition, mainly in the central airways. Despite this, there is little data that specifically examines the effect of flunisolide HFA on small airway parameters in children with asthma. We propose a randomized parallel study between flunisolide HFA 80 mcg twice a day and 160 mcg twice a day to determine the effect of each dose on spirometry and impulse oscillometry (IOS) parameters.

Based on the small molecule size and even lung deposition, we hypothesize that we will see a dose dependent significant improvement in small airway parameters (FEF 25-75%, AX, Fres, X5, R20-R5) with flunisolide. Secondary outcome measures will include clinical effects such as frequency of coughing and wheezing, number of short acting beta agonists used, oral steroid doses required, emergency department visits, and hospitalizations. If the results support our hypothesis this will address an important problem in the field and shift current clinical practice paradigms by a refinement in interventions. It may also provide the foundation for future studies to directly compare flunisolide to other coarse molecules inhaled corticosteroids.

1.1 Prevalence and Impact of Asthma

Asthma is one of the most prevalent chronic diseases worldwide, with a substantial burden of disease in the United States. The condition is characterized by extensive airway inflammation leading to variable airflow obstruction, airway hyperresponsiveness and symptoms of wheezing, coughing and dyspnea. Asthma is responsible for an estimated 450,000 hospitalizations in the United States annually (nearly 200,000 of these in children) at considerable cost. Many efforts have been made in attempting to reduce this number. Chronic therapies, consisting primarily of inhaled corticosteroids to reduce airway inflammation and beta-two agonists for acute symptoms, are well recognized by National Heart, Lung, and Blood Institute asthma guidelines for treatment. Despite this, medication adherence remains a major barrier in care.[5,6]

1.2 ICS Therapy in Asthma

As noted, chronic therapy with ICS is widely recongized as standard of care, first line therapy for patients with persistant asthma. Compared with oral corticosteroids, ICS are effective, safe, and exert a local anti-inflammatory effect directly at the site of pathology. ICS can be delivered by a number of mechanisms, the most common of which are pMDIs, dry powdered inhalers, and nebulizers. Failure to correctly use these devices are a common cause of inadvertant non-adherance and is associated with poor asthma control.[7-11] Nebulization may be an ideal delievery mechanism for very young or old patients, acutely ill patients, or those with neurologic or developmental impairments.[12] Selection of ICS by a physician is an individulized process, with the focus on selecting a product with a delivery device that the patient will be able to use easily as well as a molocule with ideal pharmacokinetics and pharmacodyamics. An ideal ICS would be one that has high lung deposition, prolonged pulmonary residency times and low systemic absoprtion (reflected by an excellent safetey profile).[13] While beyond the scope of this discussion, comprehensive reviews comparing ICS molocules have been published and are of great reference to the practioner.[13]

1.3 CFC and HFA Flunisolide

An excellent, comprehensive review of flunisolide was recently published by Melani.[12] Flunisolide was first discovered in 1965 and approved for inhalation via a CFC-MDI in the United States in 1981. Prior studies demonstrated a clinical profile similar to other CFC ICSs such as BDP, fluticasone and budesonide. Lung deposition of this formulation was estimated to be 10% of the delivered dose. Secondary to environmental concerns, CFC MDIs have been phased out with CFC flunisolide being removed from market in 2010. Reformulated versions of these drugs have been developed with HFA MDIs. While some versions of these reformulated drugs were created to match their previous CFC counterparts, others (including flunisolide) were formulated as solutions and deliver extrafine aerosols that have improved deposition even into the distal airways. The mass median aerodynamic diameter of CFC funisolide was 3.8 μm while the HFA formulation has a MMAD of only 1.2 μm. Studies have demonstrated that this smaller particle size results in significantly less deposition in the mouth, pharynx and GI tract and greater deposition in the peripheral lung with improved homogeneity of deposition throughout the respiratory tract. This results in reduced local side effects such as thrush as well as less systemic bioavailability. HFA flunisolide is FDA approved and has recently been marketed in the US at strength of 80 μg per dose. The device has a 50 mL inhalation chamber attached to assist with medication delivery to the lungs. The recommended starting dose in adults is 160 μg twice daily (recommended maximum dose 320 μg twice daily) and in children (ages 6-11) is 80 μg twice daily (recommended maximum dose 160 μg twice daily).

1.4 Clinical Pharmacology

This section (through 1.6) is derived from data directly from the package insert for flunisolide HFA:

Mechanism of Action: Flunisolide has demonstrated marked anti-inflammatory activity in classical test systems. It is a corticosteroid that is several hundred times more potent than cortisol in animal anti-inflammatory assays, and several hundred times more potent than dexamethasone in anti-inflammatory effect as determined by the McKenzie skin blanching test. The clinical significance of these findings is unknown. The precise mechanism of corticosteroid action is unknown. Airway inflammation is an important component in the pathogenesis

of asthma. Corticosteroids have been shown to have a wide range of anti-inflammatory effects, inhibiting both inflammatory cells (e.g. mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and release of inflammatory mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non-allergic mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Pharmacokinetics: All the data described below is based on studies conducted in subjects 18 to 51 years of age.

Absorption: Flunisolide is rapidly absorbed after oral inhalation. Mean values for the time to maximum concentration, Tmax, of flunisolide range from 0.09 to 0.17 hr after a single 320 mcg dose of AEROSPAN Inhalation Aerosol. The corresponding mean values for the maximum concentration, Cmax, of flunisolide vary from 1.9 to 3.3 ng/mL. Oral bioavailability is less than 7%. Over the dose range of 80 mcg to 320 mcg of

AEROSPAN Inhalation Aerosol, values for Cmax increase proportionately with dose after single as well as multiple dose administration.

Distribution: Flunisolide is extensively distributed in the body, with mean values for apparent volume of distribution ranging from 170 to 350 L after a single 320 mcg dose of AEROSPAN Inhalation Aerosol.

Metabolism: Flunisolide is rapidly and extensively converted to 6ß-OH flunisolide and to water-soluble conjugates during the first pass through the liver. Conversion to 6ß-OH flunisolide, the only circulating metabolite detected in man, is thought to occur via the cytochrome P450 enzyme system, particularly the enzyme CYP3A4. 6ß-OH flunisolide has a low corticosteroid potency (ten times less potent than cortisol and more than 200 times less potent than flunisolide). Maximum levels of 6ß-OH flunisolide were 0.66 mcg/mL after a single 320 mcg dose of AEROSPAN Inhalation Aerosol, and 0.71 mcg/mL after multiple doses of AEROSPAN Inhalation Aerosol.

Excretion: Urinary excretion of flunisolide is low. Less than 1% of the administered dose of flunisolide is recovered in urine after inhalation. The half-life values for 6ß-OH flunisolide range from 3.1 to 5.1 hrs after administration of AEROSPAN Inhalation Aerosol in the dose range of 160 mcg to 320 mcg.

Disposition and Elimination: Twice daily inhalation administration of flunisolide hemihydrate for up to 14 days did not result in appreciable accumulation of flunisolide. Upon multiple dosing with 160 mcg and 320 mcg, the Cmax values were 1.0 ng/mL and 2.1 ng/mL, respectively. The corresponding AUC0-12hr values were 1.2 ng.hr/mL and 2.5 ng.hr/mL.

Flunisolide is rapidly cleared from the body, independent of route of administration or dose administered. Flunisolide is not detectable in plasma twelve hours post-dose. After administration of 320 mcg of AEROSPAN Inhalation Aerosol the elimination half-life ranges from 1.3 to 1.7 hours. After a single 320 mcg dose, mean oral clearance values, not adjusted for bioavailability, range from 83 to 167 L/hr.

Special Populations: There were no gender differences for flunisolide after single and multiple dose administration of the AEROSPAN Inhalation Aerosol. Formal pharmacokinetic studies using flunisolide were not carried out in any other special populations.

Pharmacodynamics: Dose finding for AEROSPAN Inhalation Aerosol was based on comparability of systemic exposure to flunisolide CFC inhalation aerosol. The effect of flunisolide CFC inhalation aerosol and AEROSPAN Inhalation Aerosol on pharmacokinetics and 12-hour plasma cortisol levels was investigated in two studies. In both studies, the Cmax and AUC of flunisolide, 6β-OH flunisolide, and 12-hour plasma cortisol measurements were comparable for 1000 mcg of flunisolide CFC inhalation aerosol and 320 mcg of AEROSPAN Inhalation Aerosol. The first was a parallel arm study in 31 subjects. Pharmacokinetics and plasma cortisol levels were determined after single and multiple doses of flunisolide CFC inhalation aerosol 1000 µg and AEROSPAN Inhalation Aerosol 160 µg or 320 µg administered twice daily for 13.5 days. At steady state, flunisolide mean peak plasma concentrations from flunisolide CFC inhalation aerosol 1000 mcg and AEROSPAN Inhalation Aerosol 320 mcg were found to be 2.6 ng/mL and 3.4 ng/mL, respectively. The corresponding mean AUC values for the 12-hr dosing interval were 5.7 ng.hr/mL and 4.7 ng.hr/mL, respectively. At steady state, the mean peak plasma concentrations of 6β-OH flunisolide from flunisolide CFC inhalation aerosol 1000 mcg and AEROSPAN Inhalation Aerosol 320 mcg were found to be 0.9 ng/mL and 0.3 ng/mL, respectively. The corresponding mean AUC values for the 12-hr dosing interval were 3.8 ng.hr/mL and 1.1 ng.hr/mL, respectively. The second was a crossover study in 11 subjects after single doses of flunisolide CFC inhalation aerosol

1000 mcg or AEROSPAN Inhalation Aerosol 320 mcg. The mean peak plasma concentrations of flunisolide from the flunisolide CFC inhalation aerosol 1000 mcg and AEROSPAN Inhalation Aerosol 320 mcg were found to be 2.5 ng/mL and 3.3 ng/mL, respectively. The corresponding mean AUC values were 5.1 ng.hr/mL and 5.8 ng.hr/mL, respectively. The mean peak plasma concentrations of 6β-OH flunisolide from flunisolide CFC inhalation aerosol 1000 mcg and AEROSPAN Inhalation Aerosol 320 µg were found to be 0.8 ng/mL and 0.3 ng/mL, respectively. The corresponding mean AUC values were 3.8 ng.hr/mL and 2.3 ng.hr/mL, respectively.

1.5 **Pediatric Use of Flunisolide:**

The safety and effectiveness of AEROSPAN Inhalation Aerosol has been studied in children 4- 17 years of age. In clinical studies, the efficacy of AEROSPAN Inhalation Aerosol was not established in children 4-5 years of age, although the adverse reaction profile observed in patients exposed to AEROSPAN Inhalation Aerosol was similar between the 4-5 year age group (n=21), the 6-11 year age group (n=210), the 12-17 year age group (n=30), and those patients 18 years of age and older (n=258). The safety and effectiveness of AEROSPAN Inhalation Aerosol has not been studied in patients less than 4 years of age.

Effects on Growth: Controlled clinical studies have shown that orally inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately one cm per year (range 0.3 to 1.8 cm per year) and appears to depend upon the dose and duration of exposure. This effect was observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The growth of pediatric patients receiving orally inhaled corticosteroids, including AEROSPAN Inhalation Aerosol, should be monitored routinely (e.g., via

stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks/benefits of treatment alternatives. To minimize the systemic effects of orally inhaled corticosteroids, including AEROSPAN Inhalation Aerosol, each patient should be titrated to the lowest dose that effectively controls his/her symptoms. The potential effect of AEROSPAN on growth rates in children was assessed in a 52 week randomized, placebo controlled study conducted in 242 prepubescent children age 4 to 9.5 years (145 males, 97 females) with mild persistent asthma. Treatment groups were AEROSPAN 160 mcg twice daily and placebo. Growth velocity was estimated for each patient using the slope of the linear regression of height over time using observed data in the intent to treat population who had at least 3 height measurements. The mean growth velocities were 6.19 cm/year in the placebo group and 6.01 cm/year in the AEROSPAN treated group (difference from placebo -0.17 cm/year; 95% CI: -0.58, 0.24).

1.6 **Efficacy of Flunisolide HFA:**

The efficacy of AEROSPAN Inhalation Aerosol has been studied in two double-blind, parallel, placebo-and active-controlled clinical trials of 12 weeks duration involving more than 1250 patients, one in adults and adolescents 12 years of age and older, and one in patients 4-11 years of age. In adults and adolescents, efficacy was evaluated in patients previously treated with inhaled corticosteroids. In children 6 to 11 years of age, efficacy was evaluated in patients previously treated with bronchodilators alone or inhaled corticosteroids. Both trials had a 2- week run-in period followed by a 12-week randomized treatment period. During the run-in period all patients received flunisolide CFC inhalation aerosol 500 mcg twice daily. Patients were then randomized to double-blind treatment with different doses of AEROSPAN Inhalation Aerosol or flunisolide CFC inhalation aerosol and monitored for lung function changes to see if they maintained, improved, or lost stability. Baseline was assessed at the end of the run-in period. The primary endpoint was the change from baseline in percent predicted FEV1 after 12 weeks treatment.

Adult and Adolescent Patients 12 Years of Age and Older: Efficacy was evaluated in 669 asthma patients, 12 to 78 years of age, including 88 patients 12-17 years of age and 581 patients 18 years and older. Mean FEV1 at screening was 2.44 L and mean FEV1 at baseline was 2.72 L following the 2-week run-in period. Patients were randomized to AEROSPAN Inhalation Aerosol 80 mcg, 160 mcg or 320 mcg twice daily, flunisolide CFC inhalation aerosol 250 mcg, 500 mcg, or 1000 mcg twice daily, or placebo. Change from baseline in percent predicted FEV1 over 12 weeks treatment demonstrated that placebo patients deteriorated 4.3% from baseline after 12 weeks of treatment, whereas patients treated with AEROSPAN Inhalation Aerosol 160 mcg or 320 mcg twice daily maintained FEV1 over the course of the study. Results for the comparison to placebo were statistically significant for the 160 and 320 mcg twice daily AEROSPAN Inhalation Aerosol doses (see Figure 1), but not for the 80 mcg dose. Secondary endpoints of AM peak expiratory flow rate, AM and PM asthma symptoms, nocturnal awakenings requiring a β2 agonist, and as needed use of inhaled β2 agonists showed differences from baseline favoring AEROSPAN Inhalation Aerosol over placebo. AEROSPAN Inhalation Aerosol and flunisolide CFC inhalation aerosol gave comparable results.

Pediatric Patients 4 to 11 Years of Age: The trial enrolled 583 asthma patients, 4 to 11 years of age, although the primary efficacy parameter was evaluated only in the population of 513 patients 6 to 11 years of age. In these patients, the mean FEV1 at screening was 81.2% predicted, and the mean FEV1 at baseline following a two week run-in period was 87.5% predicted. Patients were randomized to

AEROSPAN Inhalation Aerosol 80 mcg or 160 mcg twice daily, flunisolide CFC inhalation aerosol 250 mcg or 500 mcg twice daily, or placebo. Change from baseline in percent predicted FEV1 over 12 weeks in patients 6 years of age and older demonstrated that placebo patients deteriorated 4.0% from baseline after 12 weeks of treatment; whereas patients treated with AEROSPAN Inhalation Aerosol 80 mcg or 160 mcg twice daily maintained FEV1 over the course of the study. Results for the comparison to placebo were statistically significant for the 80 mcg and 160 mcg doses of AEROSPAN Inhalation Aerosol, but there was no added benefit for the 160 mcg BID dose over the 80 mcg BID dose (see Figure 2). AEROSPAN Inhalation Aerosol and flunisolide CFC inhalation aerosol gave comparable results in patients 6 years of age and older.

1.7 Rational for lung function as primary endpoint

We are using change in lung function parameters (FEV1, FEF25-75% from spirometry, R5, R5-R20, AX, Fres from IOS) as a means of assessing response as this provides an objective means of demonstrating improvement in both large and small airways. FEV1 is a well-established parameter in assessing lung function and overall asthma control while FEF25-75% is recognized for its ability to determine small airway obstruction. [14] IOS is an emerging pulmonary function test using sound waves reflected down the pulmonary airway and back designed to assess airway parameters in an effort independent fashion. While the details of its full clinical use is beyond the scope of this article, there are several recent review articles that provide a detailed discussion of the utility of IOS.[15,16] One key attribute of IOS is that data suggests it may be more sensitive in detecting changes in the small airways than traditional spirometry.[17-20] Lung function is routinely used in practice as a means of assessing control and thus these findings will be readily applicable to the clinician. While the pivotal trials of Aerospan looked only at FEV1 changes (a measure of large airway dysfunction), our study proposes to look into small airway function as well.

1.8 Secondary endpoints

Secondary endpoints include asthma symptom control as defined by the standardized asthma control test (ACT). We will also examine the number of corticosteroid courses, ED visits, and admissions patients in each group has over the study period.

2 STUDY RATIONALE

Studies involving the efficacy of flunisolide have primarily been done on the older CFC formulation as discussed above. In addition, none of these studies were targeted at asthma patients specifically with small airway disease. Our goal is to provide greater clarity on the effect of HFA flunisolide at different doses in this unique patient population as HFA flunisolide has a smaller particle size than its CFC predecessor and thus improved deposition in the targeted areas.

3 STUDY OBJECTIVES

3.1 Primary Objective

To assess the impact on lung function of two different doses of HFA flunisolide in asthma patients with small airway disease

4 STUDY DESIGN

4.1 Study Overview

This is a single center, open label, parallel group trial comparing the efficacy of two different strengths of HFA flunisolide on lung function in asthma patients with small airway disease. We will enroll approximately 50 pediatric patients (ages 6-18, see discussion on sample size below) with mild to moderate asthma based upon the National Heart, Lung, and Blood Institute asthma guidelines.[21] These patients will be recruited from new patients presenting to a pediatric pulmonary clinic as well as from general pediatric clinics associated with the University of Louisville, School of Medicine. Patients will have been steroid-naïve for at least four weeks. Prior to enrollment, patients will have demonstrated small airway disease based on pre-bronchodilator FEF $_{25-75\%}$ of less than 65% predicted.[22] Patients will be randomized to receive flunisolide at either 80mcg twice a day or 160mcg twice a day with every other consecutive patient receiving alternating therapy (Figure 1). Prior to starting therapy, baseline IOS and spirometry pre and post bronchodilator (BD) will be obtained (Table 1). Patients will be randomized as described above and will be followed up at six weeks. At that point, repeat IOS and spirometry will be obtained again.

4.2 Primary Efficacy Endpoint

The average change in FEV1 and FEF25-75% measured by spirometry at baseline visit and again 6 weeks later as well the average change in R5, Area of Reactance (AX), and X5 between the two visits as measured by IOS.

4.3 Secondary Efficacy Endpoints

The number of protocol-defined asthma exacerbations requiring treatment with oral steroids between the two groups will be monitored. We will also track frequency of albuterol use for acute symptoms, number of emergency room visits and hospital admissions for acute asthma exacerbations between the two groups.

4.4 Safety Evaluations

Rates of adverse events, withdrawal, adherence to treatment, and frequency of exacerbations; and resting respiratory rate and room air oxygen saturations over the 6 week treatment period, between patients in each treatment group. As we are using an FDA-approved drug for age-appropriate population, and with approved dosages, we anticipate no major safety issues.

5 SUBJECT SELECTION

5.1 Study Population

Subjects with a diagnosis of asthma who meet all of the inclusion and none of the exclusion criteria will be eligible for participation in this study.

5.2 Subject Eligibility Criteria

5.2.1 Inclusion Criteria

1. Diagnosis of asthma by pediatrician or asthma specialist
2. Informed consent by parent or legal guardian
3. 6 years to 18 years of age at Screening Visit
4. Ability to comply with medication use, study visits and study procedures as judged by the site investigator
5. FEF25-75% < 65% of predicted as a marker for small airway disease

5.2.2 Exclusion Criteria

1. Acute wheezing at Screening visit or at Baseline visit
2. Acute intercurrent respiratory infection, defined as an increase in cough, wheezing, or respiratory rate with onset in 1 week preceding Screening visit or 3 weeks preceding Baseline visit
3. Oxygen saturation < 95% at Screening visit or at Baseline visit
4. Clinically significant upper airway obstruction as determined by the Site Investigator (e.g. severe laryngomalacia, markedly enlarged tonsils, significant snoring, diagnosed obstructive sleep apnea)
5. Severe gastroesophageal reflux, defined as persistent frequent emesis despite anti-reflux therapy
6. Physical findings that would compromise the safety of the subject or the quality of the study data as determined by site investigator
7. ICS use within 7 days of Baseline visit, systemic steroid use within 30 days of Baseline visit
8. CF, ILD, history of severe BPD or other underlying significant respiratory disease apart from asthma
9. Potential subjects who are pregnant may not enroll in the study

6 CONCURRENT MEDICATIONS

Subjects should be maintained on the same chronic medications throughout the entire study period, as medically feasible. Each patient will be provided with an albuterol sulfate HFA inhaler as well as a spacer to be used with that device to be used for acute symptoms. Patients will be directed to use this as opposed to other albuterol inhalers they might have during the duration of the study.

6.1 Allowed

All standard therapies are allowed except as in 6.2.

6.2 Prohibited

Other ICS or combination ICS/LABA therapies at any time during the study period are prohibited.

7 STUDY TREATMENTS

7.1 Method of Assigning Subjects to Treatment Groups

We will use a block randomization scheme to promote balance at the end of the study. Block randomization ensures that after each block of individuals are enrolled in the study (n individuals in total); an equal number of individuals will be assigned to each group (n/2 individuals in each group). We will use random block sizes of 8-12. Data about grouping will be kept by study coordinator in a secure, locked location in the clinic. A password protected electronic database will also be created to store patient data in which will be kept on an encrypted, password protected computer.

7.2 Test Formulation

Subjects will be randomized equally to receive HFA Flunisolide 80mcg (AEROSPAN Inhalation Aerosol, MEDA Pharmaceuticals, Somerset, NJ) 1 inhalation BID or HFA Flunisolide 80mcg 2 inhalations BID. All inhalations will be delivered using the built-in spacer device without any other attached devices, holding chambers, spacers, or masks. Patients will be fully instructed on how to administer the medication exactly according to manufacturer's specifications as discussed in the package insert.

7.2.1 Packaging and Labeling

As this is an open label study, patients will be given the device in standard packaging from MEDA Pharmaceuticals.

7.2.2 Handling/Dispensing

Study Test Drug will be distributed by MEDA Pharmaceuticals to the clinic site. Albuterol sulfate (PROAIR HFA, TEVA Respiratory, Inc, Sellersville, PA) will be dispensed to each patient at the time of enrollment.

7.2.3 Dosage/Dosage Regimen

Flunisolide HFA: Subjects will be instructed to administer Study Drug with one or two inhalations twice a day depending on the group per the manufacturer's specifications as discussed in the package insert.

Albuterol: In order to standardize each participant's rescue therapy for acute symptoms, each enrollee will be provided with albuterol sulfate for breakthrough symptoms.

7.2.4 Administration Instructions

Each study subject and family will be provided step-by-step instructions on how to properly administer their medication.

7.2.5 Storage

Study Drug and albuterol sulfate should be stored in the site pharmacy in a secure location at room temperature/humidity.

7.3 Study Medication Accountability

An accurate and current accounting of the dispensing and return of Study Drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of doses of Study Drug dispensed and returned by the subject will be recorded. The study monitor will verify these documents throughout the course of the study.

7.4 Measures of Treatment Compliance

Parents of subjects will be asked to bring all used and unused Study Drug containers to each study visit. Albuterol use can be documented via changes in the counter.

8 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject's legal representative in accordance with site IRB requirements.

8.1 Overview of Evaluations and Visits

8.1.1 Screening Evaluation

At the Screening visit, eligibility for the visit will be determined by the investigator based on inclusion and exclusion criteria. All eligible subjects will undergo spirometry to ensure that baseline values fit the inclusion criteria.

8.1.2 Baseline Visit

Eligible patients may proceed to the Baseline visit (Visit 2) no sooner than the next day but no later than 56 days following the Screening visit. Specific procedures taken at this visit are listed below. If the 56 day window is exceeded, subjects must repeat the Screening visit prior to repeating the Baseline visit. Refer to section 12 for clarification regarding screen failure and re-screening.

8.1.3 Interim Visits

Enrolled subjects will return at 6 weeks as detailed below.

8.2 Clinical Assessments

8.2.1 Demographics

Demographic information (date of birth, gender, race, ethnicity) will be recorded at the Screening Visit.

8.2.2 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, diagnosis through newborn screening, exposure to environmental tobacco smoke, and information regarding underlying diseases will be reviewed and recorded at the Screening Visit.

8.2.3 Concomitant Medications and Pulmonary Exacerbations

All concomitant medication and concurrent therapies will be documented at the Baseline visit. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured. An interim history and chart review will be performed at each subsequent study visit, including interim hospitalizations for respiratory symptoms and interim courses of steroids (date, route, indication).

8.2.4 Physical Examination

A complete physical examination will be performed by a physician (either the investigator or a co-investigator) at the Screening visit. An abbreviated physical examination will be performed by a physician (either the investigator of co-investigator) at Visits 2 and 3. Qualified staff (MD, NP, RN) may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

8.2.5 Height and Weight

Weight and height will be recorded at each visit.

8.2.6 Vital Signs

Heart rate, respiratory rate, and blood pressure will be measured with the subject at rest at each study visit. Body temperature will also be obtained.

8.2.7 Oximetry

Oxygen saturation will be measured on room air with the subject at rest at each study visit.

8.2.8 Adverse Events

Occurrence of treatment emergent adverse events will be assessed throughout the study. Onset, duration, severity, outcome, treatment and relation to study treatment will be documented.

9 EVALUATIONS BY VISIT

9.1 Visit 1 (Screening) (Day -1 to -56)

1. Obtain written informed consent and HIPAA authorization
2. Assign the subject a unique subject identification number
3. Review medical history, including a history of asthma, diagnosis date, and prior treatments
4. Review concomitant medications
5. Record demographic data
6. Obtain Vital Signs (temperature, resting HR, respiratory rate, and blood pressure)
7. Measure oxygen saturation on room air (oximetry)
8. Perform spirometry (pre and post bronchodilator)
9. Perform physical examination (Investigator)
10. Review inclusion/exclusion criteria to determine eligibility for study drug (Investigator)
11. If patient is female and has had menarche, will perform urine pregnancy test in office to exclude pregnancy.

9.2 Visit 2 (Baseline) (Day 0)

Subjects who meet eligibility criteria at Visit 1 will be scheduled to return for Visit 2 no sooner than the next day but no later than 56 days following the Screening Visit. The following procedures will be completed:

1. Obtain standardized asthma control score from parent/legal guardian
2. Review current health status/medical history
3. Review concomitant medications
4. Obtain vital signs (temperature, heart rate, respiratory rate and blood pressure)

5. Measure oximetry
6. Measure height and weight
7. Perform abbreviated physical examination (Investigator)
8. Have patient perform IOS pre-bronchodilator
9. Have patient perform spirometry pre-bronchodilator
10. Have patient perform IOS post-bronchodilator
11. Have patient perform spirometry post-bronchodilator

If the subject meets all eligibility:

12. Randomize to flunisolide HFA 80mcg 1 puff BID or flunisolide HFA 80mcg 2 puffs BID
13. Dispense Study Drug and albuterol sulfate with holding chamber.
14. Review instructions for Study Drug administration
15. Schedule subject for Visit 3 (Week 6 ± 1 week)

9.3 Visit 3 (Week 6 ± 3 days)

1. Obtain standardized asthma control score from parent/legal guardian.
2. Review current health status/medical history and adverse events
3. Review concomitant medications.
4. Obtain vital signs (temperature, resting heart rate, respiratory rate and blood pressure)
5. Measure oximetry
6. Measure height and weight
7. Perform abbreviated physical examination
8. Have patient perform IOS pre-bronchodilator
9. Have patient perform spirometry pre-bronchodilator
10. Have patient perform IOS post-bronchodilator
11. Have patient perform spirometry post-bronchodilator

10 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign, symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the subject CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study medication, or if unrelated, the cause. Again, as this is an FDA approved medication being used in approved ages with approved dosages, we do not anticipate significant AEs.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0, should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in 2 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 2. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

Table 3. AE Relationship to Study Drug Administration

Relationship to Study Drug Administration	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the Study Drug ; that follows a known or expected response pattern to the Study Drug administration; that is confirmed by stopping or reducing the dosage of the Study Drug ; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the Study Drug; that follows a known or expected response pattern to the administration of the Study Drug; that is confirmed by stopping or reducing the dosage of the Study Drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the Study Drug; that follows a known or expected response pattern to administration of the Study Drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to administration of the Study Drug.

Table 4. AE Relationship to Pulmonary Function Testing (Spirometry/IOS)

Relationship to PFTs	Comment
Definitely	Previously known event that follows a reasonable temporal sequence from spirometry/IOS; that follows a known or expected response pattern to spirometry/IOS; that is confirmed by stopping spirometry/IOS; and that is not explained by any other reasonable hypothesis.

Probably	An event that follows a reasonable temporal sequence from the spirometry/IOS; that follows a known or expected response pattern to the spirometry/IOS; that is confirmed by stopping spirometry/IOS; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from the spirometry/IOS; that follows a known or expected response pattern to the spirometry/IOS; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the spirometry/IOS.

10.2 **Serious Adverse Experiences (SAE)**

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

- Results in death
- Is considered life threatening (i.e., in the view of the investigator the adverse experience places the subject at immediate risk of death from the reaction, as it occurred; it **does not** include a reaction that, had it occurred in a more severe form, might have caused death)
- Requires hospital admission or prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is an important medical event (i.e., when based upon appropriate medical judgment, the adverse experience may jeopardize the subject and may require medical or surgical intervention to prevent one of the above listed outcomes)

10.2.1 Serious Adverse Experience Reporting

All SAEs that occur after informed consent is obtained until the end of subject's participation in the study (whether Test Drug related or not) will be documented in an SAE Report. All SAEs will be reviewed by the investigator.

If only a partial SAE report is available, preliminary information will be documented on an SAE Report form, reviewed by the investigator, and reported to the PI within one business day of learning of the event. When additional relevant information is available, this information will be submitted promptly on a new SAE Report form.

Reporting of SAEs to the Independent Review Board (IRB) will be performed by the investigator in accordance with the standard operating procedures and policies of the IRB.

10.3 **Medical Monitoring**

The on-call medical monitor should be contacted directly at the following number to report medical concerns or questions regarding safety:

- Medical Monitor's Pager: (502) 478-0074

11 SCREEN FAILURES AND RE-SCREENING OF SUBJECTS

Subjects who fail to meet eligibility criteria at either the Screening visit or at the Baseline visit will be classified as screen failures and will not be randomized. Subjects who fail eligibility at the Baseline visit may repeat a Baseline visit, following resolution of failed eligibility criteria as applicable, within the 56 day window following the Screening visit. If the 56 day window is exceeded, the subject will be classified as a screen failure, but can be re-consented and re-screened at a later date.

12 SUSPENSION OF STUDY DRUG, WITHDRAWALS, EARLY TERMINATION PROCEDURES, AND SUBJECT REPLACEMENT

12.1 **Discontinuation of Study Drug, Subject Withdrawals, Early Termination Procedures**

A subject may permanently discontinue study drug at any time if the subject, the site investigator, or the Sponsor feels that it is not in the subject's best interest to continue. If a subject discontinues treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized. If study drug is permanently discontinued, the participant should be encouraged to remain in the study and to complete all study visits and procedures,

The following is a list of possible reasons for discontinuation of study drug or withdrawal. Note that in the case of the second two reasons, the participant should be encouraged to complete the remaining study visits rather than withdraw:

- *subject withdrawal of consent*
- *subject is not compliant with study procedures*
- *adverse event*
- *study drug intolerance*

12.2 Replacement of Subjects

Subjects who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following: failure to meet inclusion/exclusion criteria, or incorrectly following protocols laid out in this document. The Principal Investigator will determine if a protocol violation will result in subject withdrawal.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the Investigator. A copy of the form will be filed in the site's regulatory binder.

14 DATA SAFETY MONITORING

As this is an FDA approved drug being used in approved populations at approved doses, the elements listed under "safety evaluations" as above will be tracked by the PIs but no formal data safety review board will be in place.

15 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

15.1 Analysis of Physiologic Effects (Lung Function)

The primary goal of the current study is to determine the effects of Aerospan on lung function in children with small airway obstruction. Participants recruited into this randomized parallel group study will be randomly assigned to either receive (1) 80 mcg of Aerospan twice a day or (2) 160 mcg of Aerospan twice a day, during the six-week study period. Outcomes will be measured at baseline and at six-week follow-up as described above.

First we will start with straightforward tests for differences among the two groups to test if our randomization scheme was successful. Analysis of Variance (ANOVA) techniques will be used to test for difference among continuous variables, while Kruskal-Wallis, Fischer's Exact Tests and Wilcoxon methods will be used to test for differences among categorical variables.

The primary endpoint will be changes in outcomes, over time, from baseline to six-week follow-up. The change in scores from baseline to six-week follow-up will initially be compared using paired t-tests and Chi-squared tests for trend. Repeated measurements will be analyzed using generalized linear mixed-effects regression modeling (GLMM) techniques. For continuous outcomes (e.g., FEV1, FEF 25-75%, Fres, X5, AX, R5-R20.) the identity link function and normal distribution will be used. For count data (e.g., use of Beta-agonists, episodes of

coughing, episodes of wheezing, etc.) the log link function and the Poisson distribution will be used. If we dichotomize outcomes (e.g., a Beta-agonist was used, coughing occurred, etc.) the logit link function and Bernoulli distribution will be used. Statistical analyses will be performed using SAS® Version 9.3 (SAS Institute Inc., Cary, NC).

15.2 Sample Size

Based on our preliminary studies, we anticipate that 10% of all potential participants will not be eligible and/or willing to participant; and that 10% of the eligible/willing participants will be lost to follow-up. Therefore, we will recruit a total of n=50 individuals for the current study. This is a feasible sample size for the research team to recruit and enroll in the current study. Power calculations were based on the anticipated total sample size (n=40) that will be available for complete analysis.

We will develop separate mixed-effects general linear models for each of the continuous outcomes. From the anticipated sample size (n=40) the study has 86% power to detect a 10% main effect of each treatment for each outcome, our anticipated effect size given preliminary studies. When using count data the study has 94% power to detect a 10% decrease in the rate of outcomes (coughing, wheezing, etc.), our anticipated change in the rate. Using the dichotomized version of some outcomes, this study has 80% power to detect on odds ratio of 1.32 with a two sided α=0.05 (n=40). Therefore, we have more than sufficient numbers of participants in each comparison group.

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data collection

Data that will be collected during the study include: enrollment and randomization information, spirometry/IOS data, other subject data collected during the study visit, and asthma controls scores. This data will be kept in a secure, locked filing cabinet in the pediatric pulmonary clinic office.

An electronic database of data will be created using Microsoft Excel. This database will be encrypted, password protected, and stored exclusively on a password protected computer in the pediatric pulmonary clinic.

16.2 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the IRB upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived. All study documents (subject files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of three years.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all lung function data, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a subject's name to a subject identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.1.1 Protocol Amendments

Any amendment to the protocol will be written by the Study Principal Investigators.

A protocol amendment intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRBs are notified within five working days.

17.1.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain a list of IRB members or other assurance of compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning subject recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRBs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect

adversely the safety of the subjects of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.1.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form and HIPAA authorization and provide the documents to the IRB. The consent form generated by the Investigator must be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations.

A properly executed, written, informed consent and HIPA authorization will be obtained from the legal guardian of each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects' legal representatives must be given ample opportunity to inquire about details of the study. A copy of the signed consent form will be given to the legal representative of the subject and the original will be maintained with the subject's records.

17.1.4 Publications

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

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