A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED TRIAL TO STUDY EFFICACY AND SAFETY OF THE VIASKIN® MILK FOR TREATING MILK INDUCED EOSINOPHILIC ESOPHAGITIS IN CHILDREN (SMILEE STUDY)

Test Drug: Viaskin® Milk: Allergen extract of Milk in Viaskin® epicutaneous delivery system

Protocol Number: SMILEE
Study Phase: IIA
IND number: 16518
Version and Date: 8.0, 21 August 21, 2017

Sponsor:
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This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Conference on Harmonization (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements.

CONFIDENTIAL

1. SIGNATURES

Representatives of Sponsor
I have read and agree to the SMILEE protocol, entitled 'A double-blind, placebo-controlled, randomized trial to Study efficacy and safety of the Viaskin® Milk for Treating milk induced Eosinophilic Esophagitis in children (SMILEE study)**.** I am aware of my responsibilities under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities.

Jonathan Spergel, MD, PhD

_____ _____
Signature Date

_____ _____

_____ _____

Investigator

I have read and agree to the protocol SMILEE protocol, entitled 'A double-blind, placebo-controlled, randomized trial to Study efficacy and safety of the Viaskin® Milk's for Treating milk induced Eosinophilic Esophagitis in children (SMILEE study). I am aware of my responsibilities as an Investigator under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

Clinical Site: The Children's Hospital of Philadelphia

Perelman School of Medicine

Site Principal Investigator:

Antonella Cianferoni, MD, PhD	Assistant Professor of Pediatrics
Print Name	Title
Signature	Date

2. SYNOPSIS

NAME OF SPONSOR: Jonathan Spergel	**PROTOCOL No.:** SMILEE
NAME OF STUDY TREATMENT: Viaskin® Milk (DBV: Allergen extract of milk in Viaskin® epicutaneous delivery system)	
TITLE OF STUDY: A double-blind, placebo-controlled, randomized trial to Study efficacy and safety of the Viaskin® Milk for Treating milk induced Eosinophilic Esophagitis in children	
STUDY CENTERS: This is a single site study conducted in United States. The only site will be The Children's Hospital of Philadelphia.	
STUDY PERIOD: Recruitment will stop when approximately 22 subjects have been randomized in the study. Subject's participation in the study will last approximately 2 years	**PHASE OF DEVELOPMENT:** Phase IIA
PLANNED STUDY DURATION: approximately 3 years.	
OBJECTIVES: The objectives of this study are: • To assess the efficacy of Viaskin® Milk epicutaneous immunotherapy (EPIT) in subjects with milk-induced eosinophilic esophagitis. • To evaluate the safety of Viaskin® Milk EPIT in subjects with milk-induced eosinophilic esophagitis.	
STUDY DESIGN AND METHODOLOGY: This is a double-blind, placebo-controlled, randomized trial to study the efficacy and safety of Viaskin® Milk, an allergen extract of milk administered epicutaneously using the Viaskin® epicutaneous delivery system in subjects from 4 to 17 years old with a milk induced Eosinophilic Esophagitis. The trial will be conducted at The Children's Hospital of Philadelphia (CHOP). The first four patients will be 8-17 years old and after these patients are randomized, we will open the study to all ages 4-17 years old. Subjects with a documented medical history of Eosinophilic Esophagitis after ingestion of milk and currently following a strict milk-free diet will be considered for participation in the SMILEE study. A screening/standard of care upper endoscopy and biopsy will be performed after introduction of milk (minimum of 30 ml/day for 1 week to 2 months). If the endoscopy shows greater than or equal to 15 eosinophils per high power field (HPF), it will confirm the diagnosis of Eosinophilic Esophagitis. In addition, milk will be removed from the diet and a standard of care-upper endoscopy and biopsy will be performed after a minimum of 6 weeks under milk-free diet to confirm the diagnosis of milk-induced Eosinophilic Esophagitis. If the biopsy after milk elimination shows 0 to 10 eosinophils per HPF, the subjects will be eligible for participation in the study, and will be randomized in a 3:1 ratio into two different treatment groups, to receive EPIT with Viaskin® Milk (500 µg of milk proteins) or placebo. If a subject has SOC endoscopy in 12 months prior to study, they will not need repeat endoscopies to be eligible for the study and will be randomized as above. A minimum of two standard of care endoscopy procedures will be performed to obtain milk EoE diagnostic results needed for study qualification, and the results of additional SOC endoscopies will be allowed to assess eligibility, if the	

endoscopies are required for clinical care purposes. Milk will be reintroduced into the diet of the subject after 9 months of treatment at equivalent amounts and duration as performed during the screening period. A third research upper endoscopy and biopsy will be performed at the end of the milk-reintroduction period. After the 3rd upper endoscopy, all subjects will continue treatment with open-label Viaskin® Milk (500 µg of milk proteins). Subjects with ≥15 eosinophils/hpf on the 3rd upper endoscopy will restart milk-free diet for 9 additional months while on treatment with active therapy. Then, they will reintroduce milk into their diet at equivalent amounts and duration as performed during the screening period, at which time a 4th upper endoscopy will be done. For subject with < 15 eosinophils/hpf on the 3rd upper endoscopy, they will continue on milk for up to 11 additional months (if symptoms re-appear, milk-free diet should restart) while on treatment with active therapy, at which time a 4th upper endoscopy will be done. A final follow-up visit will be done 2 weeks after completion of treatment and after the last endoscopy.

In total, during this study, eligible subjects will be required to attend 17 study visits.

In addition to endoscopy and biopsy, subjects will undergo other efficacy parameter assessments at months 1, 3, 6, 9, 11, 14, 17, 20 and 22. Key assessments of safety will be performed at each study visit including vital signs, physical examinations and laboratory assessments. In between visits, subjects will report safety data on the diary cards

STUDY POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:
Pediatric subjects, aged 4 to 17 years, with milk induced Eosinophilic Esophagitis will be enrolled and randomized following confirmation of all eligibility criteria.

Inclusion Criteria:

1. Subjects between 4 and 17 years of age at the time of signing the informed consent
2. Well-documented symptoms suggestive of EoE after ingestion of milk and currently following a strict milk-free diet.
3. Upper endoscopy and biopsy at clinical evaluation during screening showing greater than or equal to15 eosinophils per high power field (HPF) isolated to the esophagus meeting the consensus diagnosis of Eosinophilic Esophagitis, after milk was re-introduced into the subject's diet (30 ml/day for 1 week to 2 months), while the subject was on proton pump inhibitor. A clinical decision has been made to perform a minimum of two standard of care endoscopy procedures to obtain milk EoE diagnostic results.
4. Upper endoscopy and biopsy at clinical evaluation during screening showing 0 to 10 eosinophils per HPF isolated to the esophagus after a minimum of 6 weeks under milk-free diet, and while the subject is on proton pump inhibitor. A clinical decision has been made to perform a minimum of two standard of care endoscopy procedures to obtain milk EoE diagnostic results.
5. Negative pregnancy test for female subjects of childbearing potential. Females of childbearing potential must use effective methods of contraception to prevent pregnancy and agree to continue to practice an acceptable method of contraception for the duration of participation in the study. Sexual abstinence will be accepted as an effective method of contraception for girls below 18 years of age.

6. Subjects and/or parents/guardians willing to comply with all study requirements during their participation in the study.
7. Signed informed consent from parent(s)/guardian(s) of children < 18 years + children's assent (for children ≥ 7 years).
8. Subjects agree to maintain a constant diet during the trial, with the exception of milk as per protocol requirement.
9. Subjects will maintain constant medications for asthma and allergic rhinitis during the trial.

Exclusion Criteria:

1. Subjects with a history of severe anaphylaxis to milk with the following symptoms: hypotension, hypoxia, neurological compromise (collapse, loss of consciousness or incontinence), Quincke Edema or requiring intubation.
2. Active IgE- mediated Milk allergy based on skin test or history.
3. Pregnancy or lactation.
4. Subjects with other eosinophilic gastrointestinal disorders.
5. Subjects on swallowed corticosteroids or anti-leukotrienes for Eosinophilic Esophagitis.
6. Subjects with symptomatic allergy to pollens whose symptoms during the corresponding pollen season might interfere with the recording of symptoms during the upper endoscopy/biopsy if the upper endoscopy/biopsy is conducted during the pollen season. The Investigator will have to ensure that the period for conducting the upper endoscopy for such a subject will be outside of the pollen season.
7. Subjects treated with systemic long-acting corticosteroids (depot corticosteroids) within 12 weeks prior to Visit 1 and/or systemic short-acting corticosteroid within 4 weeks prior to Visit 1 or any systemic corticosteroid at screening.
8. Subjects with asthma conditions defined as follows:
   a. uncontrolled persistent asthma by National Asthma Education and Prevention Program Asthma guidelines (2007);
   b. at least two systemic corticosteroid courses for asthma in the past year or one oral corticosteroid course for asthma in the past three months;
   c. prior intubation for asthma in the past two years.
9. Subjects on β-blocking agents, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers or tricyclic antidepressant therapy.
10. Subjects undergoing any type of immunotherapy to any food (oral immunotherapy, sublingual immunotherapy, specific oral tolerance induction) within one year prior to Visit 1.
11. Subjects presently on aeroallergen immunotherapy and unwilling or unable to discontinue.
12. Subjects currently treated with anti-tumor necrosis factor drugs (anti-TNF) or anti-IgE drugs (such as omalizumab) or any biologic immunomodulatory therapy within one year prior to Visit 1.
13. Allergy or known hypersensitivity to the Viaskin® patch material or excipients.
14. Allergy or known history of reaction to Tegaderm® with no possibility to use an alternative adhesive dressing allowed by the Principal Investigator.
15. Subjects suffering from generalized dermatologic diseases (e.g. severe atopic dermatitis, uncontrolled generalized eczema, ichthyosis vulgaris) with no intact skin

zones to apply the Viaskins® or urticarial and mast cell disorders such as chronic idiopathic urticaria.
16. Subjects (or parents of subjects) with obvious excessive anxiety and unlikely to cope with the conditions of an upper Endoscopy and biopsy.
17. Past or current disease(s), which in the opinion of the Principal Investigator, may affect the subject's participation in this study, including but not limited to active autoimmune disorders, immunodeficiency, malignancy, uncontrolled diseases (hypertension, psychiatric (especially anxiety), cardiac), or other disorders (e.g., liver, gastrointestinal, kidney, cardiovascular, pulmonary disease, or blood disorders).
18. Any history of drug or alcohol abuse in the past five years.
19. Subjects unable to follow the protocol and the protocol requirements.
20. Participation in another clinical intervention study in the three months prior to Visit 1.
21. Subjects on any experimental drugs or treatments.

NUMBER OF SUBJECTS: Approximately 22 subjects (16 subjects in the active Viaskin® Milk group and 6 subjects in the placebo group) will be randomized to obtain 18 completed subjects. This sample size will have 90% power to detect a difference of 40 in mean maximum eosinophil counts between the subjects receiving Viaskin® Milk (mean maximum eosinophil count of 10) and the subjects on placebo (mean maximum eosinophil count of 50) assuming a common standard deviation of 20 using a two group *t*-test with a two-sided significance level of 0.05.

STUDY TREATMENT(S): Viaskin Milk will be administered using the Viaskin® epicutaneous delivery system. Viaskin® Milk contains a dry deposit of natural milk protein formulated without adjuvant. The inner part of the Viaskin® Milk has a diameter of 24 mm (4.5 cm^2 surface area). In this inner part, the milk allergen extract is deposited by electrospraying the liquid milk protein formulation, which dries instantly. The outer adhesive part of the Viaskin® is composed of a 3 mm wide band of adhesive foam to stick to the skin. The outer part of the Viaskin® Milk has a diameter of 30 mm.

Subjects will be randomized to receive Viaskin® with milk protein (500 µg of milk proteins) or placebo during the first year in the study. The placebo treatment will consist of a similar formulation, but will be devoid of milk proteins. During the second year in the study (after third upper endoscopy), all subjects will receive open-label Viaskin Milk 500 µg. Once applied to the skin, the hypoallergenic adhesive film TegaDerm® must be used to cover the Viaskin® to prevent it from coming off. Other dressings could also be used as an alternative to TegaDerm® as allowed by the Principal Investigator.

In case the Viaskin® comes off, or after removing a Viaskin®, it is recommended that the subjects or subject's parent(s) wipe off the zone with a disposable napkin or a disposable tissue and wash their hands to prevent accidental transmission of allergenic protein. If possible, the subject could take advantage of their shower time to change the Viaskin®; the previous Viaskin® is removed just before the shower, and the new one will be applied a few minutes after the shower.

Repeated daily applications of the Viaskin® patch will be made with progressive increase duration of application at the start of treatment: 6 hours per day during the first week, 12 hours per day during the second week, and for an entire 24 hours daily from the third

week (Day 15) onwards. Progressive increase duration of patch application will be done again when starting the open-label treatment period.

For all subjects (4-17 years), the patch will be applied on each side of the spine in the inter-scapular area. The specific place where one Viaskin® is administered will represent a "Zone". In total, six zones will be used in each subject to apply the Viaskin®. The first Viaskin® will be applied on zone 1, the second Viaskin® on zone 2 (after removal of Viaskin® 1), etc. until all six zones have been used, and the dosing will continue with zone 1, zone 2 etc.

O1 O 4
O 2 O 5
O 3 O 6

DURATION OF TREATMENT:
Repeated daily application of Viaskin® will be made from Day 1 up to Month 9 at which time milk will be re-introduced into the diet of the subjects. The treatment will then continue during the milk reintroduction period (for 1 week to 2 months) up to the last upper endoscopy and biopsy. The treatment with open-label Viaskin Milk could also continue for up to 11 additional months during the open-label period. In total, the subjects can therefore receive the study treatment for up to 22 months.

STUDY EVALUATIONS:

Primary Efficacy Endpoint:
The primary efficacy endpoint will be each patient's maximum esophageal eosinophil count on all specimens obtained on the biopsy at the end of double-blind treatment period (Visit 10), after milk reintroduction at Visit 9.

Secondary Efficacy Endpoints:
The following secondary efficacy endpoints will be assessed:

- The symptom score at the end of each treatment periods at 11 months and 22 months.
- The change in symptom score at the end of each treatment period at 11 and 22 months compared to baseline.
- Mean Esophageal Eosinophil Count which is the average of all of the samples taken at the end of each treatment period at 11 and 22 months
- Percentage of subjects with ≤1 eosinophils/HPF (excellent response) at the end of each treatment period at 11 and 22 months.
- Percentage of subjects with 2-14 eosinophils/HPF (good response) at the end of each treatment period at 11 and 22 months.
- Percentage of subjects with ≥15 eosinophils/HPF (poor response) at the end of each treatment period at 11 and 22 months.
- Change in mean and maximum esophageal eosinophil count from baseline to the end of each treatment period at 11 and 22 months.

- Esophageal Endoscopy Score at the end of each treatment period at 11 and 22 months.
- Change in Esophageal Endoscopy Score from baseline to the end of each treatment period at 11 and 22 months.
- Change in the Eosinophilic Esophagitis Quality of Life Score from baseline to the end of each treatment period at 11 and 22 months.
- Combination Score of four measures (Eosinophils/HPF, EREFS, investigator assessment and parental assessment of symptoms)
- Time to development symptoms after milk reintroduction at month 9 and 20.
- Changes in exploratory biologic markers, including T-regulatory cells, thymic stromal lymphopoietin (TSLP), CBC with differential and milk-specific Immunoglobulin level, as well as epigenetic changes.

Safety Measurements
The following safety criteria will be determined:

- Adverse events (AEs) and Serious Adverse Events (SAEs) by system organ class, preferred term, severity and relatedness to Viaskin® Milk.
- Duration of local Viaskin® Milk-induced AEs as assessed by the subjects.
- Use of medication to control local AEs
- Systemic allergic symptoms and relatedness to Viaskin® Milk
- Laboratory data, physical examinations and vital signs.

STATISTICAL METHODS:
Demographic, baseline, disposition and enrollment data will be summarized.

Primary Efficacy Analysis
The primary efficacy endpoint will be each patient's maximum esophageal eosinophil count on all specimens obtained on the biopsy at the end of treatment (Visit 10), after milk reintroduction at Visit 9.

The null hypothesis is that the mean maximum eosinophils count in the active treatment group is the same as that in the placebo treatment group. This hypothesis will be evaluated using an analysis of covariance (ANCOVA) model with treatment group, baseline patient's maximum esophageal eosinophil count, and age group (4-11 years old versus 12-17 years old) as covariates. The primary comparison will be tested at the 5% significance level. The least square means for the treatment groups, difference in least square means between the treatment groups, effect size calculated as the absolute difference in least square means between active group and placebo divided by the root mean square, and p-value for difference between treatment groups will be presented.

Secondary Efficacy Analyses
The mean Esophageal Eosinophil Count of the all specimens obtained at the end of treatment and end of the open label extension and percentage of subjects with less than 15 eosinophils/HPF at the end of treatment will be summarized descriptively by treatment group. Changes in individual and total symptoms scores will be summarized descriptively

by treatment group. For the upper endoscopies, visual score at baseline and at the end of treatment at double blind and open label extension will be summarized. Comparisons between groups using a Student's t-test or a Mann-Whitney test for continuous variables and a chi-square tests for categorical variables will be presented.
VERSION AND DATE: 8.0 (Amendment 7), 21 August 2017

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
ATS	American Thoracic Society
CFR	Code of Federal Regulations
CMA	Cow's Milk Allergy
CRO	Clinical research organization
DBPCFC	Double Blind Placebo Control Food Challenge
DSMB	Data and Safety Monitoring Board
eCRF	Electronic case report form
EoE	Eosinophilic Esophagitis
EPIT	Epicutaneous immunotherapy
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERD	Gastro-Esophageal Reflux Disease
GMP	Good Manufacturing Practice
HPF	High Power Field
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Independent Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
OFC	Oral Food Challenge
PP	Per protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event
TSLP	Thymic stromal lymphopoietin
US/USA	United States/United States of America
WHO	World Health Organization
WMA	World Medical Association

5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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6. INTRODUCTION

6.1 Disease Review, an unmet medical need

Eosinophilic Esophagitis (EoE) is a recently described disease with rapid rise in the last 20 years with a prevalence of 1/2000[1-7]. Currently, there are no FDA approved therapies for this orphan disease and no cures. EoE is characterized by eosinophilia of the esophagus, an organ typically devoid of eosinophils without infiltration in other parts of the gastrointestinal tract[8,9].

EoE is suspected in patients that have symptoms similar to those caused by gastro-esophageal reflux (GERD) but do not respond to medications for GERD. More specifically typical symptoms are vomiting, abdominal pain, regurgitation, and dysphagia and in young children and infants feeding difficulties and failure to thrive. Dysphagia appears to be more common in older children and adults[7,8,10,11]. Because of these diverse and non-specific symptoms, EoE can be diagnosed only by esophageal biopsy with the finding of 15 eos/hpf (peak value)[12]. Peak value is used instead of mean value in the current definition due to patchy nature of the disease. [7,8,10,11]

EoE is a chronic disease with almost no resolution without treatment[7,13]. When the diagnosis is established, it is important to treat the disease not only to control the presenting symptoms, but also to prevent acute and chronic complications such as, food impaction, esophageal stricture, narrow-caliber esophagus, and esophageal perforation [7,9].

Unlike other food allergies, EoE is probably not IgE mediated. The evidence is based on murine and clinical evidence. In murine models of EoE, IgE knockout mice still develop esophageal eosinophilia. Knockout of T cells eliminates T cells in esophagus. In clinical studies, food elimination diets based on IgE testing (skin testing or *in vitro* specific IgE) have not been successful with response rates of 16%.[14] EoE is clearly an allergic disease as the patients have higher incidence of atopy, which has been reported with prevalence between 70% and 93% [7,15,16].

EoE appears to be T cell mediated disease as Th2-cytokines, especially IL-13, are associated with esophageal eosinophilia[17-27]. In EoE, Th2 inflammation appears to be driven by TSLP secreted by esophageal epithelial cells [28,29] and TSLP has been identified as a genetic risk factor[18,28,29].

Foods have been shown to be the cause of EoE through the use of elimination diets or elemental formulas in nearly all children and adults [7,30-32]. The mechanism underlying the immunologic reaction to foods in EoE is probably **NOT** IgE mediated, but cell mediated. Removal of all foods can induce remission in greater than 95% of children indicating that food can cause disease. Kelly and colleagues demonstrated that the introduction of skin test–negative foods into the diet could induce clinical disease meeting Koch's postulate that food reintroduction reintroduces disease[30]. However, removal of skin test positive foods have low rate of success (13% in adults and less than 30% in pediatrics)[10,33] further supporting that this not an IgE mediated disease. In addition, the use of anti-IgE has no effect on disease state[34-36].

6.2 Treatment options for Eosinophilic Esophagitis

There are two current treatment options for EoE and neither is a cure. One option is treating symptomatically with off label use of topical steroids. Topical corticosteroids are effective in inducing EoE remission in 50-90% of patients depending on the dose and topical steroid used. The two most common topical steroids used are swallowed fluticasone or budesonide[37-43]. However, when steroids are stopped, inflammation and symptoms reoccur. In addition, long-term data on safety and efficacy is not available. As the concern, from experience for topical steroid use in asthma, we know that moderate or high dose of topical steroids like the one used to treat EoE, are associated with significant reduction in growth in children [44,45].

The second option is through diet. Foods have been shown to be the cause of EoE through the use of elimination diets or elemental formulas [7,30]. The two basic approaches for elimination diets are removal of foods based on testing[46,47] or removal of the most common food allergens[31,33]. Both methods have similar rates of improvement, about 70% of cases[48]. Based on reintroduction studies from both allergy directed diets or empiric diets, milk is the most common allergy seen in 50-70% of the adults and children[14,49,50]. In fact, 30% of the children are just allergic to milk[49,51].

Oral desensitization to foods is a very effective treatment for several IgE-mediated food allergies but not for EoE. In fact, there is an increasing number of patients that resolve their IgE-mediated food allergy using oral desensitization but develop EoE once the food is reintroduced in the diet, confirming that IgE mediated food allergy and EoE have a different mechanism[52,53]. Overall, the current oral immunotherapy induces EoE in 10 to 20% of the studies depending on the criteria.

6.2.1 Monitoring of EoE

There are no markers for the diagnosis and management of EoE. Symptom scores do not always correlate with esophageal biopsies. As patients can have esophageal inflammation with no symptoms or the reverse-abdominal pain with normal esophageal biopsies.[54,55] Therefore, the current guidelines recommend an upper endoscopy with biopsy 2-3 months after any therapeutic measure.[8,12] The current guidelines and gold standard for diagnosis recommends using maximum eosinophil counts due to the patchy nature of the disease. Recent work has suggested potential other ways of measuring EoE disease activity including patient reported symptom score[54]. Thus, as a secondary endpoints to the study, a patient-reported symptom score, Eosinophilic Esophagitis Quality of Life Scale[56] , and visual endoscopy scale[57] will be used.

6.2.2 Natural History of EoE

Unlike most IgE-mediated food allergies, patients with food induced EoE do not outgrow it. Less than 5% of our patients have outgrown their food allergy based on biopsy and symptom changes.[7] Similar results have been seen in adult populations with no patients having outgrown EoE in 20 years of follow-up.[58] It is also known that a delay in diagnosis increases the risk of fibrosis and strictures.[58,59] Therefore, a therapy that changes the natural history of EoE is needed.
As typical standard of care, an endoscopy is performed to confirm the diagnosis. Prior to the endoscopy, a patient is treated with a proton pump inhibitor to treat possible reflux, which can mimic symptoms of EoE. The first endoscopy includes biopsy of esophagus, stomach and duodenum to ensure that eosinophilic inflammation is isolated to the esophagus. A repeat

endoscopy is performed 2 months after any therapeutic measure (diet or medication changes).[7,9] When a food is identified, the food is generally reintroduced about 2 years later followed by an upper endoscopy with biopsy as part of standard of care treatment at CHOP. However, at other institutions, foods are introduced as soon as 2 months after endoscopy.

6.3 The New Strategy for EoE

Therefore, we propose to use epicutaneous (EPIT) desensitization to cure milk-induced Eosinophilic Esophagitis. This technology has been successfully used to desensitize children with cow's milk induced IgE mediated reactions. Dupont and colleagues were able to successfully increase the cow's milk mean cumulative tolerated dose by 12-fold in the active group compared to no increase in the placebo group[60]. For Eosinophilic Esophagitis, Mondoulet and colleagues have developed a murine model based on repeat exposure to peanut. The mice developed profound eosinophilic inflammation in the gastrointestinal tract (predominantly in the esophagus). They have also found similar results in pig model of eosinophilic gastrointestinal disease. They found that use of peanut EPIT can block this inflammation.[61,62] In preliminary results, EPIT appears to induce both natural and induced T-regulatory cells leading to tolerance.

We will measure two key endpoints for this disease

- Maximal number of eosinophils per high power field isolated to the esophagus
- Quality of life measures using a validated EoE module[56,63]

6.4 Compound Review

The Investigational New Drug, Viaskin® Milk is a milk immunotherapy comprised of an epicutaneous delivery system (Viaskin® or Viaskin® patch) containing a dry deposit of a formulation of cow's milk protein extract. The milk protein allergens are deposited on the backing of an occlusive chamber by electrospraying a liquid formulation of the milk protein extract. The epicutaneous delivery system (Viaskin® or Viaskin® patch) is made of a titanium-unit comprising a protective liner and functional layers.

The drug substance is an unmodified lyophilized milk extract produced from the extraction of skimmed milk powder as source material (Refer to the Viaskin® Milk Investigator Brochure for full details).

6.4.1 Non-Clinical Studies

Nonclinical studies have been conducted to support the safety of Viaskin® Milk for clinical development. These include toxicology studies performed with the combined product (Viaskin with milk extract deposit), i.e. repeat-dose, genotoxicity and tolerance studies, as well as ISO 10993-compliant biocompatibility studies performed with the device component alone. Details regarding the nonclinical studies conducted with Viaskin® Milk are presented in the Investigator Brochure.

Moreover, efficacy studies using EPIT were conducted in peanut-sensitized mice with esophago-gastro-enteropathy[61] and in peanut-sensitized pigs with allergic eosinophilic gastritis.

6.4.2 Clinical Studies

The Investigational New Drug, Viaskin® Milk is a dry deposit of a formulation of milk protein extract intended for EPIT. EPIT is an emerging allergen-Specific ImmunoTherapy (known as SIT) approach for the treatment of atopic diseases. The Investigational New Drug called Viaskin® Milk is a ready-to-use and easy-to-administer form of allergen immunotherapy, particularly adapted to the pediatric population. Viaskin® Milk is intended to induce clinical desensitization/tolerization to milk in subjects with moderate to severe IgE-mediated allergy to milk. Viaskin® Milk includes the natural and complete set of milk proteins that can interact with the local antigen presenting cells such as the epidermic Langerhans and dendritic cells and can initiate the process of clinical desensitization/tolerization. Moreover, by utilizing the epicutaneous route of administration, Viaskin® Milk is able to initiate these immunomodulatory processes while minimizing the potential safety concerns associated with systemic exposure to food allergens. Recently, EPIT was successfully used for the treatment of IgE-mediated grass pollen allergy[64] and peanut allergy.

Milk EPIT in Food Allergy

An earlier study of milk EPIT was completed by Dupont and colleagues, and involved 18 subjects (intent-to-treat population) [60]. This double-blind, placebo-controlled, randomized pilot study evaluated the safety and efficacy of EPIT for the treatment of cow's milk allergy (CMA) in highly sensitive IgE-mediated CMA children. This study was performed utilizing an atopy patch test based on the same technology as the commercially available diallertest® diagnostic product. Diallertest is a ready-to-use cow's milk allergen atopy patch test that has been made available by DBV Technologies on the French market since June 2004 for the diagnosis of CMA. The eligible children were randomized (1:1) to receive active treatment patch (containing cow's milk powder) or placebo for 3 months of blinded therapy, followed by an open-label dosing with the active patch up to an additional 6 months The active treatment tended to increase the milk cumulative tolerated dose from a mean ± SD of 1.77 ± 2.98 mL at day 0 to 23.61 ± 28.61 mL at day 90 (p-value of 0.18), while it did not vary in the placebo group (4.36 ± 5.87 mL at day 0 vs. 5.44 ± 5.88 mL at day 90). The mean cumulative tolerated dose increase was 12-fold in the active group versus 8% in placebo group (P = .13). Thus, milk tolerance was increased, although this preliminary study failed to demonstrate a statistically significant improvement of the cumulative tolerated dose.

With regards to safety, localized eczema was more frequently observed in the active group than in the placebo group; topical corticosteroids were used in 1 patient from each group. There was no specific difference in the nature of the AEs reported between the two groups, except for the gastrointestinal symptoms (2 diarrheas and 1 vomiting) that were reported only in the active group. Treatment was well tolerated by all patients. No child interrupted treatment because of an AE, and none received epinephrine or was seen at the emergency department or hospital[60].

A Double-Blind, Placebo-Controlled, Randomized Trial to Study the Viaskin® MILk Efficacy and Safety for Treating IgE-Mediated Cow's Milk Allergy in Children, (MILES study, NCT 02223182) using Viaskin Milk as Investigational Product is ongoing. This study is divided into 2 consecutive parts (Part A and Part B). Part A initially evaluated the safety of 3 escalating doses

of Viaskin Milk (150 µg, 300 µg and 500 µg) over 3 weeks of treatment. Part B will evaluate the efficacy and safety of the 3 doses of Viaskin Milk versus Placebo.

Peanut EPIT in Peanut Allergy

Several clinical studies have also been conducted with another product called Viaskin® Peanut, in peanut-allergic subjects. These studies include a completed Phase 1b safety study (100 subjects, NCT 01170286), a pilot Phase 2 study called Arachild (54 pediatric subjects, NCT 01197053) and a recently successfully completed Phase 2b study called VIPES (221 subjects, NCT 01675882), and its follow-up study OLFUS-VIPES (NCT 01955109) currently ongoing.

Results of the VIPES study have been released by DBV Technologies. The trial was prospectively organized across three dose levels (50, 100, 250 µg peanut proteins) with two patient strata composed of three different patient age groups; children (113 subjects, ages 6-11) for the first stratum and adolescents (73 subjects, ages 12-17) plus adults (35 subjects, ages 18-55) for the other stratum. All patients received a daily application of the Viaskin® Peanut patch over a 12-month treatment period. Trial responders were defined as patients who, after 12 months of treatment with Viaskin® Peanut and using a double-blind, placebo controlled food challenge, started to react at a dose of peanut protein equal to or greater than 1,000 mg, or at least a 10-fold increase in the eliciting dose of peanut protein compared to baseline. As a secondary efficacy endpoint, Cumulative Reactive Dose, or CRD, was also used to establish the total quantity of peanut protein that begun triggering patient reactions at month 12 versus placebo. Serological markers were also measured as additional secondary endpoints at baseline, 3, 6, and 12 months in order to characterize the immunological changes in subjects. Overall, the 250 µg dose showed the highest efficacy with statistical significance for these endpoints. In terms of peanut consumption and immunological changes, a consistent dose effect was observed. A total of 56 patients were randomized to the Viaskin® Peanut 250 µg dose. In this arm, 50% of patients responded, compared to 25% in the placebo group, showing statistical significance (p=0.0108).

Specifically, 53.6% of children responded to treatment compared to a 19.4% response in placebo (p=0.008). Children treated with Viaskin® showed a strong increase in peanut consumption, with an increase in LS mean (Least Squares Mean is a statistical model adjusted for multiple factors including both categorical, such as treatment, country and continuous covariates, such as baseline peanut dose measures allowing to better isolate solely the effect of treatment) change of CRD from baseline of 390.4 mg ($p<0.001$). Serological responses also showed treatment effect. In treated children, peanut-specific immunoglobulin E (IgE) increased over the first 3 months before decreasing toward initial levels at 12 months, while peanut-specific immunoglobulin G4 (IgG4) increased by more than 19 times over 12 months of treatment with the highest dose of Viaskin® Peanut. Both biomarkers suggest a powerful desensitization effect.

Animal Studies of EPIT in EoE

In animal models of Eosinophilic Gastrointestinal disease, treatment with peanut EPIT lead to resolution of esophageal eosinophilia. Mice were sensitized with peanut allergen via oral route and sustained oral exposure to peanuts with cholera toxin in sensitized mice led to severe esophageal eosinophilia and intestinal villus sub-atrophia, i.e. significantly increased influx of

eosinophils into the esophageal mucosa (136 eosinophils/mm^2) and reduced villus/crypt ratios ($p<0.001$ compared to naïve mice). In the sera, specific IgE levels significantly increased as did secretion of Th2 cytokines by peanut-reactivated splenocytes.

For mice treated 8 weeks with peanut EPIT, there was significantly reduced Th2 immunological response (IgE response and splenocyte secretion of Th2 cytokines) as well as esophageal eosinophilia (49.6 compared to Sham 136.2 eosinophils/mm^2, $p < 0.05$), mRNA expression of Th2 cytokines in tissue (eotaxin ($p<0.05$), IL-5 ($p<0.05$), and IL-13 ($p<0.05$), GATA-3 ($p<0.05$)) and intestinal villus sub-atrophia (2.3 +/- 0.18 vs Sham, $p < 0.01$)[61]. EPIT also increased specific IgG2a ($p<0.05$) and mRNA expression of Foxp3 ($p<0.05$) in the esophageal mucosa.[61]

In an additional experiment aiming at evaluating the crucial role of intact skin for epicutaneous treatment, it was confirmed that EPIT on intact skin significantly reduced Th2 immunological response as well as esophageal eosinophilia ($p<0.01$ compared to Sham), mRNA expression of Th2 cytokines in tissue and intestinal sub-atrophia ($p<0.05$ compared to Sham).[62] By contrast, EPIT on stripped skin reinforced Th2 systemic immunological responses as well as eosinophil infiltration, mRNA expression of Th2 cytokines and duodenal villus/crypt-ratio.

In another pre-clinical study, the efficacy of EPIT was evaluated in piglets sensitized to peanuts, followed by the induction of eosinophilic gastritis. The analysis of histological samples showed a high level of eosinophils in stomach mucosa. In that model, EPIT was efficient to decrease eosinophils infiltration in stomach to the levels observed in control animals.

Based on immunological changes seen in murine and pig models as well as changes seen in EPIT therapy in human, we will examine T regulatory cell expression and cytokine expression in the peripheral blood. Epigenetics changes have been seen in animal model using EPIT[65] and milk oral immunotherapy.[66] Therefore, epigenetic changes in T cells with changes in GATA-3 will be explored. As we found a strong molecular and genetic link for TSLP in EoE[28], we will also assess expression of TSLP as an exploratory endpoint.

6.4.3 Clinical Study Rationale

The SMILEE study is the first pilot study to assess the efficacy and safety of Milk-EPIT using Viaskin® Milk in Eosinophilic Esophagitis subjects. It is acting as a proof of concept study.

7. STUDY OBJECTIVES

- To assess the efficacy of Viaskin® Milk EPIT in subjects with milk-induced eosinophilic esophagitis
- To evaluate the safety of Viaskin® Milk EPIT in subjects with milk-induced eosinophilic esophagitis.

7.1 Efficacy Objectives

The main efficacy objective is to determine the efficacy of Viaskin® Milk to significantly desensitize milk-induced Eosinophilic Esophagitis subjects at the end of treatment period.

The study will analyze the maximum eosinophil count on all specimens obtained at the end of treatment period in esophageal biopsy after milk reintroduction in subjects with Eosinophilic Esophagitis. This is the gold-standard for the diagnosis of EoE. [7,8,10,11]

7.2 Safety Objectives

The study will evaluate the safety of Viaskin® Milk EPIT treatment in children and adolescents with milk-induced Eosinophilic Esophagitis.

Adverse events (AEs) and Serious Adverse Events (SAEs) by system organ class, severity and relatedness to Viaskin® Milk, duration of local skin reactions induced by Viaskin® Milk, use of medications to treat AEs, systemic allergic symptoms and relatedness to Viaskin® Milk, changes in laboratory results, physical exams and vital signs will be assessed.

8. INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This is a double-blind, placebo-controlled, randomized trial to study the efficacy and safety of Viaskin® Milk, an allergen extract of milk administered epicutaneously using the Viaskin® epicutaneous delivery system in children (4 to 17 years old) with milk-induced Eosinophilic Esophagitis (EoE). The trial will be conducted at The Children's Hospital of Philadelphia, who has Investigators and staff trained and experienced in the diagnosis and the management of Eosinophilic Esophagitis and who are experienced in performing an upper endoscopy with biopsies. Viaskin® Milk will be evaluated in this study versus placebo.

Patients suspected of having milk-induced Eosinophilic Esophagitis will be eligible to participate in the study and will perform screening visits (Visits 1-3) to confirm their diagnosis and eligibility in the study. After confirmation of the diagnosis of milk-induced Eosinophilic Esophagitis by a minimum of two clinical care endoscopies, eligible subjects will be enrolled and randomized in a 3:1 ratio into two different treatment groups, to receive EPIT with Viaskin® Milk (500 µg of milk proteins) or placebo. Double-blind treatment will last up to 11 months (from visits V4 to V10). Each eligible subject will undergo a minimum of two clinical care upper endoscopies and biopsies, and one research procedure during their participation in the study: a clinical care endoscopy with biopsies during screening after milk-introduction, a clinical care endoscopy with biopsies during screening while on milk-free diet, and a third endoscopy with biopsies for research at the end of the double-blind treatment period after milk-reintroduction (Visit 10). If additional SOC endoscopies are required for clinical purposes, the results of these SOC endoscopies can be used to help establish eligibility for this study. For example, if a patient is discovered to not be following a clinically prescribed diet or taking recommended medications, the gastroenterologists may place the patient on the more restrictive diet (which the patient was supposed to be on) and then follow-up with SOC endoscopy to confirm diagnosis. Milk will be reintroduced at 9 months after the second endoscopy. Results of the clinical care procedures, and study-mandated endpoints (Table 3) during the screening period will be available to confirm eligibility for enrollment and randomization to the two study arms (at Visit 4).

The rationale for up to 11 months of therapy (9 months off milk and up to 2 months after milk reintroduction) is based on preliminary data for IgE-mediated food allergy with efficacy being generally evaluated after 12 months of epicutaneous therapy (EPIT). In addition, the pre-clinical data in the pig model of eosinophilic gastritis was seen after around 3 months of therapy. It was extrapolated that between 9 to 11 months of EPIT in this pilot study, would be adequate. After the third endoscopy at the end of the double-blind treatment period (Visit 10), the study will be extended by one additional year and all subjects will receive open-label Viaskin® Milk (500 µg of milk proteins) for up to 11 months. A fourth endoscopy with biopsies for research will be done at the end of the open-label treatment period (Visit 16). The extension of the study will permit to assess the long-term safety and efficacy of Viaskin® Milk for up to 22 months of treatment in subjects with milk-induced Eosinophilic Esophagitis.

For EoE, there is no definitive treatment to mitigate disease progression of disease except for avoidance. In the standard of care, it is considered normal to periodically reintroduce foods to see if the subject has outgrown it. The first two endoscopies will be standard of care. The first endoscopy will permit to confirm the diagnosis of EoE and the second endoscopy will be used to confirm the diagnosis of milk-induced EoE. In our typical standard of care, the endoscopy will be performed, after treatment with proton pump inhibitor. The first endoscopy (standard of care) includes biopsy of esophagus, stomach and duodenum to ensure that eosinophilic inflammation is isolated to the esophagus. The second (standard of care), third (research) and fourth (research) endoscopies will include biopsies of esophagus only.

For safety purposes and to minimize risk, the first four patients will be 8-17 years old and after these patients are randomized, we will open the study to all ages 4-17 years old.

Table 2: Upper Endoscopies with Biopsies

1	Initial Endoscopy	Standard of Care	Biopsies of esophagus, stomach and duodenum
2	Second Endoscopy	Standard of Care	Biopsies of esophagus
3	Third Endoscopy (post double-blind treatment)	Research	Biopsies of esophagus
4	Fourth Endoscopy (post open-label treatment)	Research	Biopsies of esophagus

Study Visits:

There are at least three visits during the screening period that will occur before enrollment and randomization to the active treatment phase of the SMILEE study. The timing of Visits 2 and 3 are not mandated as part of this study protocol, since these two visits are standard of care (during which study endpoint information is collected, Table 3). After confirmation of eligibility, subjects will be enrolled to the active phase of the study, randomized to study arms,

and treated with either Viaskin Milk EPIT or Viaskin placebo patch. Fully eligible subjects will be required to attend 17 study visits in total as follows:

- **Screening Period:**

- The GI collaborative team will help identify potentially eligible SMILEE study participants. Potentially eligible subjects will be enrolled to the study (Visit 1), to confirm Treatment Period study eligibility and obtain a number of study endpoints (see Table 3). The GI group will follow standard of care procedures, but the dates of the first (Visit 2) and second (Visit 3) endoscopies with biopsies will not be mandated by the investigative team, but by the GI group for clinical care. The second upper endoscopy/biopsy will be done at a minimum of 6 weeks after milk-removal, per clinical care. If a patient meets eligibility criteria for the Treatment Period of SMILEE, s/he will be referred to the Allergy / Immunology division for continuation in the study. If the results of the first or second endoscopy with biopsies confirm ineligibility, the subject may be considered as screen failed and may not continue in the study. However, if the GI group decides to obtain additional clinical care endoscopies with biopsies for confirmation or clarification of clinical diagnosis, results from these additional biopsies are allowed in the screening period (see Table 3, Study Flow Chart, below).
- Visit 1: Informed Consent obtained. Milk introduction.
- Visit 2: 1 week to 2 Months after milk-introduction. Standard of Care Upper endoscopy/Biopsy. Milk removed from the diet.
- Visit 3: 6 weeks minimum after Milk-free diet. Standard of Care upper endoscopy/biopsy.

    - If a patient has endoscopies that confirm milk responsive EoE in the preceding 12 months, they will not need a repeat endoscopy to be eligible for the study.
    - A minimum of two standard of care endoscopy procedures will be performed to obtain milk EoE diagnostic results needed for study qualification. Results from additional endoscopy procedures are allowed, if required for clinical purposes
    - Subjects' clinical care GI and Allergy physicians will determine the order of screening standard of care endoscopies.

- **Treatment Period:**

- Visit 4 (Day 1): Chart review, confirmation of eligibility. Randomization. Treatment start.
- Visit 5 (Day 8)
- Visit 6 (Month 1)
- Visit 7 (Month 3)
- Visit 8 (Month 6)
- Visit 9 (Month 9): Milk reintroduction.
- Visit 10: 1 week to 2 Months after milk reintroduction. (During this time, subjects will have weekly calls to monitor symptoms) End of double-blind treatment.
- Upper endoscopy/biopsy (research).

In addition, the patients could be contacted via telephone calls or email between visits to monitor symptoms, when symptoms reoccur-research endoscopy will be scheduled. The open-label treatment period will start on that day.

Open label Extension
- Visit 11: Day 8 after the Visit 10 research biopsy
- Visit 12: Month 1 after the Visit 10 research biopsy
- Visit 13: Month 3 after the Visit 10 research biopsy
- Visit 14: Month 6 after the Visit 10 research biopsy
- Visit 15: Month 9: 1 week to 2 months for milk reintroduction
- Visit 16: Upper endoscopy/biopsy (research)

- **Last Assessment and End of Study Period/ Early Withdrawals:**
- Visit 17: 2 weeks after Visit 16.

It is planned to randomize approximately 22 subjects in the study (16 Viaskin® Milk subjects and 6 Placebo subjects). A flowchart outlining study assessments and time of assessments is shown in Table 3. A schematic diagram of the study design is shown in Figure 1.

Table 3A: Study Flow Chart (Visits 1 to 10)

Study Assessments	Screening Period#				Double-blind Treatment Period						
	V1	V2*	V3	V4**	V5	V6	V7	V8	V9		V10*
		1 week to 2 months after Milk Re-Intod.	Minimum 6 weeks after Removing Milk	D1	D8 ± 3 days	M1 ± 7 days	M3 ± 14 days	M6 ± 14 days	M9 ± 14 days	Telephone calls****	1 week to 2 months after V9
Informed Consent	X										
Medical History[1]	X										
Demographics [2]	X										
Physical Examination[3]	X	X	X	X	X	X	X	X	X		X
Vital signs[4]	X	X	X	X	X	X	X	X	X		X
Quality of Life		X	X								X
Symptom Score	X	X	X	X	X	X	X	X	X		X
Laboratory Tests[6]	X							X			X
Urine Pregnancy Test[7]	X			X							X
Milk Introduction	X								X		X[10]
Milk-free Diet		X[#]	X	X	X	X	X	X			
Diet History/Diary	X	X	X						X		X
Standard of Care Upper Endoscopy and Biopsy		X	X								
Research Upper Endoscopy and Biopsy											X
Research Bloods		X	X								X
Endoscopy Score		X	X								X
Check Eligibility/Randomization				X							
Adverse Events (AEs)	X	X	X	X	X	X	X	X	X	X	X
Prior/ Concomitant Medications	X	X	X	X	X	X	X	X	X		X
Diary Cards (dispense/check)				X	X	X	X	X	X		X
Dispense the investigational product to the subject[8]				X	X	X	X	X	X		X
Apply Viaskin® patch(es) on site				X	X	X	X	X	X		X
Check the used/unused investigational product dispensed to the subject					X	X	X	X	X		X
Check skin reaction under the Viaskin® patch and grade it[9]				X	X	X	X	X	X		X
Photography of the site(s) of application of the Viaskin® patch				X	X	X	X	X	X		X

Footnotes are 2 pages forward

Table 3B: Study Flow Chart (Visits 11 to 17)

Study Assessments	Open-Label Treatment Period							Last Assessment and End of Study/Termination
	V11 Post V10-D8 ± 3 days	V12 Post V10 M1 ± 7 days	V13 Post V10 M3 ± 14 days	V14 Post V10 M6 ± 14 days	V15 Post V10 M9 ± 14 days	Telephone calls****	V16* 1 week to 2 months after V15	V17*** 2 weeks after V16 or ET ± 3 days
Informed Consent								
Medical History[1]								
Demographics[2]								
Physical Examination[3]	X	X	X	X	X		X	X
Vital signs[4]	X	X	X	X	X		X	X
Quality of Life							X	
Symptom Score	X	X	X	X	X		X	X
Laboratory Tests[6]							X	
Urine Pregnancy Test[7]							X	
Milk Introduction	X[%]	X[%]	X[%]	X[%]	X[%]		X[10]	X[10]
Milk-free Diet	X[%]	X[%]	X[%]	X[%]	X[%]			
Diet History/Diary	X				X		X	
Standard of Care Upper Endoscopy and Biopsy								
Research Upper Endoscopy and Biopsy							X	
Research Bloods							X	
Endoscopy Score							X	
Check Eligibility/Randomization								
Adverse Events (AEs)	X	X	X	X	X	X	X	X
Prior/ Concomitant Medications	X	X	X	X	X		X	X
Diary Cards (dispense/check)	X	X	X	X	X		X	X
Dispense the investigational product to the subject[8]	X	X	X	X	X			
Apply Viaskin® patch(es) on site	X	X	X	X	X			
Check the used/unused investigational product dispensed to the subject	X	X	X	X	X		X	
Check skin reaction under the Viaskin® patch and grade it[9]	X	X	X	X	X		X	X
Photography of the site(s) of application of the Viaskin® patch	X				X		X	X

Footnotes are on the next page

#- If a patient has a endoscopies that confirm milk responsive EoE in the preceding 12 months, they will not need a repeat endoscopy to be eligible for the study.
*: Visit 2 (screening period) Visit 10, and Visit 16 have to be performed after 1 week to 2 months of milk introduction. The milk introduction period should be the same, as much as possible, as compared to that which occurred during the screening period for an individual subject.

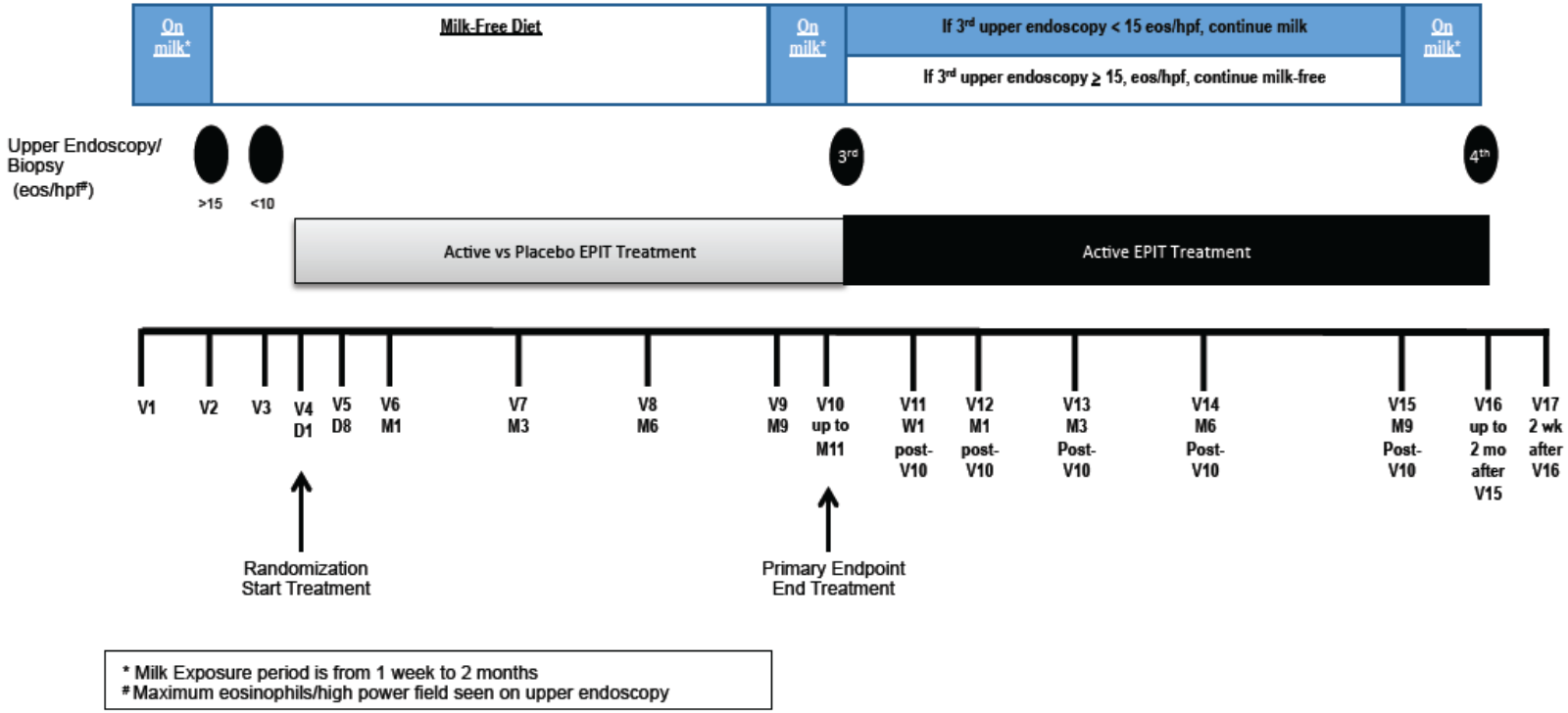
*During screening, a minimum of two standard of care endoscopy procedures will be performed to obtain milk EoE diagnostic results needed for study qualification. Scopes may be repeated if clinically necessary and may affect screening visit timelines and total time on study. The results of additional SOC endoscopies will be allowed to assess eligibility, if the endoscopies are required for clinical care purposes. The order of the endoscopies will be determined by clinical care.
**: Visit 4 can be performed as soon as the results of the upper endoscopy and biopsy at Visit 3 are available and confirmed eligibility into the study.
***: Procedures at Visit 17 have to be performed 2 weeks after Visit 16 for completers. These procedures have also to be performed for subjects prematurely withdrawing. This will also be their End of Study Visit.
****: Patients may be contacted via telephone calls or email between visits to monitor symptoms, when symptoms reoccur-research endoscopy will be scheduled. Telephone calls will be made monthly between visit 5 and 16
#: Milk free diet starts after the visit

*Milk free diet may be extended if additional SOC scopes are needed. As mentioned above, the order of the endoscopies will be determined by clinical care.
% Milk free if upper endoscopy ≥15 eosinophils/hpf isolated in the esophagus; may continue milk if upper endoscopy is <15 eosinophils/HPF in the esophagus

1. Including history of milk allergy and other allergies.
2. Including weight (kg) and height (cm).
3. Including a complete skin examination.
4. Heart rate, blood pressure, respiratory rate, temperature.
6. Laboratory tests. Hematology: hemoglobin, hematocrit, platelets, red blood cells, white blood cells. Biochemistry: aspartate aminotransferase, alanine aminotransferase, total bilirubin, total protein, blood urea nitrogen, creatinine.
7. Urine pregnancy test for female of childbearing potential only.
8. One Viaskin® patch will be applied each day: 6 h/day during the first week, 12 h/day during the second week and for an entire 24h daily from the third week (Day 15) onwards during the Double-Blind Treatment period. The first application of Viaskin® patch during the Open-Label Treatment period will occur at V10 with again progressive increase duration of patch application: 6h/day during the first week, 12h/day during the second week and for an entire 24h daily from the third week onward.
9. Check the reaction of the skin during the recommended period of observation of the subject on site at the following time points: 1 hour, 2 hours and 3 hours after the Viaskin® is applied depending on the required duration of observation at each visit;. Grading to be done per Section 11.13 Table5.
10. Patient may continue with milk introduction if improved on Viaskin® patch
11. Research bloods-TSLP, Epigenetics, T cell studies

V = visit, D = day, M = month, ET = Early Termination

Figure 1: Diagram of Study Design



* ≥15 eosinophils/hpf on upper endoscopy and biopsy is diagnostic of Eosinophilic Esophagitis; 0-10 eosinophils/HPF is considered normal

8.2 Discussion of Study Design

The current study is a pilot study powered to show statistical significance versus placebo. The design of this study is based on standard procedures used in clinic practice.

This study is also randomized and double-blinded with regard to treatment with Viaskin® Milk and matching placebo in order to prevent bias in treatment allocation and in the assessment of both safety and efficacy. The use of a placebo group in this trial is justified to obtain reliable scientific evidence for the evaluation of new medicinal products. The overall benefit to risk ratio for this trial is favorable. Subjects eligible to participate in this study must have a positive upper endoscopy with biopsy showing greater than or equal to 15 eosinophils/hpf when on milk containing diet, and that normalized (0-10 eosinophils/hpf) when milk was removed from the diet. The prospect of direct benefit is resolution of food allergy in EoE, which will be the first cure in the disease. The risk of the trial is due to the Viaskin® Milk EPIT patch, which resulted in non-serious adverse events in the phase 1 trial. The other risks are one research upper endoscopy with biopsies under sedation or general anesthesia, which the investigative team believes is a minor increase above minimal risk procedure when done by board certified gastroenterologist. The second risk is reoccurrence of EoE symptoms in placebo group or non-responders. Therefore, we have incorporated a period of 1 week to 2 month to milk re-exposure to minimize symptoms of EoE. The primary endpoint in this study will be assessed at the end of the treatment period, after up to 11 months of EPIT treatment. After the initial double-blind phase, all subjects will receive open-label active treatment for up to additional 11 months for collection of safety and efficacy data.

8.3 Study Duration

The planned duration of the clinical study is approximately 3 years (Start-up + Screening period + Treatment period + Closeout). Subject participation will be approximately 2 years (including up to 3 months and 2 weeks screening period, 11 months treatment period, 11 month open label extension and 2-week follow-up). Recruitment into the study will stop when approximately 22 subjects have been randomized to treatment. The study will be stopped when the last subject receiving the double-blind treatment completes the study or when the last ongoing subject has discontinued treatment, whichever occurs first.

8.4 Study Population

Pediatric subjects (4 to 17 years old) with milk-induced Eosinophilic Esophagitis will be randomized in this study.

8.4.1 Inclusion Criteria

Subjects **MUST** satisfy all of the following entry criteria:

1. Subjects between 4 and 17 years of age at the time of signing the informed consent.
2. Well-documented symptoms suggestive of EoE after ingestion of milk and currently following a strict milk-free diet.
3. Upper endoscopy and biopsy at clinical evaluation during screening showing greater than or equal to 15 eosinophils/HPF isolated to the esophagus meeting the consensus diagnosis of Eosinophilic Esophagitis, after milk was re-introduced into the subject's diet (30 ml/day for 1 week to 2 months), while the subject was on proton pump inhibitor (PPI). Patients will be on PPI for the length of the study as that is standard of care for the treatment of EoE. A clinical decision has been made to perform a minimum of two standard of care endoscopy procedures to obtain milk EoE diagnostic results.
4. Upper endoscopy and biopsy at clinical evaluation during screening showing 0 to 10 eosinophils per HPF isolated to the esophagus after a minimum of 6 weeks under milk-free diet, and while the subject is on proton pump inhibitor. (Standard of care for EoE is an upper endoscopy with biopsies to evaluate for disease activity). A clinical decision has been made to perform a minimum of two standard of care endoscopy procedures to obtain milk EoE diagnostic results.
5. Negative pregnancy test for female subjects of childbearing potential. Females of childbearing potential must use effective method of contraception to prevent pregnancy and agree to continue to practice an acceptable method of contraception for the duration of participation in the study. Sexual abstinence will be accepted as an effective method of contraception for girls below 18 years of age.
6. Subjects and/or parents/guardians willing to comply with all study requirements during their participation in the study.
7. Signed informed consent from parent(s)/guardian(s) of children < 18 years + children's assent.
8. Subjects agree to maintain a constant diet during the trial, with the exception of milk.
9. Subjects will maintain constant medications for asthma and allergic rhinitis during the trial.

8.4.2 Exclusion Criteria

If any of the following apply, the subject **MUST NOT** enter the study:

1. Subjects with a history of severe anaphylaxis to milk with the following symptoms: hypotension, hypoxia, neurological compromise (collapse, loss of consciousness or incontinence), Quincke Edema or requiring intubation.
2. Active IgE- mediated milk allergy based on skin test or history.
3. Pregnancy or lactation.
4. Subjects with other eosinophilic gastrointestinal disorders.
5. Subjects on swallowed corticosteroids or anti-leukotrienes for Eosinophilic Esophagitis.
6. Subjects with symptomatic allergy to pollens whose symptoms during the corresponding pollen season might interfere with the recording of symptoms during the upper endoscopy/biopsy, if the upper endoscopy/biopsy is conducted during the pollen season. The Investigator will have to ensure that the period for conducting the upper endoscopy for such a subject will be outside of the pollen season.
7. Subjects treated with systemic long-acting corticosteroids (depot corticosteroids) within 12 weeks prior to Visit 1 and/or systemic short-acting corticosteroid within 4 weeks prior to Visit 1 or any systemic corticosteroid at screening.
8. Subjects with asthma conditions defined as follows:

a. Uncontrolled persistent asthma by National Asthma Education and Prevention Program Asthma guidelines (2007).
b. At least two systemic corticosteroid courses for asthma in the past year or one oral corticosteroid course for asthma in the past three months;
c. Prior intubation for asthma in the past two years.

9. Subjects on β-blocking agents, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers or tricyclic antidepressant therapy.
10. Subjects undergoing any type of immunotherapy to any food (oral immunotherapy, sublingual immunotherapy, specific oral tolerance induction) within one year prior to Visit 1.
11. Subjects presently on aeroallergen immunotherapy and unwilling or unable to discontinue.
12. Subjects currently treated with anti-tumor necrosis factor drugs or anti-IgE drugs (such as omalizumab) or any biologic immunomodulatory therapy within one year prior to Visit 1.
13. Allergy or known hypersensitivity to the Viaskin® patch material or excipients.
14. Allergy or known history of reaction to Tegaderm® with no possibility to use an alternative adhesive dressing allowed by the Principal Investigator.
15. Subjects suffering from generalized dermatologic diseases (e.g. severe atopic dermatitis, uncontrolled generalized eczema, ichthyosis vulgaris) with no intact skin zones to apply the Viaskin®, or urticarial and mast cell disorders such as chronic idiopathic urticaria.
16. Subjects (or parents of subjects) with obvious excessive anxiety and unlikely to cope with the conditions of an upper endoscopy and biopsy.
17. Past or current disease(s), which in the opinion the Principal Investigator, may affect the subject's participation in this study including but not limited to active autoimmune disorders, immunodeficiency, malignancy, uncontrolled diseases (hypertension, psychiatric (especially anxiety), cardiac), or other disorders (e.g., liver, gastrointestinal, kidney, cardiovascular, pulmonary disease, or blood disorders).
18. Any history of drug or alcohol abuse in the past five years.
19. Subjects unable to follow the protocol and the protocol requirements.
20. Participation in another clinical intervention study in the three months prior to Visit 1.
21. Subjects on any experimental drugs or treatments.

8.4.3 Withdrawal and Replacement of Subjects

8.4.3.1 Criteria for Subject Withdrawal

In accordance with the Declaration of Helsinki (Appendix 1) and other applicable regulations, a subject has the right to withdraw from the study at any time for any reason without prejudice to his or her future medical care by the physician or at the institution.

Subjects may withdraw from the study/schedule of assessments for any of the following reasons:

- Adverse Event. The patch treatment will be temporary discontinued for any subject with Grade 4 local skin reactions possibly, probably, or definitely related to the investigational product.
- A subject will be discontinued from further participation in the study for >2 grade 4 local skin reaction possibly, probably or definitely related to investigational product

- The Investigator decides that it is the subject's best interest to be withdrawn from the study.
- The subject is unwilling to continue in the study (consent withdrawal).
- Lack of compliance with protocol requirements and procedures.
- The Sponsor- Investigator or Regulatory Authorities, for any reason, stops the study.
- The subject fails to return to the clinic for scheduled visits and does not respond to telephone or written attempts at contact (lost to follow-up).
- Subject's death

The reason for withdrawal will be recorded in the clinical records and the electronic Case Report Form (eCRF) and reported annually in the IND Annual Report (21 CFR 312.33). All subjects who are withdrawn or discontinue should be provided with alternative medical care, if applicable.

8.4.3.2 Study Stopping Rules

Study enrollment will be suspended pending an expedited safety review by an independent DSMB if any of the following occur:

1. Any death related to Viaskin® dosing.
2. Any Stage 3 anaphylaxis related to Viaskin® application.
3. Marked increase in EoE symptoms with daily vomiting or severe abdominal pain in more than one patient
4. ≥ 1 SAE related to the investigational product or a study intervention
5. ≥ 2 Grade 3 AEs related to the investigational product

Upon safety review, one of the following outcomes will be determined:
- Accrual to the study may continue without modification.
- Accrual to the study may continue with modifications as prescribed by the DSMB.
- Accrual to the study should be discontinued.

All actions will be reported in compliance with local and federal regulations.

8.4.3.3 Evaluations at Withdrawal

For any subject who is withdrawn before completing all study visits, the Investigator should:
- Perform an end of study visit: all subjects who are withdrawn early from the trial will undergo the procedures planned for Visit 17 (see Section 9). End of study visits will be performed no later than 2 weeks after withdrawal/discontinuation.
- Complete all appropriate subject Diary and eCRF pages, providing the date and explanation for the subject's withdrawal/discontinuation.
- When indicated, arrange for appropriate follow-up and/or alternative medical care of the discontinued subject.

If the subject fails to attend for a scheduled end of study visit, there will be at least two attempts to contact the subject via telephone and written communication. If these receive no reply, the subject will be considered lost to follow-up.

8.4.3.4 Replacement of Subjects

Subjects who are withdrawn after beginning the treatment phase of the study will not be replaced. However, sufficient subjects will be included to ensure the minimum sample size (see Section 12.2).

8.5 Treatment

8.5.1 Treatments Administered

The Investigator must ensure that the investigational product will be used only in accordance with the protocol.

Following the confirmation of milk-induced Eosinophilic Esophagitis at screening, subjects will be randomized in a 3:1 ratio at Visit 4 (Day 1) into two different double-blind treatment groups to receive EPIT with Viaskin® Milk (500 µg of milk proteins**)** or placebo.

Repeated daily application will be made from Day 1 up to Month 9 at which time milk will be re-introduced into the diet of the subjects. The treatment will then continue during the milk re-introduction period (for 1 week to 2 months) up to the last endoscopy and biopsy. In total, the subjects can therefore receive the study treatment for up to 11 months.

Application of the Viaskin® patch will be made with progressive increase duration of application at the start of treatment: 6 hours/day during the first week, 12 hours/day during the second week, and for an entire 24 hours daily from the third week (Day 15) onwards. During the period of 24 hours of daily application, flexibility of 24 hours ± 4 hours of daily application is permitted.

For all subjects (4-17 years), the patch will be applied on each side of the spine in the inter-scapular area. The specific place where one Viaskin® is administered will represent a “Zone”. In total, six zones will be used in each subject to apply the Viaskin® : the first Viaskin® will be applied on zone 1, the second Viaskin® on zone 2 (after removal of Viaskin® 1), etc. until all six zones have been used, and the dosing will continue with zone 1, zone 2 etc.

O 1	O 4
O 2	O 5
O 3	O 6

Once applied to the skin, Tegaderm® must be used to cover the Viaskin® to prevent it from coming off. Other dressings could also be used as an alternative to Tegaderm® as allowed by the Principal Investigator.

In case the Viaskin® comes off, or after removing a Viaskin®, it is recommended that the subjects or subject's parent(s) thoroughly wipe off the zone with a moist disposable napkin or a disposable tissue and wash their hands to prevent accidental transmission of allergenic protein. If possible, the subject could take advantage of their shower time to change the Viaskin®. The previous Viaskin® is removed before the shower (or bath) and discarded, and the new one applied a few minutes after the shower (or bath) and after careful drying the skin.

The time of application and removal of each Viaskin® will be noted on the subject diary cards (see Section 10.10), along with any observed AE(s) (local and/or distant). Application of the Viaskin® at a similar time for each application (am or pm) is recommended.

After Visit 10, all subjects will continue treatment with open-label Viaskin® Milk 500 µg for up to 11 additional months. It is permitted at the discretion of the Investigator, to postpone the application of the first patch up to a maximum of 7 days after V10.

To increase the safety of subjects at the beginning of the open-label treatment period, in particular for subjects crossing over from placebo to the active Viaskin Milk treatment, the daily duration of application will again be adapted from Visit 10 for the first weeks of treatment: 6 hours/day during the first week, 12 hours/day during the second week, and for an entire 24 hours daily from the third week onwards. During the period of 24 hours of daily application, flexibility of 24 hours ± 4 hours of daily application is permitted.

8.5.2 Study Treatment Formulation

Viaskin® Milk will be administered using the Viaskin® epicutaneous delivery system. Viaskin® Milk contains a dry deposit of milk protein formulated without adjuvant. The Viaskin® is round-shaped. The inner part of the Viaskin® Milk has a diameter of 24 mm (4.5 cm^2 surface area). In this inner part, the milk allergen extract is deposited by electrospraying the liquid milk protein formulation, which dries instantly. The outer adhesive part of the Viaskin® is composed of a 3 mm wide band of adhesive foam to stick to the skin. The outer part of the Viaskin® Milk has a diameter of 30 mm.

The placebo treatment will consist of a similar formulation, but will be devoid of milk proteins. Once applied to the skin, the hypoallergenic adhesive film TegaDerm® must be used to cover the Viaskin® to prevent it from coming off. Other dressings could also be used as an alternative to Tegaderm® as allowed by the Principal Investigator.

AMATSI, Saint Gély du Fesc, France, will manufacture both the active and placebo Viaskin® in accordance with the requirements of Good Manufacturing Practices (GMP) and will perform the primary packaging activities (i.e. place one Viaskin® patch per pouch).

8.5.3 Study Treatment Labelling and Packaging

The secondary packaging and pharmaceutical release activities will be performed by CREAPHARM (Le Haillan, France). This manufacturer will label and package the investigational product: the containing boxes as well as each pouch will be labeled. The labeled pouches will be placed in labeled treatment boxes/kits to be delivered to subjects at each visit, with enough quantity

of Viaskin® to cover the period between two consecutive visits. The labeled and packaged investigational product will be stored according to the requirements of GMP under the storage conditions established by stability studies performed with Viaskin® Milk.

Upon reception at the clinical site, the study drug will be stored in the Investigational Pharmacy. The pharmacist will receive and store the study drug until the time of dispensing to the Investigators. Patients will return unused patches and they will be destroyed by Investigational Pharmacy. At the end of the study, the pharmacist will be responsible for destroying any unused investigational product and will provide a corresponding certificate of destruction.

8.5.4 Blinding of Study Medication

This is a randomized, double-blind, placebo-controlled study with limited access to the randomization code. Active and placebo Viaskin® will be similar in physical appearance. The treatment each subject will receive will not be disclosed to the Investigator, study center personnel, subject, Sponsor or their representatives. The treatment codes will be held according to the interactive Web response system (IWRS).

The second phase of the study will be on open-label extension with all patients receiving unblinded Active Viaskin® milk patch. There will be no blinding of study medication during this part of the study.

For details of the emergency procedure for unblinding of individual subjects, see Section 8.5.10, below.

8.5.5 Study Treatment Storage and Accountability

It is forbidden to use investigational drug material for purposes other than as defined in this protocol.

8.5.5.1 Study Treatment Storage

All investigational product will be stored between 2°C to 8°C ([35.6ºF to 46.4ºF]; see USP Controlled Room Temperature) until time of dispensing. However, storage at ambient temperature for short and/or intermittent periods of time, including transportation is accepted.

8.5.5.2 Study Treatment Accountability

All supplies of Viaskin® (active and placebo) will be accounted for in accordance with GCP. There will be an individual study drug accountability record for each subject and the Investigator will maintain accurate records of the disposition of all trial medication supplies received during the study. These records will include the amounts and dates that clinical drug supplies were received, dispensed to the subject, returned by the subject, and returned to the Investigator or destroyed on site. The unused Viaskin patches will be returned on subsequent study visits. The excessive and used study drug will be destroyed by The Children's Hospital of Philadelphia Research Pharmacy using standard protocols. The research pharmacist will provide a corresponding certificate of destruction.

8.5.6 Dose Adjustments and Dose Escalation

No dose adjustments or dose escalation are planned apart from the adjustment in the duration of application during the first weeks of treatment.

Even though the subjects should ideally reach the daily 24-hour application regimen from the 15th day of patch application onwards, for subjects who may experience some severe local reactions at the initiation of the treatment, the daily duration of patch application should be adapted/reduced if necessary, to limit the severe reactions.

In case of local unbearable skin reactions or in case of systemic allergic reactions, the Viaskin® patch should be removed immediately in order to allow the reactions to subside rapidly. The next patch would be re-applied only the following day at the expected time and the reactions will be observed. If or when the local severe reactions recur, the patch can be removed at that time. This process can be repeated the following days until the time the subject can bear the patch for 24 hours a day.

If a subject is having systemic symptoms including worsening of EoE symptoms, the subject will have return for study visit and possible decrease in daily exposure to the Viaskin patch with gradually increase in exposure as tolerated.

Only one dose is being investigated in this pilot study, at the highest dose of Viaskin Milk currently under development (500 µg of cow's milk proteins) due to the limited number of subjects to be recruited.

8.5.7 Prior and Concomitant Therapy

All medications used in the last 6 months or being administered at the time of screening and along the study will be recorded on the appropriate eCRF pages.

Application of a topical corticosteroid to treat any local AE (eczematous lesions, pruritus, edema, etc.) is allowed. An ointment with 1% hydrocortisone will be distributed to each randomized subject at discharge on Day 1 (V4). In case the 1% hydrocortisone ointment is not sufficient to treat the local reaction, an ointment containing a more potent corticosteroid can be prescribed and locally applied. Should skin reactions not be resolved by topical steroid, see Section 8.5.6 above.

Oral antihistamine or oral corticosteroids are allowed to treat AE determined as being allergic reactions. These treatments should be limited in time and stopped as soon as the AE has resolved. The Investigator will determine the best choice of treatment(s), the dose and the regimen according to the subject's age, and the type and the degree of severity of the reaction. Cetirizine is recommended as the oral antihistamine of choice. Medications will be documented in the concomitant medication log (including dosage, duration, and indication.). It is expected the subjects will maintain constant medications for asthma and allergic rhinitis during the trial.

All other treatments prescribed by the Investigator or any other physician to treat an AE are also permitted. Administration of concomitant medications must be reported in the appropriate section of the eCRF along with dosage information, dates of administration, and reasons for use. Generic names for concomitant medication should be used. The total daily dose should be provided.

Prohibited Treatments during participation in the study include:

- Any investigational drug or device other than Viaskin Milk or placebo
- Swallowed corticosteroids or anti-leukotrienes
- Beta-blocking agents, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers or tricyclic antidepressant therapy
- Immunotherapy to any food or aeroallergens
- Anti-TNF or anti-IgE drugs (such as omalizumab), or any other biologic immunomodulatory therapy

8.5.8 Treatment Compliance

It is the Investigators' responsibility to ensure that subjects are correctly instructed on how to take their study medication. Records of study medication used and intervals between visits will be kept during the study. Subjects will be asked to return their unused medication (box(es)) when they come back for their study visits. All unused medication (boxes) should be returned at the end of the study. The study drug will be dispensed by the Investigator, or by a qualified individual under the Investigator's supervision. An up-to-date treatment inventory/dispensing record must be maintained (see Section 8.5.5.2).
At each visit, prior to dispensing trial medication, previously dispensed trial medication will be retrieved by the Investigator and compliance assessed. A compliance of > 80% over the treatment period is sought. Subjects exhibiting poor compliance as assessed by counts and response to the question "Did you take your Viaskin® regularly?" will be counseled on the importance of good compliance to the study dosing regimen.

Non-compliance is defined as taking less than 80% of trial medication during any evaluation period (visit to visit). Subjects who are persistently non-compliant may be withdrawn from the study.

8.5.9 Assignment to Treatment

Throughout the screening period until allocation of a treatment number or treatment kit, subjects will be assigned a screening number. The screening number will be a number combining the site number plus the number assigned to a subject according to her/his chronological order of screening at that site. The screening number will be used as the subject identifier throughout the study. An IWRS will randomize subjects and assign the appropriate treatment number or kit number.

8.5.10 Unblinding Procedures

In case of emergency, the Principal Investigator can ask for unblinding of a subject, i.e., informing the nature of the investigational product (active or placebo) to which the subject has been assigned. Such procedures should only be utilized in emergency situations when the identity of the treatment

group must be known by the Investigator in order to provide appropriate medical treatment. Before unblinding the subject, the unblinding request will be sent to the chair of the DSMB, Stacie Jones, MD. She will notify the study investigator, Dr. Cianferoni, if the unblinding is necessary for treatment. The unblinding will be done by our pharmacovigilance agent, Jennifer Heimall, MD.

Reasons for unblinding must be clearly explained and justified in the eCRF, along with the date on which the subject was unblinded.

Unblinding of the study can also be done at the request of the regulatory agency or DSMB at any point in the study for safety or other concerns. In this case, unblinding will be done by our pharmacovigilance agent, Jennifer Heimall, MD.

8.6 Efficacy and Safety Variables

8.6.1. Efficacy Measurements

8.6.1.1 Primary Efficacy Endpoint:

The primary efficacy endpoint will be each patient's maximum esophageal eosinophil count on all specimens obtained on the biopsy at the end of treatment (Visit 10), after milk reintroduction at Visit 9.

8.6.1.2 Secondary Efficacy Endpoints:

The following secondary efficacy endpoints will be assessed:

- The symptom score at the end of each treatment period at 11 and 22 months.
- The change in symptom score at the end of each treatment period at 11 and 22 months compared to baseline.
- Mean Esophageal Eosinophil Count which is the average of all of the samples taken at the end of each treatment period at 11 and 22 months.
- Percentage of subjects with ≤1 eosinophils/HPF (excellent response) at the end of each treatment period at 11 and 22 months.
- Percentage of subjects with 2-14 eosinophils/HPF (good response) at the end of each treatment period at 11 and 22 months.
- Percentage of subjects with ≥15 eosinophils/HPF (poor response) at the end of each treatment period at 11 and 22 months.
- Change in mean and maximum esophageal eosinophil count from baseline to the end of each treatment period at 11 and 22 months.
- Esophageal Endoscopy Score at the end of each treatment period at 11 and 22 months.
- Change in Esophageal Endoscopy score from baseline to the end of each treatment period at 11 and 22 months.
- Change in the Eosinophilic Esophagitis Quality of Life Score from baseline to the end of each treatment period at 11 and 22 months.
- Combination Score of four measures (Eosinophils/HPF, EREFS, investigator assessment and parental assessment of symptoms)
- Time to development symptoms after milk reintroduction at month 9 and 20.

- Changes in exploratory biologic markers, including T-regulatory cells, TSLP, CBC with differential and milk-specific Immunoglobulin level, as well as epigenetics.

8.6.2 Safety Measurements

The following safety criteria will be determined:

- Adverse events (AEs) and Serious Adverse Events (SAEs) by system organ class, preferred term, severity and relatedness to Viaskin® Milk.
- Duration of local Viaskin® Milk-induced AEs, as assessed by the subjects.
- Use of medications to control local AEs.
- Systemic allergic symptoms and relatedness to Viaskin® Milk.
- Laboratory data, physical examinations and vital signs.

9. STUDY EVALUATIONS BY VISIT

Subjects with known established Eosinophilic Esophagitis (EoE) based on 2011 consensus diagnosis criteria will be considered for participation in the study. All subjects for whom a written informed consent has been obtained will enter the screening period, and only subjects who fulfill all eligibility criteria will be eligible and randomized for the double-blind treatment period. The duration of the screening period may vary among subjects and will be dependent of the exact duration of the milk-introduction period (from 1 week to 2 months) and of the duration of the milk- diet period (minimum of 6 weeks).

All screening records for potential eligibility by the gastroenterology collaborators will be reviewed and confirmed before entry into the double-blind treatment period; thereafter, dates of all study visits will be scheduled relative to the date of entry into the double-blind treatment period (Visit 4).

9.1 Visit 1: Screening

At the time of the screening Visit 1, the following assessments/procedures will be performed:

- Signed written informed consent for screening questionnaires, CBC, CMP and chart review. Medical history (including milk allergy history, other allergies, diet history).
- Demographics (including weight in kg and height in cm).
- Physical examination (including a complete skin examination).
- Vital signs (including heart rate, blood pressure, respiratory rate, and temperature).
- Eosinophilic Esophagitis Symptom Score (see Section 11.12).
- Blood collection for laboratory tests (hematology, biochemistry).
- Urine pregnancy test for female of childbearing potential.
- Milk introduction (30 ml/day for 1 week to 2 months) while the subject is on a proton pump inhibitor.
- Dietary History.
- Record all AEs (volunteered or in response to an open question) since the ICF was signed.

- Record prior (over last six months) and all concomitant medications.

9.2 Visit 2: Screening; 1 week to 2 months after Milk Re-Introduction

Subjects will have a minimum of two standard of care upper endoscopies and biopsy performed to confirm the diagnosis of Eosinophilic Esophagitis. They will have an upper endoscopy from 1 week to 2 months after introduction of a minimum of 30 ml of milk daily into their diet, and while on proton pump inhibitor. When the subjects are symptomatic, they will have an endoscopy 1-2 weeks after symptoms occur. We will review the medical records to review the number of eosinophils in the esophageal biopsy. Research parts of the visit will include EoE Quality of life measures and research blood samples. Subjects' clinical care GI and Allergy physicians will determine the order of screening standard of care endoscopies.

The following assessments/procedures will be performed:
- Physical examination (including a complete skin examination).
- Vital signs (including heart rate, blood pressure, respiratory rate, and temperature).
- Eosinophilic Esophagitis Symptom Score (see Section 11.12).
- Milk-free Diet.
- Diet History.
- Eosinophilic Esophagitis (Age-specific) Quality of Life Measure (Appendix 2).
- Upper endoscopy and biopsies of the esophagus, stomach and duodenum (see section 11.8) with upper endoscopy score (Appendix 2).
- Record all AEs (volunteered or in response to an open question).
- Record of all concomitant medications.

9.3 Visit 3: Screening; Minimum 6 weeks after Removing Milk

Subjects will have a minimum of two standard of care upper endoscopies and biopsy to confirm milk induced EoE performed, after a minimum of 6 weeks under milk-free diet and while on proton pump inhibitor. Results of the standard of care endoscopy and biopsy will be obtained by review of medical records. Research procedures at this visit include EoE Quality of life measure, and collection of any AEs. Subjects' clinical care GI and Allergy physicians will determine the order of screening standard of care endoscopies.

The following assessments/procedures will be performed:
- Physical examination (including a complete skin examination).
- Vital signs (including heart rate, blood pressure, respiratory rate, and temperature).
- Eosinophilic Esophagitis Symptom Score (see Section 11.12)
- Eosinophilic Esophagitis (Age-specific) Quality of Life Measure (Appendix 2).
- Milk-free Diet
- Diet History
- Upper endoscopy and biopsies of the esophagus (see Section 11.8) with upper endoscopy score (Appendix 2)
- Record all AEs (volunteered or in response to an open question).
- Record of all concomitant medications.

9.4 Visit 4: Eligibility/Randomization Treatment Period; Day 1

Visit 4 corresponds to the first day of treatment.
The following assessments/procedures will be performed:

- Review Pathology reports of the upper endoscopy and biopsy. Confirm eligibility by chart review of clinical records/randomize subject.
- Physical examination (including a complete skin examination).
- Vital signs (including heart rate, blood pressure, respiratory rate, and temperature).
- Eosinophilic Esophagitis Symptom Score (see Section 11.12).
- Urine pregnancy test for female of childbearing potential.
- Milk-free Diet
- Dispense diary cards (instruct subject how to complete).
- Dispense the first treatment box of investigational product to the subject.
- The investigator will take one Viaskin® patch from the box, apply the first Viaskin® to the subject, and train the subject on the proper technique and timing for applying the other patches.
- The subject will remain either in the CHOP clinic exam room or in the waiting room for at least 3 hours under observation. Patients will regularly be assessed by study staff. Should a patient experience an adverse reaction, or emergency, the patch will immediately be removed and the site cleaned. Patient will then be treated per CHOP allergy clinic emergency procedures.
- Check the skin under the Viaskin® and grade any local skin reaction after 1 hour after the patch is applied (see Section11.13).
- Take a photograph of the site of application of the Viaskin® and keep it in the subject's medical records or source documents
- Record all AEs (volunteered or in response to an open question).
- Record all concomitant medication(s).

The subject may be discharged after a minimum observation period of 3 hours.

9.5 Visits 5, 6 and 7: Treatment Period; Day 8 (± 3 days), Month 1 (± 7 days), Month 3 (±14 days)

The following assessments/procedures will be performed:

- Physical examination (including a complete skin examination).
- Vital signs (including heart rate, blood pressure, respiratory rate, and temperature).
- Eosinophilic Esophagitis Symptom Score (see Section 11.12).
- Milk-free Diet
- Record all AEs (volunteered or in response to an open question).
- Record all concomitant medication(s).
- Dispense diary cards (re-instruct subject on use if necessary).
- Review 'diary' and ensure that the diary has been completed accurately and that the subject is comfortable with using the diary.
- Check unused medication and assess medication compliance.
- Dispense the new treatment box to subject. Apply one Viaskin® patch to subject.
- Check skin under the Viaskin® and grade any local skin reaction (see Section 11.13).
- Take a photograph of site(s) of application of Viaskin® and keep in the subject's medical records or source documents.

The subject may be discharged after a minimum observation period of 1 hour (for Visit 5 only). There is no specific observation period required for Visits 6 or 7.

9.6 Visit 8: Treatment Period; Month 6 (± 14 days)

The following assessments/procedures will be performed:
- Physical examination (including a complete skin examination).
- Vital signs (including heart rate, blood pressure, respiratory rate, and temperature).
- Eosinophilic Esophagitis Symptom Score (see Section 11.12)
- Blood collection for laboratory tests (hematology, biochemistry)
- Milk-free Diet
- Record all AEs (volunteered or in response to an open question).
- Record all concomitant medication(s).
- Dispense diary cards (re-instruct subject on use if necessary).
- Review 'diary' and ensure that the diary has been completed accurately and that the subject is comfortable with using the diary.
- Check unused medication and assess medication compliance.
- Dispense the new treatment box to subject. Apply one Viaskin® patch to subject.
- Check skin under the Viaskin® and grade any local skin reaction (see Section 11.13).
- Take a photograph of site(s) of application of Viaskin® and keep in the subject's medical records or source documents.

9.7 Visit 9: Treatment Period; Month 9 (±14 days)

The following assessments/procedures will be performed:
- Physical examination (including a complete skin examination).
- Vital signs (including heart rate, blood pressure, respiratory rate, and temperature).
- Eosinophilic Esophagitis Symptom Score (see Section 11.12)
- **Milk reintroduction (similar amount and duration as done during the screening period)** while the subject is on a proton pump inhibitor.
- Dietary History.
- Record all AEs (volunteered or in response to an open question).
- Record all concomitant medication(s).
- Dispense diary cards (re-instruct subject on use if necessary).
- Review 'diary' and ensure that the diary has been completed accurately and that the subject is comfortable with using the diary.
- Check unused medication and assess medication compliance.
- Dispense the new treatment box to subject. Apply one Viaskin® patch to subject.
- Check skin under the Viaskin® and grade any local skin reaction (see Section 11.13).
- Take a photograph of site(s) of application of Viaskin® and keep in the subject's medical records or source documents.

9.8 Visit 10: Treatment period; (1 week to 2 months after Visit 9, 3rd endoscopy)

Subjects will have an upper endoscopy and biopsy performed at this visit. They will have an upper endoscopy from 1 week to 2 months after reintroduction of a minimum of 30 ml of milk

daily into their diet, and while on proton pump inhibitor, as done during the screening period. When the subjects are symptomatic, they will have an endoscopy 1-2 weeks after symptoms occur.

The milk consumption should be equivalent to what the subjects were taking at the beginning of the study.

Visit 10 corresponds to the last day of double-blind treatment and the start of open-label treatment period. Standard Operating Procedures will be followed for endoscopy procedure[67]. Patients will need to be healthy for this procedure. Any subject who has had a viral upper respiratory infection or gastroenteritis within 7 days will need to be rescheduled.

The following assessments/procedures will be performed:
- Physical examination (including a complete skin examination).
- Vital signs (including heart rate, blood pressure, respiratory rate, and temperature).
- Eosinophilic Esophagitis (Age-specific) Quality of Life Measure (Appendix 2)
- Eosinophilic Esophagitis Symptom Score (see Section 11.12)
- Blood collection for laboratory tests (hematology, biochemistry)
- Urine pregnancy test for female of childbearing potential.
- Diet History
- Upper endoscopy and biopsies of the esophagus (see Section 11.8) with upper endoscopy score (Appendix 1)
- Record all AEs (volunteered or in response to an open question).
- Record all concomitant medications.
- Dispense diary cards (re-instruct subject on use if necessary).
- Review 'diary' and ensure that the diary has been completed accurately and that the subject is comfortable with using the diary.
- Check unused medication and assess medication compliance.
- Check skin under the Viaskin® and grade any local skin reaction (see Section 11.13)
- Take a photograph of site(s) of application of Viaskin® and keep in the subject's medical records or source documents.
- Dispense the new treatment box to subject. Apply one Viaskin® patch to subject. It is permitted at the discretion of the Investigator, to postpone the application of the first patch up to a maximum of 7 days after V10.

9.9 Visit 11: Treatment period; 8 days (±3 days) after visit 10

The following assessments/procedures will be performed:
- Physical examination (including a complete skin examination).
- Vital signs (including heart rate, blood pressure, respiratory rate, and temperature).
- Eosinophilic Esophagitis Symptom Score (see Section 11.12)
- **Milk diet options**
    - **If the 3rd upper endoscopy (Visit 10) has≥15 eosinophils/HPF isolated in the esophagus, the subject will stop milk consumption**
    - **If the 3rd upper endoscopy (visit 10) has < 15 eosinophils/HPF, the subject may continue milk consumption at the previous levels as per Investigator's recommendations.**
- Dietary History.

- Record all AEs (volunteered or in response to an open question).
- Record all concomitant medication(s).
- Dispense diary cards (re-instruct subject on use if necessary).
- Review 'diary' and ensure that the diary has been completed accurately and that the subject is comfortable with using the diary.
- Check unused medication and assess medication compliance.
- Dispense the new treatment box to subject. Apply one Viaskin® patch to subject.
- Check skin under the Viaskin® and grade any local skin reaction (see Section 11.12).
- Take a photograph of site(s) of application of Viaskin® and keep in the subject's medical records or source documents.

9.10 Visits 12, 13, and 14: Treatment Period; Month 1 (± 7 days), Month 3 (±14 days), Month 6 (±14 days),

The following assessments/procedures will be performed:
- Physical examination (including a complete skin examination).
- Vital signs (including heart rate, blood pressure, respiratory rate, and temperature).
- Eosinophilic Esophagitis Symptom Score (see Section 11.11).
- Milk-free Diet (if applicable)
- Record all AEs (volunteered or in response to an open question).
- Record all concomitant medication(s).
- Dispense diary cards (re-instruct subject on use if necessary).
- Review 'diary' and ensure that the diary has been completed accurately and that the subject is comfortable with using the diary.
- Check unused medication and assess medication compliance.
- Dispense the new treatment box to subject. Apply one Viaskin® patch to subject.
- Check skin under the Viaskin® and grade any local skin reaction (see Section 11.13).
- If the subjects develops symptoms of EoE, they may support milk during this period

9.11 Visit 15: Treatment Period; Month 9 (±14 days) after visit 10

The following assessments/procedures will be performed:
- Physical examination (including a complete skin examination).
- Vital signs (including heart rate, blood pressure, respiratory rate, and temperature).
- Eosinophilic Esophagitis Symptom Score (see Section 11.12)
- **Milk reintroduction (similar amount and duration as done during the screening period) if not already on milk**
    - **Otherwise, continue the current milk dose** while the subject is on a proton pump inhibitor.
- Dietary History.
- Record all AEs (volunteered or in response to an open question).
- Record all concomitant medication(s).
- Dispense diary cards (re-instruct subject on use if necessary).
- Review 'diary' and ensure that the diary has been completed accurately and that the subject is comfortable with using the diary.
- Check unused medication and assess medication compliance.

- Dispense the new treatment box to subject. Apply one Viaskin® patch to subject.
- Check skin under the Viaskin® and grade any local skin reaction (see Section 11.13).
- Take a photograph of site(s) of application of Viaskin® and keep in the subject's medical records or source documents.

9.12 Visit 16: Treatment period; 1 week to 2 months after Visit 15

Subjects will have an upper endoscopy and biopsy performed at this visit. They will have an upper endoscopy from 1 week to 2 months after reintroduction of a minimum of 30 ml of milk daily into their diet, and while on proton pump inhibitor, as done during the screening period. If subjects develop symptoms between visits 11 and 14, they will also restart milk with the same milk consumption should be equivalent to what the subjects were taking at the beginning of the study.

Visit 16 corresponds to the last day of treatment. Standard Operating Procedures will be followed for endoscopy procedure[67]. Patients will need to be healthy for this procedure. Any subject who has had a viral upper respiratory infection or gastroenteritis within 7 days will need to be rescheduled.

The following assessments/procedures will be performed:
- Physical examination (including a complete skin examination).
- Vital signs (including heart rate, blood pressure, respiratory rate, and temperature).
- Eosinophilic Esophagitis (Age-specific) Quality of Life Measure (Appendix 2)
- Eosinophilic Esophagitis Symptom Score (see Section 11.12)
- Blood collection for laboratory tests (hematology, biochemistry)
- Urine pregnancy test for female of childbearing potential.
- Diet History
- Upper endoscopy and biopsies of the esophagus (see Section 11.8) with upper endoscopy score (Appendix 1)
- Record all AEs (volunteered or in response to an open question).
- Record all concomitant medications.
- Dispense diary cards (re-instruct subject on use if necessary).
- Review 'diary' and ensure that the diary has been completed accurately and that the subject is comfortable with using the diary.
- Check unused medication and assess medication compliance.
- Check skin under the Viaskin® and grade any local skin reaction (see Section 11.13)
- Take a photograph of site(s) of application of Viaskin® and keep in the subject's medical records or source documents.

9.12.1 Telephone Calls:

- Patients will be called monthly between visit 5 and visit 16 to monitor for reoccurrence of symptoms while wearing the Viaskin® milk patch.
- When the subject has reoccurrence of symptoms after milk re-introduction (or maximum exposure of 2 months to milk), the research endoscopy will be scheduled.

9.13 Visit 17: End of Study; Visit 16 plus 2 weeks or Early Termination (± 3 days)

Visit 17 will be performed 2 weeks after Visit 16 for completers. This visit and assessments procedures have also to be performed for subjects prematurely withdrawn. This will be the End of Study Visit.

The following assessments/procedures will be performed:
- Physical examination (including a complete skin examination).
- Vital signs (including heart rate, blood pressure, respiratory rate, and temperature).
- Eosinophilic Esophagitis Symptom Score (see Section 11.11).
- Record all AEs (volunteered or in response to an open question).
- Record all concomitant medication(s).
- Collect and review 'diary' and ensure that the diary has been completed accurately.
- Check skin where the Viaskin® patch was applied and grade any local skin reaction (see Section 11.13).
- Take a photograph of site(s) of application of Viaskin® and keep in the subject's medical records or source documents.

Additional days up to 21 days may be added to visit period if due changes in patient's school calendar, vacation, or illness.

10. RISK AND RISK-BENEFIT RATIO

10.1 Risks from epicutaneous immunotherapy (EPIT).

In the previous pilot clinical study in cow's milk-allergic children with a related drug product (patch test with the same technology as diallertest), there was no serious AEs reported during the trial and no child required interruption of treatment because of an AE. The expected Adverse reactions with Viaskin Milk during EPIT are described in the Viaskin Milk Investigator's Brochure.

The potential risks observed in other Viaskin studies have been primarily localized dermatitis not considered serious in any subjects. There have been no reports of systemic reactions with Viaskin patch. But, if systemic reactions occurred in this study, the symptoms would be worsening EoE with abdominal pain and possible vomiting.

10.2 Risks from Upper Endoscopy and Biopsy.

The safety of multiple biopsies is supported by studies on adult patients with Barrett's esophagus that have shown that multiple esophageal biopsies (as many as 35 to 120 esophageal biopsies in an individual patient) do not produce esophageal perforation or bleeding when performed by an experienced team of physicians, nurses, and technicians[68]. In addition, a recent NIH study demonstrated that obtaining multiple mucosal biopsies for research purposes during elective endoscopy is well-tolerated and appears to have no more than minimal risk without appreciably increasing the risk of otherwise routine endoscopy[69]. Importantly, there was no statistically

significant association between the number of biopsies, type of procedure, anatomic location of research biopsies, endoscopist, or the use of nonsteroidal anti-inflammatory drugs and the risk of complications.

The incidence of perforation associated with upper endoscopy was recently reviewed in an 11 year retrospective study at CHOP. A total of 21,345 esophagogastroduodenoscopy (EGD) were performed between February 1998 and November 2008 including patients with esophageal strictures or crepe-paper esophagus. Three perforations occurred with EGD (0.02%, 95% CI 0-0.04%), and 2 with colonoscopy (0.04%, 95% CI 0-0.11%). Two of the three EGD-related perforations occurred after therapeutic EGD (foreign body removal, and dilatation of a proximal esophageal stricture and esophageal web removal), for an incidence of 0.18% (95% CI 0-0.47%). **None of the EGD-related perforations was the result of esophageal mucosal biopsies.** The presence of crepe-paper esophagus or strictures does not increase the risk for EGD-related perforations based on this review, thus these patients were not excluded from our proposed cohort. Identified risk factors for perforation on diagnostic (non-therapeutic) endoscopy were Crohn's disease (2 colonoscopy perforations) and severe hemorrhagic gastritis (1 EGD perforation of the stomach). The incidence of perforation associated with pediatric gastrointestinal endoscopy performed by pediatric gastroenterologists in this case series from CHOP was low and less than that previously reported in adults. Based upon this retrospective study, the estimated incidence of perforation from EGD at CHOP is 1 in 7,115 EGD procedures.[70,71]

There are standard risks from moderate intravenous sedation or general anesthesia for the one research biopsy. To minimize the risks, all anesthesia will be done by pediatric anesthesiologist. For the intravenous sedation, the risk of assisted ventilation is 0.1-0.2% and no patients have required intubation and no history of permanent injury based on current literature. For general anesthesia, the overall risk for a serious adverse event is 1/250,000. Total adverse events with nausea and vomiting being the most common are seen in 1/29 cases[72-74].

Since the EGD procedure with biopsy is conducted under conscious sedation or anesthesia, this needs to be considered for the total risk assessment. The investigative team considers the overall risk of the single research EGD procedure with biopsy under conscious sedation or anesthesia to be at most a minor increase above minimal risk[75].

10.3 Risk-Benefit Ratio

While subjects in the active arm are in a study group that is exposed to greater than minimal risk, there is the prospect of direct benefit, in that these subjects may potentially be cured of milk-induced Eosinophilic Esophagitis or have reduced symptoms. Currently, the only therapy for this life-long disease is milk avoidance or off-label use of topical steroids. In addition, there will be additional knowledge gained about the disease and potential development of tolerance in Eosinophilic Esophagitis.

Both patients on the placebo arm and non-responders to therapy, we may have exacerbations of EoE symptoms including abdominal pain, and vomiting. To minimize this issue, we are using 3:1 randomization of active to placebo therapy. Also, we have incorporated a period of 1 week to 2 month to milk re-exposure to minimize symptoms of EoE.

The placebo arm will be at risk of the single research endoscopy with biopsy under sedation or anesthesia, which the investigative team believes is a minor increase above minimal risk. This arm will help inform the natural history of the disease and will serve as a meaningful control group. There is no treatment for the disease other than that outlined in section 6.2. Thus, avoidance of milk would be the continued recommendation for the placebo study arm. If the therapy is effective, the placebo subjects may benefit of the active treatment during the open-label treatment period.

In summary, the risks include application of Viaskin® Milk EPIT patches and the two research upper endoscopies and biopsies under conscious sedation or anesthesia. The main risk from the EPIT include rashes with local erythema or other local skin reactions, but serious adverse reactions cannot be excluded. Based on the experience at CHOP, the risk from upper endoscopy with biopsy under sedation or general anesthesia is a minor increase above minimal. Therefore, there is a prospect of direct benefit for the treatment arm with greater than minimal risk to these subjects, while there is no prospect of direct benefit for the placebo arm during the double-blind period, with minor increase above minimal risk.

11. METHODS OF ASSESSMENT

11.1 Medical History

Complete medical history will include history and duration of all allergies (including milk allergy) and current medical conditions, number of allergic reactions and treatments in the previous 12 months, past or present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, psychiatric, and genitourinary disorders, drug and surgical history and any other diseases or disorders.

11.2 Pregnancy Test

Pregnancy will be determined by evaluation of urine pregnancy tests. Subjects who are pregnant at screening are excluded from the study. Subjects who become pregnant during treatment must be discontinued from the study.

The Principal Investigator will collect information on any female subject who becomes pregnant while participating in this study. The subject will also be followed to determine the outcome of the pregnancy.

11.3 Physical Examination

Physical examinations will be performed by a physician or nurse practitioner and will include examination of the following: general appearance, head, ears, eyes, nose and throat, neck, complete skin examination, cardiovascular system, respiratory system, abdominal system and nervous system. For each body system an assessment of normal or abnormal will be recorded in the eCRF at screening and the abnormality will be documented. During the study, any clinically relevant changes observed during physical examinations will be reported as AEs.

Physical examinations must be performed before the upper endoscopy/biopsy.

11.4 Vital Signs and Weight

Vital signs will include sitting systolic and diastolic blood pressure, heart rate, respiratory rate and temperature. Systolic blood pressure and diastolic blood pressure will be measured on the same arm after the subject has been in a sitting position for 5 minutes. Heart rate will be recorded simultaneously with blood pressure measurements, followed by respiratory rate and body temperature.

Body weight (kg) will be measured without shoes or jacket. Height (cm) will be determined at screening.

During the study, the measurement of vital signs may be repeated at the discretion of the Investigator for safety reasons. Clinically relevant abnormal findings will be reported as AEs.

Vital signs must be performed before the upper endoscopy/biopsy.

11.5 Eosinophilic Esophagitis Quality of Life

Quality of life is a measurement of a subject's overall well-being. QOL will be measured by the validated age specific Eosinophilic Esophagitis tool for 5-7 years of age, 8-12 years of age, and 13-18 years of age (Appendix 2) developed by Franciosi and colleagues, based on the age of the subject at Visit 2. The subjects will complete the same questionnaire throughout the study.

11.6 Clinical Laboratory Testing

Venous blood samples will be taken for hematology and biochemistry testing. The following parameters will be determined:
Hematology: hemoglobin, hematocrit, platelets, red blood cells, white blood cells.
Biochemistry: aspartate aminotransferase, alanine aminotransferase, total bilirubin, total protein, blood urea nitrogen, creatinine.

Analysis of blood samples will be conducted by CHOP laboratory. Fresh blood will be collected from the above described patients per above protocol. Blood (max lesser of 50 ml or 3 ml/kg in a 6-8 week period) will be obtained by venipuncture during outpatient visit or obtained by IV during endoscopy procedure. Blood will be collected only after informed consent/assent is given. Participants will be given an opportunity and the time of consent to opt in or opt out of future use in subsequent research. The estimated volume of blood collected from each subject during the entire (22 month) study will be approximately 215mL.Additional and repeat laboratory safety testing may be performed at the discretion of the Investigator.

11.7 Research Laboratory Testing

Research labs include TSLP, Epigenetics, and T cell studies. They will be processed and stored at the Cianferoni Research Laboratory at the Children's Hospital of Philadelphia.

11.8 Upper Endoscopy with Biopsy

All subjects will undergo a minimum of four upper endoscopies with biopsies during their participation in the study (two each of proximal and distal, plus any inflamed areas) as per standard clinical practice: at least two at Screening as Standard of Care (Visit 2 and Visit 3) and two at the end of each treatment period as Research (Visit 10 and Visit 16). The results of additional SOC endoscopies will be allowed to assess eligibility, if the endoscopies are required for clinical care purposes The samples will be processed by the Department of Pathology at The Children's Hospital of Philadelphia and the number of eosinophils will be counted using hematoxylin and eosin stain. The handling of samples will be done following ASGE Standard on Endoscopic Mucosal Tissue Sampling.[67]

Upper endoscopy will be scored using a validated standardized measure. [57] The measure examines four major esophageal features (rings, furrows, exudates and edema) and the presence of minor features of narrow caliber esophagus, feline esophagus, stricture and crepe paper esophagus. The features are graded:

- Rings (0-none, 1 mild, 2-moderate, 3-severe)
- Exudates (0-none, 1-mild, 2-severe)
- Furrows- (0-mild, 1-present)
- Edema- (0-mild, 1-present)
- Stricture (0-mild, 1-present)
- Crepe paper esophagus (0-mild, 1-present)

11.9 Histological Evaluation

Prior to randomization, esophageal biopsy samples will be evaluated to confirm eligibility. Biopsy samples will be stained with hematoxylin and eosin stain. Intraepithelial eosinophils will be counted in all HPFs using 400X light microscopy. A HPF will be counted only if at least half of the field is occupied by tissue. The maximum eosinophil count per HPF will be reported for each esophageal biopsy site (at each of 2 levels). In addition to the evaluation for eosinophilia, all biopsy samples will be assessed for other histologic changes including epithelial hyperplasia, intercellular edema, and fibrosis. Histologic evaluation to be completed by a blinded Pathologist at CHOP.

At the end of each treatment period (Visit 10 and Visit 16), the esophageal biopsy specimens from all subjects will be evaluated in a blinded fashion by an independent pathologist. Specimens will be examined with respect to the maximum eosinophil counts and other histologic changes. Together with the EoE Clinical Symptom Score, the maximum eosinophil count per HPF for each specimen (from the total of all specimens) will be used to determine response to treatment.

The maximum eosinophil count will be defined as the highest number of eosinophils observed in any single HPF from an esophageal specimen. All specimens from all esophageal sites will be considered in determining the resolution of eosinophilia. A maximum eosinophil count will be recorded for the esophagus. The highest peak counts at a given timepoint (screening or end of each treatment visit) will be referred to as the maximum eosinophil count for that timepoint. The

mean Esophageal Eosinophil count will be the mean score of each of the high power fields from the all biopsy specimens.

As a confirmatory marker of EoE disease activity, we will use paraffin-embedded esophageal biopsies already obtained for routine clinical care to identify innate immune cell populations as well as chemokine expression through immunohistochemistry staining.

11.10 Diet Diary

Subjects will indicate the duration and amount of milk and milk products taken on a daily basis during the screening period and once milk is re-introduced into the subject's diet during the treatment period (Milk reintroduction at Visit 9 and Visit 15).

The milk introduction period and amount of milk and milk products taken should be the same, as much as possible, at both timeframes.

11.11 Subject Diary

Diary cards will be provided to each subject. Subjects will be asked to record on a daily basis in their diary cards for the first 3 months the time of application and removal of each Viaskin®, along with reason(s) for early removal (should that occur) and any observed AE(s) to the Viaskin® (local and/or systemic) or any other AEs. After 3 months, the subjects are instructed to report only the day/period when the patch was not applied as per protocol. Subjects will also be instructed to record any concomitant medication or treatment taken for any type of AEs.

The diaries may also be used to record the dietary information during the milk reintroduction periods at screening and at the end of treatment. In addition, the diary cards will also be used for the subjects to report any accidental consumption of milk that could have occurred in the study, during the milk-diet required period.

Subjects must bring their diary back to the Investigator at each visit, and the Investigator must check the diary for completeness and accuracy. It is the Investigators' responsibility to instruct the subject about the use of the diary, and to ensure that the subject completes the diary accurately. Any problems with completing the diary will be addressed with the subject. Completed pages of the diary cards will be collected and kept by the investigator at each visit. The remaining blank pages of the diary cards will be given back to the subject at each visit before discharge. All diary cards must be returned at completion of the study, or if the subject discontinues.

11.12 Eosinophilic Esophagitis Symptom Score

Symptoms of Eosinophilic Esophagitis range from abdominal pain, gastroesophageal reflux, vomiting, and difficult swallowing. The symptoms will range from none to very severe as in Spergel[54]. The symptoms will be in 3 categories and individual symptoms and total symptoms scores will be collected on a range of 0-4 (0-none, 1-mild, 2-moderate, 3-severe and 4-very severe).

Table 4: Eosinophilic Esophagitis Score

Symptoms	Score
Abdominal/Chest Pain	0-4
Vomiting/Regurgitation	0-4
Dysphagia	0-4
Total Score	0-12

11.13 Skin Reaction and Photography

Skin reactions under the Viaskin® will be graded (ideally by the same site person) at each visit according to the modified recommendations of the EAACI/GA^{2}LEN position paper in Turjanmaa et al (23):

Table 5: Skin Reaction Grading System

Grade	Skin Reaction
Grade 0	Negative
Grade 1	Only erythema, or erythema + infiltration
Grade 2	Erythema, few papules
Grade 3	Erythema, many or spreading papules
Grade 4	Erythema, vesicles

Viaskin® patches are transparent and the degree of local reactions under the Viaskin® can be easily seen. Grades of local skin reactions will be recorded after 3 hours of application for the first day of treatment (V4), after 1 hour of application at Day 8 of treatment (V5) and when subjects arrive for a visit for other protocol visits.

Photographic records will be taken of site(s) of application of the Viaskin® and filed in the subject's medical records or source document in case a further review of local reactions is required.

12. SAFETY MEASUREMENTS AND VARIABLES

12.1 Adverse Events Definition

An AE is any untoward medical occurrence that does not necessarily have a causal relationship with the investigational medicinal product. An AE can therefore be any unfavorable or unintended sign, including an abnormal laboratory finding, symptom or disease temporally associated with the use of an investigational medicinal product whether or not considered related to the investigational medicinal product.

AEs will be monitored throughout the entire study. Investigators will ask the subject at each visit if they have experienced any untoward effects since the last study visit. All AEs will be recorded on the eCRFs provided. A description of the event, severity, time of occurrence, duration, any action

(e.g. treatment and follow up tests) and the outcome should be provided along with the Investigator's assessment of the relationship to the study treatment.

AEs will be recorded from the time written screening informed consent is signed until the time of the End of Study visit. AEs still ongoing at the time of End of study visit will be followed for an additional period to encompass a total period of 14 days of AE follow-up after administration of the last dose of treatment.

If known, the name or diagnosis of the illness should be recorded, rather than a listing of individual signs or symptoms. AEs must be graded as being mild, moderate or severe and their start and end dates given. Definitions of severity are as follows:

Mild:	an AE usually transient in nature and generally not interfering with normal activities
Moderate:	an AE that is sufficiently discomforting to interfere with normal activities;
Severe:	an AE that is incapacitating and prevents normal activities.

Even if the Investigator feels there is no relationship to the study drug, all adverse experiences MUST be recorded in the eCRF. The Investigator is requested to assess the relationship of any clinical adverse experience to treatment using the following definitions:

Unrelated: those AEs which are clearly and incontrovertibly due to extraneous causes (concurrent drugs, environment etc.) and do not meet the criteria for drug relationship listed under Unlikely, Possible, Probable or Related.

Unlikely: an adverse experience may be considered unlikely if it includes at least the first two features:
- It does not follow a reasonable temporal sequence from administration of the 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 to the suspected drug.
- It does not reappear or worsen when the drug is re-administered.

Possible: an adverse experience may be considered possible if it includes at least the first two features:
- It follows a reasonable temporal sequence from administration of the drug.
- It could readily have been produced by the subject's clinical state, environment or toxic factors, or other modes of therapy administered to the subject.
- It follows a known response pattern to the suspected drug.

Probable: an adverse experience may be considered probable if it includes at least the first three features:
- 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 decreased on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the drug (e.g. bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc).
- It follows a known pattern of response to the suspected drug.

Related: an adverse experience may be considered related if it includes all of the following features:
- 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 decreased on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the drug. For example: bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.
- It follows a known pattern of response to the suspected drug.
- It reappears or worsens if the drug is re-administered.

12.2 Serious Adverse Events

A SAE is any untoward medical occurrence or effect that fulfills any of the following criteria:
- results in death;
- is life-threatening;
- requires hospitalization or prolongation of existing in-subject hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital abnormality/birth defect;
- important medical events not captured by the above but which may, for example, require medical intervention to prevent one of the outcomes above.

Events associated with hospitalization for the following will not be considered as an SAE:
a) Evaluation or treatment of a pre-existing condition and non-exacerbating condition as long as the condition(s) associated with the hospitalization: existed prior to the subject's entry into the study and has been recorded in the subject's medical history as documented in the eCRF (e.g. degenerative disease) has not worsened in severity or frequency during the subject's exposure to study medication has not required a change in treatment management during the subject's exposure to the study medication

b) Treatment which is elective or pre-planned of a pre-existing condition and non-exacerbating condition.

Unanticipated Problems Involving Risk to Subjects or Others:
Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related to participation in the research</u> (i.e. related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Unexpected, suspected adverse reaction: A suspected adverse reaction is considered "unexpected" if it is not listed in the general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

12.3 Reporting of Serious Adverse Events, Unanticipated Problems, and Serious Unexpected Suspected adverse reactions

This trial will be conducted under an investigator initiated IND held by Dr. Jonathan Spergel. The Principal Investigator will be responsible for the conduct of the trial and adherence to CHOP IRB SOP 408 Unanticipated Problems Involving Risks to Subjects and FDA Regulations 21 CFR 312.32 IND Safety Reporting. This includes but is not limited to collecting, assessing, reporting all adverse experiences, and monitoring/assessing the safety implications of any new pre-clinical, clinical, or manufacturing updates that occur during the course of the study investigation. If the Principal Investigator determines the new information significantly impacts safety they will promptly notify the IRB, FDA, and any other protocol specified safety committee or monitor.

Reporting requirements for SAEs will be managed by the investigator. Full details of the procedures to be adopted will be documented in a safety management plan will be prepared by Westat:

Any AE which occurs in any subject after signing the screening informed consent through the last visit must be reported. All SAEs that occur before the end of study following cessation of the last dose of treatment with the study drug, whether or not considered related to the investigational product must also be reported. All subjects with SAEs must be followed up for outcome.

All SAEs will be reported to the CHOP IRB and FDA per current regulations (CHOP IRB SOP 408 Unanticipated Problems Involving Risks to Subjects and FDA Regulations 21 CFR 312.32 IND Safety Reporting).

See Appendix 4 for monitoring plan.

12.4 Monitoring of Subjects with Adverse Events

Each subject must be carefully monitored for AEs. This includes clinical laboratory variables. Assessments must be made of the seriousness, intensity and relationship to the administration of the study treatment. After the initial AE/SAE report, the investigator is required to follow up each subject proactively and provide further information as needed to the CHOP IRB and FDA as required.

12.5 Procedures to be Followed in the Event of Abnormal Laboratory Test Values

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

12.6 Clinical Laboratory Parameters and Abnormal Laboratory Test Results

Clinically significant changes in laboratory parameters (abnormalities), in the judgment of the Investigator, will be recorded as AEs and appropriate countermeasures taken.

12.7 Abnormal Physical Examination Findings

Clinically significant changes in physical examination findings (abnormalities), in the judgment of the Investigator, will be recorded as AEs and appropriate countermeasures taken.

12.8 Additional Safety Assessments

Safety will be assessed using AEs, observed local and systemic allergic symptoms, physical examinations, including skin reactions, hematology, biochemistry, and vital signs.

Drug accountability will be noted by the field monitor during site visits and at the completion of the trial.

12.9 Treatment of Overdose of Study Medication

There is no experience of overdosing with Viaskin® patches. No specific treatment for overdosing is known. Treatment given to a subject in case of overdosing should be symptomatic and supportive.

Any overdose, with or without associated AEs, in a clinical study must be reported to the local IRB and FDA as required. Overdose will be reported in the eCRF. All reports of overdoses must be filed in the Study Center File. Any AEs associated with the overdose should be reported on relevant AE/SAE sections in the eCRF.

12.10 Procedures in Case of Pregnancy

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All pregnancies and outcomes of pregnancy must be reported to IRB.

12.11 Adverse Events of Special Interest

AEs of special interest in this study include Grade 4 local skin reactions upon application and removal of the Viaskin®. Skin reactions at the site of Viaskin® Patch application will be examined at the time points specified at each visit and graded according to Section 11.13 (Table 5). Specifically, the appearance of any vesicle(s) or ulcerative skin lesion(s) or any other significant skin lesion which could potentially lead to skin barrier disruption at sites of Viaskin® applications will be considered AEs of special interest. Any occurrence of systemic (or distant) allergic reaction related to Viaskin® Milk application will also be considered an AE of special interest.

13. DATA MANAGEMENT AND STATISTICAL ANALYSIS

The data management and statistical analysis of this study will be performed by an external BDMC (Biostatistics and Data management Core) at CHOP managed by Westat.

13.1 Data Management

An eCRF will be used for the current study, and a data management plan will be prepared by the BDMC (Biostatistics and Data management Core) at CHOP managed by Westat.

Previous and concomitant medications will be coded using the latest available World Health Organization (WHO) Drug Reference Dictionary. Coexistent diseases and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by written agreement between the investigator and the Westat BioStat unit.

13.2 Sample Size Estimation

This is a pilot study in which we aim to identify efficacy of the Viaskin® Milk treatment. Sample size is based on projected subject volume. If efficacy is shown, our pilot data could be used to perform a power analysis for a larger study.

We will recruit 38 subjects and plan to have approximately 22 evaluable subjects with milk-induced EoE confirmed by endoscopy and biopsy.

A total sample size of 22 evaluable subjects (16 subjects in the active Viaskin® Milk group and 6 subjects in the placebo group) will achieve 90% power to detect a difference of 40 in mean maximum eosinophil counts between the two treatment groups (mean maximum eosinophil counts of 10 and 50 in Viaskin® Milk and in placebo, respectively) assuming that a common standard deviation is 20 using a two group *t*-test with a two-sided significance level of 0.05.

Approximately 22 subjects will be randomized to obtain 18 completed subjects with 10% drop-out.

13.3 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be written and finalized prior to database lock. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol. Additional analyses may be added. Tables, listing and figures shells will also be provided.

13.4 Randomization

This is a double-blind, placebo-controlled study. The actual treatment given to individual subjects is determined by a randomization schedule. The associated treatment assignments giving details of individual subject treatment are assigned from a randomization list. After entry criteria are confirmed at the end of Visit 3, subjects will be randomized at Visit 4 (Day 1) using a 3:1 ratio to receive either the Viaskin® Milk or placebo.

13.5 Analysis Populations

All the analysis populations will be identified and finalized in the SAP.

13.5.1 Safety Population

The safety population will be comprised of all subjects who are randomized and received at least one dose of study drug. This population will be used to assess comparative safety information.

13.5.2 Intent-to-treat Population

The intent-to-treat (ITT) population (full analysis set) will be comprised of all subjects who are randomized. This population will be used to assess comparative efficacy information.

13.5.3 Per Protocol Population

The per protocol (PP) population will include all subjects in the ITT population who do not have pre-defined major deviations from the protocol that may affect the primary (and secondary) endpoints (for instance, subjects who have not gone through the third upper endoscopy and biopsy at the end of treatment, subjects with a compliance below 80% etc.) The deviations to consider will be listed more exhaustively in the SAP. The PP population will be used to perform confirmatory analyses of the primary efficacy evaluation.

13.6 Statistical Methods

The statistical analyses for the entire study as further outlined in the SAP will be included in the Clinical Study Report for this protocol. The SAP will give a detailed description of the summaries and analyses (primary and secondary) that will be performed and clearly describe when these analyses will take place. The SAP will be finalized prior to database lock to preserve the integrity of the statistical analysis and study conclusions.

All pre-defined statistical analyses will be performed after the database is released for unblinding. Statistical analyses will be performed using SAS® Version 9.1 or higher (SAS Institute, Cary, NC

27513)

Descriptive statistical analysis of all data obtained will be conducted using inferential and graphical exploratory data analytic techniques. Descriptive statistics will be presented as means and standard deviations or median and interquartile ranges or minimum and maximum for continuous variables and frequency counts and percentages for categorical variables. The denominator for percentages will be the number of subjects in the population with data available unless otherwise stated.

13.6.1 Missing Data

Every attempt must be made by the Investigator to provide complete data. The primary analysis can be performed on data without imputation. However, exploratory analyses using the multiple imputation method and last observation carried forward should be utilized to assess the robustness of the data.

Analyses of primary and secondary efficacy measures will be based on the intent-to-treat (ITT) population, with missing values imputed using the last value carried forward analysis.

13.6.2 Demographic and Baseline Data

Descriptive statistics will be produced as means, standard deviations, medians, and ranges for continuous demographic and baseline characteristics (including age, height, weight and maximum Esophageal Eosinophil Count) and frequency counts and percentages for the categorical demographic and baseline characteristics (including race, ethnicity, medical history) will be produced by treatment group and overall. Distribution of the continuous outcomes will be evaluated using histograms. Transformation of some of these continuous variables will be performed wherever deemed more appropriate. The balance of the demographic and baseline measures between the treatment groups will be compared using two-sample t-tests or the Mann-Whitney tests as appropriate for continuous variables and the chi-square tests for categorical variables.

All individual subject demographic and baseline characteristic data will be listed.

13.6.3 Subject Disposition

Subject disposition will be summarized for the intention-to-treat population. The number and percentage of subjects randomized, subjects in each study population (Safety, ITT, PP), and subjects who received study medication, who completed the double-blind period, who discontinued the double-blind period, and the primary reason for discontinuation from the double-blind period will be tabulated by treatment group and overall.

13.6.4 Efficacy

13.6.4.1 Primary Efficacy Variable

The primary efficacy endpoint is defined as the maximum esophageal eosinophil count on all specimens obtained on the biopsy at end of double-blind treatment (Visit 10), after milk reintroduction at Visit 9. The null hypothesis is that the mean maximum esophageal eosinophil

count in active treatment group is the same as that in the placebo group. This hypothesis will be evaluated using an analysis of covariance (ANCOVA) model with treatment group, baseline patient's maximum esophageal eosinophil count, and age group (4-11 years old versus 12-17 years old) as covariates. The null hypothesis will be tested against the alternative hypothesis that the results are different in each treatment group at the 0.05 significance level. The least square means for the treatment groups, difference in least square means between the treatment groups, effect size calculated as the absolute difference in least square means between active group and placebo divided by the root mean square, and p-value for difference between treatment groups will be presented.

13.6.4.2 Secondary Efficacy Variables

The following secondary efficacy endpoints will be assessed:

Esophageal Eosinophil Count

The mean Esophageal Eosinophil Count of all specimens obtained at the end of treatment as well as the change from baseline will be summarized by treatment group.

The null hypothesis that the mean Esophageal Eosinophil Count eliciting doses at the end of treatment are the same in each treatment group will be analyzed using ANCOVA model with treatment group, baseline patient's mean esophageal eosinophil count, and age group (4-11 years old versus 12-17 years old) as covariates. This null hypothesis will be tested against the alternative hypothesis that the results are different in each treatment group at the 0.05 significance level.

Esophageal Endoscopy Score

The total score for each subject will be calculated (for endoscopy) and summary statistics will be presented for each treatment group at baseline and the end of study. This will be based on each symptom being graded for severity as 0, 1, 2 or 3 (respectively none, mild, moderate and severe). The total scores at the end of treatment between two treatment groups will be examined using ANCOVA model with treatment group, baseline patient's total score, and age group (4-11 years old versus 12-17 years old) as covariates. The change from baseline to end of treatment will also be presented. The change in Esophageal endoscopy scores between two treatment groups will be examined using a two sample Student's t-test or Mann-Whitney test.

Eosinophilic Esophagitis Symptom Score

Improvement in symptom scores will be defined as a decrease in total symptom scores of two or more from baseline to end of treatment. Subjects will be categorized based on whether they improved their symptoms. Subjects who improved their symptom scores were considered as responders and patients who did not improve their symptom scores were considered as non-responders. The percentage of responders between the active treatment group and placebo group will be compared using Fisher's exact test. In addition, all of the summaries of severity of symptoms above will be repeated, split by responder/non-responder groups.

In addition, the change from baseline to end of treatment of the total symptom score and individual symptom scores (Abdominal/chest pain score, Vomiting score, and Dysphagia score) will be generated by treatment group and overall. The comparison of the change of individual symptom scores between the two treatment groups will be evaluated by using Fisher's exact tests.

The responses will be divided into three categories as suggested: Poor <30% improvement, good 30-70% improvement and excellent >70% improvement from baseline.

Percentage of subjects per response rate
The percentage of subjects showing an excellent response (≤1 eos/HPF), good response (2-14 eos/HPF), or poor response (≥15 eos/HPF) at the end of treatment will also be presented and analyzed between the two treatment groups using Fisher's exact test.

Eosinophilic Esophagitis Quality of Life Score
The Quality of Life score will also be reported for each treatment group at baseline and the end of treatment. The change from baseline to end of treatment will also be presented. The change in QOL scores between two treatment groups will be compared with two-sample t-test or Mann-Whitney test depending on the distribution of the change of the QOL score.

Combination Score:
Combination Score of four measures (Eosinophils/HPF, EREFS, investigator assessment and parental assessment of symptoms) will be calculated at baseline, end of treatment and end of study. The combination score will be calculated as (maximum eosinophils per high power field) + [10*esophageal endoscopy score (EREFS)] + [2* Parent assessment of esophageal symptoms (PEESS)] + [5*investigator assessment of EoE symptom activity]. The change from baseline to end of treatment will also be presented. The change in QOL scores between two treatment groups will be compared with two-sample t-test or Mann-Whitney test depending on the distribution of the change of the QOL score.

13.6.5 Pharmacokinetics

Not applicable, no pharmacokinetic assessments will be performed during this study.

13.6.6 Safety

No formal statistical analysis of safety endpoints will be carried out.

13.6.6.1 Adverse Events

All AEs will be coded by system organ class and preferred term using MedDRA.
Treatment-emergent AEs (TEAEs) will be defined as any AEs, regardless of relationship to study drug, which occur during AE collection period of study drug or any event already present that worsens in either intensity or relationship to study drug following exposure to the Viaskin®. If relationship information is missing, the TEAE will be considered drug-related.

An overall summary of TEAEs will be provided showing the number and percentage of subjects in each treatment group with any TEAE, any potentially drug-related TEAE, any severe TEAE, any serious TEAE, any TEAE leading to discontinuation, and any TEAE leading to death. The number of events will also be presented.

The number of AEs as well as the number and percentage of subjects who experienced at least one AE will be summarized by system organ class, preferred term and treatment group. The incidence of the following events will be summarized:

- Local skin tolerance: incidence, severity and duration of local TEAE at site of Viaskin® application as reported by subjects in the diary card
- TEAEs: incidence, severity and duration.
- Potentially drug-related TEAEs
- Discontinuations due to TEAEs
- Laboratory data, physical examinations, and vital signs Systemic allergic symptoms in the active and placebo groups
- Potentially drug-related systemic allergic symptoms
- SAEs
- Potentially drug-related SAEs

In addition, TEAEs will be summarized by relationship to study drug and by severity. If a subject has more than one occurrence of the same TEAE with different severities or relationship to study drug, then the TEAE will be assigned to the highest severity category and/or most related relationship category. If the intensity or relationship is missing, then the 'worst case' will be assumed (i.e., severe for intensity and drug-related for relationship).

The proportion of subjects that experience systemic allergic symptoms will be summarized by treatment. All TEAEs will be listed.

13.6.6.2 Laboratory Assessments

Descriptive statistics will be calculated for clinical laboratory tests (hematology and biochemistry) performed at baseline (Day 1), Visit 10 (end of DBPC treatment) and visit 16 (end of open label extension). Categorical variables will be summarized by frequency and percentages of subjects in corresponding categories. Changes from baseline will also be presented.
In addition, summaries of laboratory values categorized based on CTC (common toxicity criteria) grade will also be presented.

All laboratory data will be listed. Listing of values that are out of normal range will be flagged in the data listings.

13.6.6.3 Vital Signs

Observed vital sign values and changes from baseline will be descriptively summarized by visit and treatment group. All vital signs data will be listed.

The analysis of vital signs will focus on the incidence of clinically relevant abnormalities. The number of subjects evaluated and the number and percentage of subjects with clinically relevant post-baseline abnormalities at each visit will be presented.

Table 6 Criteria to Determine Clinically Relevant Abnormalities in Vital Signs - Children

Vital Sign	Criteria for Abnormalities
Temperature	<35°C and a decrease from pre-dosing of at least 1°C > 38.5°C and an increase from pre-dosing of at least 1°C
Pulse	> 120 beats per minute or an increase from pre-dosing of > 20 beats per minute, or < 50 beats per minute or a decrease from pre-dosing of > 20 beats per minute
Systolic blood pressure	> 140 mmHg or an increase from pre-dosing of > 40 mmHg, or < 90 mmHg or a decrease from pre-dosing of > 30 mmHg
Diastolic blood pressure	> 90 mmHg or an increase from pre-dosing of > 30 mmHg, or < 50 mmHg or a decrease from pre-dosing of > 20 mmHg

13.6.6.4 Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary. A summary of concomitant medications will be produced by preferred drug name and treatment group. All concomitant medications will be listed.

13.6.7 Additional Data

Diary card data, Viaskin® site examination and physical examination data will be summarized where appropriate and listed. Study drug compliance and accountability will be listed.

13.6.8 Data and Safety Monitoring Board

A DSMB will be composed to review the safety and/or efficacy data of the study at any time judged necessary during the course of the study and after the first 3 patients are enrolled and then annually. Members of the DSMB will be selected and confirmed as early as possible, in any case before the first data review is convened. Ideally, the DSMB should be composed of experts in food allergy and in the methodology of clinical trials. The DSMB will review either blinded or unblinded data during the course of the study (see below). Various recommendations will then be made by the DSMB. The three members of the DSMB are Stacie Jones, MD, Chief of Allergy and Immunology, Arkansas Children's Hospital, Univ. of Arkansas School of Medicine; Seema Aceves, MD, PhD, Director of Eosinophilic Esophagitis Center, Rady's Children's Hospital, University of California at San Diego; and David Fleischer, MD, Univ. of Colorado School of Medicine. Westat will supply blinded study results to the DSMB unless unblinded results are requested by the DSMB for safety reasons. For details of the emergency procedure for unblinding of individual subjects, see Section 8.5.10

14. MONITORING PROCEDURES (QUALITY ASSURANCE)

The Principal Investigator has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and ICH GCP guidelines. As such, in order to fulfill these obligations and to maintain current of study progress, the Investigator's monitors or representatives will visit the investigative site during study conduct, in addition to maintaining telephone and written communication. On-site visits, telephone calls, and regular inspection of the eCRFs will be conducted in order to assess subject enrollment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The Investigator must provide the monitor with full access to all source and study documents.

14.1 Routine Monitoring

Investigator assigned monitors will conduct regular site visits at the one clinical site (CHOP) for the purpose of monitoring various aspects of the study. The monitor will access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) for all study subjects considered for study entry for the purpose of verifying entries made in the eCRF, and assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.

CHOP staff must complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the study monitor.

See Appendix 3 for monitoring plan.

14.2 Inspections and Auditing Procedures

The Investigator monitor may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. All medical records (progress notes) must be available for audit. The Investigator agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the Investigator during or after the study. The Investigator or designee should contact the Sponsor /CRO immediately if this occurs. He/she must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

The purpose of an audit is to assess whether ethics, regulatory and quality requirements are fulfilled.

15. STUDY MANAGEMENT AND MATERIALS

15.1 Electronic Case Report Forms

An eCRF will be used to store and transmit subject information. The eCRF must be reviewed and electronically signed and dated by the Investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by examining personnel or the study coordinator. The eCRF must be completed as soon as possible after any subject evaluation or communication. If data is to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

15.2 Data Collection

During each study visit, a physician participating in the study will maintain progress notes, in ink, in the subject's medical records to document all significant observations. At a minimum, these notes will contain:

- The date of the visit and the corresponding day or visit in the study schedule (e.g., screening, Day 1, Day 8, etc.).
- General condition and status remarks by the subject, including any *significant* medical findings. The severity, frequency, duration, and resolution of any reported AE, and the Investigator's assessment as to whether or not the reported AE is study drug-related should be recorded.
- Changes in concomitant medications or dosages.
- A general reference to the procedures completed.
- The signature or initials of all physicians making an entry in the medical record (progress notes).

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the medical record (progress notes), as described above.
Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the eCRF.

Changes to information in the medical record (progress notes), eCRF, and other source documents will be initialed and dated on the day the change are made by the Investigator or designee. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change.

15.3 Source Documents Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs and recorded data from automated instruments.

All source documents from this study will be maintained by the Investigator and made available for inspection by authorized persons. The original signed informed consent for each subject shall be filed with records kept by the Investigator, and a copy shall be given to the subject.

15.4 Record Maintenance

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of subjects, source documents, eCRFs and study drug inventory must be kept on file.

US Food and Drug Administration (FDA) regulations (21 Code of Federal Regulations [CFR] 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medical inventory records, must be retained by the Principal Investigator for two years after marketing application approval. If no application is filed, these records must be kept two years after the investigation is discontinued and the US FDA and the applicable national and local health authorities are notified and in accordance with CHOP Policy No. A-3-6: Retention and Destruction of Records.

The Investigator will take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the regulatory authorities.

15.5 Confidentiality

All information obtained during the conduct of the study with respect to the subject's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing.

The Investigator must ensure that each subject's anonymity is maintained. On eCRFs and other documents, subjects must not be identified by name. Instead, subjects will only be known by the unique subject number allocated to them and by coded initials in order to ensure confidentiality on all study documentation. Subjects will retain this unique number throughout the study. The Investigator will keep a separate log of these codes.

In order to comply with government regulatory guidelines and to ensure subject safety, it may be necessary for the Sponsor and its representative, the CRO personnel, the local research review board, or the US FDA to review subjects' medical records as they relate to this study. Only the subject's unique number on the eCRFs will identify him/her, but their full names may be made known to a drug regulatory authority or other authorized government or health care officials, if necessary, and to personnel designated by the Principal Investigator.

Documents that are not for submission to the eCRF (e.g., consent forms) will be maintained by the Principal Investigator in strict confidence, except to the extent necessary to allow monitoring by the

Sponsor and the CRO, and auditing by regulatory authorities. No documents identifying subjects by name will leave the investigative site and subject identity will remain confidential in all publications related to the study.

16. ETHICS

16.1 Ethics Committee

This study will be conducted in compliance with IRB and ICH GCP Guidelines including Title 21 Part 56 of the USA CFR relating to IRBs and GCP as described in the US FDA CFR (21 CFR § 50, 56, 312) - in accordance with applicable regulations regarding clinical safety data management (E2A, E2B(R3)), European Community directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9 and E10). In addition, this study will adhere to all local regulatory requirements, and requirements for data protection.

Before initiating a trial/study, the Investigator/institution must have written and dated approval/favorable opinion from the The Children's Hospital of Philadelphia IRB for the study protocol/amendment(s), written informed consent form (ICF), any consent form updates, subject recruitment procedures (e.g. advertisements), and any written information to be provided to subjects and a statement from the IRB that they comply with GCP requirements. The IRB approval must identify the protocol version as well as the documents reviewed.

16.2 Ethical Conduct of the Study

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonized Tripartite Guideline E6 (R1); FDA CFR (21 CFR § 50, 56, 312)), Declaration of Helsinki (Seoul 2008) and all applicable regulatory requirements.

16.3 Subject Information and Consent

The Investigator is responsible for and will obtain informed consent from each subject in the study, in accordance with the ICH-GCP Guidelines, the Declaration of Helsinki, and applicable regulatory requirements.

Subjects will be informed of the nature of the study, its aim, its possible risks and restrictions, its duration, and the compensation that they might receive. The protocol will be explained during a meeting prior to study enrollment, and each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time. The subject should read the ICF before signing and dating it and a copy of the signed document should be given to the subject. No subject can enter the study before his/her informed consent has been obtained. Children if able will sign assent. The parents or legal representative(s) of all children and adolescents regardless of age must also sign the ICF.

The consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the subject. In this instance approval should always be given by the CHOP IRB and existing subjects informed of the changes and re-consented. This is documented in the same way as previously described.

The Investigator should keep a copy of the consent of the subject, inform the subject's primary physician about participation in the clinical study.

17. ADMINISTRATION PROCEDURES

17.1 Regulatory Approval

Antonella Cianferoni, MD, PhD or her agents will be responsible for ensuring that appropriate regulatory authority approvals are obtained, according to FDA regulations 21 CFR 312. The Principal Investigator is also responsible for ensuring all study team members, monitors, and safety review committee members are appropriately trained and that the protocol is conducted in accordance to the IRB approved protocol and IND investigational plan.

No subject may enter the study until this approval has been obtained. A copy of the approval (where one is provided, according to local country requirements) will be provided to the Investigator and to the IRB(s)/IEC(s).

17.2 Protocol Amendments

In accordance with ICH Topic E6 (R1) Guideline for GCP the Principal Investigator should not implement any deviation from, or changes of the protocol without approval from the CHOP IRB of a protocol amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)).

Any change to the protocol must be handled as a protocol amendment. A written amendment must be submitted to the FDA and to the CHOP IRB assuming this responsibility. The Principal Investigator must await CHOP-IRB approval of protocol amendments before implementing the changes, except where necessary to eliminate apparent immediate hazard to subjects. In these cases, the CHOP-IRB must be notified within 5 days of the change.

All amendments to the protocol must be approved in writing by the CHOP-IRB. Once approved, the protocol amendment will be distributed to all recipients of the original protocol, with instructions to append the amendment to the protocol.

If, in the judgment of the local CHOP-IRB, the Sponsor, the protocol amendment alters the study design, procedures and/or increases the potential risk to the subject, the currently approved written ICF will require modification. The modified ICF must also be reviewed and approved by the Sponsor, FDA, and the CHOP IRB. In such cases, repeat informed consent must be obtained from subjects enrolled in the study before participation continues.

17.3 Protocol Adherence and Deviations

The protocol must be read thoroughly and the instructions must be followed. However, exceptions will be made in emergency situations when the protection, safety, and well-being of the subject requires immediate intervention based on the judgment of the Investigator or a responsible, appropriately trained, and credentialed professional(s) designated by the Investigator as a sub-Investigator.

In the event of a significant protocol deviation due to an emergency, accident, or error, the Principal Investigator or designee should determine whether or not the subject should continue in the study, and the decision must be documented.

17.4 Clinical Study Report

A final clinical study report will be prepared according to the ICH guideline on Structure and Contents of Clinical Study Reports. A final clinical study report will be prepared regardless of whether the study is completed or prematurely terminated.

17.5 Discontinuation of the Study

This study may be terminated prematurely by the Principal Investigator as being in the best interests of subjects, and justified on either medical or ethical grounds, or for any other reasons. In terminating the study, Principal Investigator will ensure that adequate consideration is given to the protection of the subjects' interests and the CHOP IRB and FDA are promptly notified.

17.6 Study Center File Management

The Investigator is responsible for assuring that the Study Center File is maintained. The Study Center File will contain, but will not be limited to, the information listed below:

(1) Investigator's Brochure;
(2) Current, signed version of the protocol and any previous versions of the protocol;
(3) Protocol amendments (if applicable);
(4) Operations Manual (if applicable);
(5) Current ICF (blank) and any previous versions of the ICF;
(6) Curricula Vitae of Investigator(s) and sub-investigator(s) and photocopy of their respective license(s) where required by law; Original US FDA Form 1572 (for all studies conducted under US Investigational New Drug [IND] regulations), signed by all Principal Investigators. The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required the ICH GCP and by local or national regulations;
(7) Documentation of CHOP-IRB approval of the protocol, the ICF, any protocol amendments, and any ICF revisions;
(8) All correspondence between the Investigator, and CHOP-IRB, relating to study conduct;
(9) Laboratory certification(s);
(10) Monitoring log;
(11) Study drug invoices;
(12) Signature list of all staff completing eCRFs; and

(13) Signature list of all staff completing drug accountability summaries;
(14) FDA Correspondence for the IND.

18. APPENDICE

APPENDIX 1: ENDOSCOPY SCORING SYSTEM[57]

Major features

- **Fixed rings** (also referred to as concentric rings, corrugated oesophagus, corrugated rings, ringed oesophagus, trachealisation)
  - Grade 0: none
  - Grade 1: mild (subtle circumferential ridges)
  - Grade 2: moderate (distinct rings that do not impair passage of a standard diagnostic adult endoscope (outer diameter 8—9.5 mm))
  - Grade 3: severe (distinct rings that do not permit passage of a diagnostic endoscope)
- **Exudates** (also referred to as white spots, plaques)
  - Grade 0: none
  - Grade 1: mild (lesions involving <10% of the oesophageal surface area)
  - Grade 2: severe (lesions involving >10% of the oesophageal surface area)
- **Furrows** (also referred to as vertical lines, longitudinal furrows)
  - Grade 0: absent
  - Grade 1: present
- **Oedema** (also referred to as decreased vascular markings, mucosal pallor)
  - Grade 0: absent (distinct vascularity present)
  - Grade 1: loss of clarity or absence of vascular markings
- **Stricture**
  - Grade 0: absent
  - Grade 1: present

Minor features

- **Crepe paper oesophagus** (mucosal fragility or laceration upon passage of diagnostic endoscope but not after oesophageal dilation)
  - Grade 0: absent
  - Grade 1: present

Appendix 2: Eosinophilic Esophagitis Quality of Life Score

- PEESS Patient (8-18 year of age)
- PEESS Patient Proxy (patients less 8 years of age)
- EoE QOL
    - PedsQL™ Eosinophilic Esophagitis Module Version 3 Teen Report (ages 13-18)
    - PedsQL™ Eosinophilic Esophagitis Module Version 3 Child Report (ages 8-12)
    - PedsQL™ Eosinophilic Esophagitis Module Version 3 Parent Report for Child (ages 8-12)
    - PedsQL™ Eosinophilic Esophagitis Module Version 3 Parent Report for Young Child (ages 5-7)
    - PedsQL™ Eosinophilic Esophagitis Module Version 3 Parent Report for Toddler (ages 2-4)

Appendix 3: CHOP Monitoring Policy

Introduction:

Description of the study:
This is a double-blind, placebo-controlled, randomized trial to study the efficacy and safety of Viaskin® Milk, an allergen extract of milk administered epicutaneously using the Viaskin® epicutaneous delivery system in subjects from 4 to 17 years old with a milk induced Eosinophilic Esophagitis. The trial will be conducted at The Children's Hospital of Philadelphia (CHOP).

Study objectives:
The objectives of this study are:

- To assess the efficacy of Viaskin® Milk epicutaneous immunotherapy (EPIT) in subjects with milk-induced eosinophilic esophagitis.
- To evaluate the safety of Viaskin® Milk EPIT in subjects with milk-induced eosinophilic esophagitis.

Critical data and study procedures, with particular attention to data and procedures that are unusual in relation to clinical routine and require training of study site staff

Specific risks to be addressed by monitoring:

Upper Endoscopy and biopsy-Pain or bleeding
Viaskin Patch-local skin reactions, any systematic reaction to Viaskin patch including rash, vomiting, abdominal pain or other GI symptoms

Treatment-emergent AEs (TEAEs) will be defined as any AEs, regardless of relationship to study drug, which occur during or after the initial Viaskin® application of study drug or any event already present that worsens in either intensity or relationship to study drug following exposure to the Viaskin®. If relationship information is missing, the TEAE will be considered drug-related.

Description of Monitoring Approaches

The Office of Research Compliance (ORC) will begin monitoring activities for this study within three months of the first subject's enrollment into the study. Thereafter, ORC will monitor this study annually unless circumstances necessitate more frequent monitoring, e.g., an increase in risk to the subjects, less than ideal study conduct, higher than expected accrual rates.

Monitoring activities will be guided by ICH E6 section 5.18.

Monitoring of subject data will be initiated at 100% verification of the data recorded. This may be amended, and a tapered approach to monitoring may be employed, if conduct and documentation of the study reaches a level of reliability that would permit valid conclusions based upon a sampling of data.

Communication of Monitoring Results

Monitoring reports will be communicated to the sponsor, and the IND/IDE Support Program within 30 days after the monitoring visit has concluded.

Management of Noncompliance

Any serious or persistent noncompliant activity or violation that is observed during the course of monitoring will be reported to the investigator, and to the ORC Director. The ORC Director will evaluate the report of noncompliant activities and discuss with the sponsor and/or principal investigator any necessary reporting requirements and corrective and preventative actions plans.

Ensuring Quality Monitoring

Selected monitors must be qualified by education and training to perform monitoring activities. Monitors must have completed all CHOP-specific training, e.g., CITI. The principal investigator or designee will provide protocol-specific training to the monitor.

As part of ORC's continuous quality improvement plan, the study may be audited for quality assurance to evaluate the effectiveness of the monitoring to ensure human subject protection and data integrity.

Monitoring Plan Amendments

The monitoring plan will amended as needed to address increase in risk to the subject, new information, etc.

Appendix 4: Safety of 500 mcg of milk Viaskin Patch

The dose will be 500 mcg or top dose tolerated as recommended by the MILES data safety monitoring board.

19. REFERENCE:

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2. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004; **351**(9): 940-1.
3. Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol* 2005; **115**(2): 418-9.
4. Hruz P, Straumann A, Bussmann C, et al. Escalating incidence of eosinophilic esophagitis: a 20-year prospective, population-based study in Olten County, Switzerland. *J Allergy Clin Immunol* 2011; **128**(6): 1349-50 e5.
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