**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

# Statistical Analysis Plan
# Final Version 2.0

**Sponsored by:**

Jonathan M. Spergel, MD, PhD
Division of Allergy and Immunology
The Children's Hospital of Philadelphia

Protocol Number: SMILEE
IND Number: 16518

January 05, 2018

Prepared by:
Okan U. Elci, PhD
CHOP-Westat Biostatistics and Data Management Core
Roberts Center for Pediatric Research
2716 South Street, #9362
Philadelphia, PA 19146

## Table of Contents

## List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| CBC | Complete Blood Count |
| CHOP | The Children's Hospital of Philadelphia |
| CI | Confidence Interval |
| DBP | Diastolic Blood Pressure |
| EoE | Eosinophilic Esophagitis |
| EREFS | Endoscopic Reference Score |
| EPIT | Epicutaneous Immunotherapy |
| HPF | High Power Field |
| ITT | Intention to Treat |
| LOCF | Last observation carried forward |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OR | Odds Ratio |
| PP | Per Protocol |
| PEESS | Pediatric Eosinophilic Esophagitis Symptoms Score |
| RR | Relative Risk |
| SD | Standard Deviation |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SBP | Systolic Blood Pressure |
| SOC | Standard of Care |
| SMILEE | Study Efficacy and Safety of the Viaskin® Milk for Treating Milk Induced Eosinophilic Esophagitis in Children |
| TEAE | Treatment-Emergent Adverse Event |
| TSLP | Thymic Stromal Lymphopoietin |

## 1. Introduction

This statistical analysis plan (SAP) is based on the SMILEE study (IND Number: 16518) protocol version 7.0, dated April 27, 2017. The SAP summarizes key aspects of the study to provide the context of statistical methods for analyzing the data and the descriptive measures to be reported.

## 2. Study Overview

The SMILEE study is a Phase IIA double-blind, placebo-controlled randomized trial. This section describes the design, objectives, endpoints, and treatments of this study as well as the study population and randomization.

### 2.1 Study Design

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 (EoE). 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, the study will be open to all ages 4-17 years old.

Subjects with a documented medical history of EoE 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 (SOC) 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 EoE. In addition, milk will be removed from the diet and a SOC upper endoscopy and biopsy will be performed

after a minimum of 6 weeks under a milk-free diet to confirm the diagnosis of milk-induced EoE. 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 epicutaneous immunotherapy (EPIT) with Viaskin® Milk (500 μg of milk proteins) or placebo. If a subject has a SOC endoscopy in 12 months prior to the study, they will not need to repeat endoscopies to be eligible for the study and will be randomized as above. A minimum of two SOC 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 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 the 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.

## 2.2 Study objectives and endpoints

The primary and secondary efficacy objectives and safety objectives as well as endpoints of this study are as follows:

### 2.2.1 Primary efficacy objective

The main efficacy objective is to assess the efficacy of Viaskin® Milk EPIT to desensitize milk-induced EoE in subjects at the end of the double-blind treatment period. The study will analyze the maximum esophageal eosinophil count on all specimens obtained at the end of the double-blind treatment period in esophageal biopsy after milk reintroduction in subjects with EoE. This is the gold-standard for the diagnosis of EoE.

### 2.2.2 Primary efficacy endpoint

The primary efficacy endpoint is each patient's maximum esophageal eosinophil count on all specimens obtained from the biopsy at the end of double-blind treatment (visit 10), after milk reintroduction at visit 9.

### 2.2.3 Secondary efficacy objectives

The secondary efficacy objectives are:

**a.** To describe the EoE symptoms score and global assessment score at end of each treatment period at 11 months (end of the double-blind treatment) and 22 months (end of the open-label treatment) in each treatment group and to determine if there

is a difference in improvement of the EoE symptom score between the active treatment group and the placebo group.

**b.** To assess if there is a difference in the mean esophageal eosinophil count between the active treatment group and the placebo group at end of each treatment period at 11 and 22 months.

**c.** To assess if the changes in mean and maximum esophageal eosinophil count from baseline to end of each treatment period at 11 and 22 months are different between the active treatment group and the placebo group.

**d.** To assess if the percentages of subjects with ≤ 1 eosinophils/HPF (excellent response), subjects with 2-14 eosinophils/HPF (good response), and subjects with ≥ 15 eosinophils/HPF (poor response) at the end of each treatment period at 11 and 22 months are similar between the active treatment group and the placebo group.

**e.** To assess if there is a difference in esophageal endoscopy score at the end of each treatment period at 11 and 22 months and to examine the changes in esophageal endoscopy score from baseline to the end of each treatment period at 11 and 22 months between the active treatment group and the placebo group.

**f.** To examine the changes in the eosinophilic esophagitis quality of life score from baseline to the end of each treatment period at 11 and 22 months between the active treatment group and the placebo group.

**g.** To examine the changes in the composite score, which will be calculated using four measures (Eosinophils/HPF, Esophageal Endoscopic Reference Score (EREFS), Pediatric Eosinophilic Esophagitis Symptoms Score (PEESS), and investigator assessment of EoE symptom activity), from baseline to the end of treatment period at 11 and 22 months between the active treatment group and the placebo group [Composite score = Maximum Eosinophils per HPF + 10*EREFS + 2*PEESS +5* (Investigator assessment of EoE symptom activity)].

**h.** To assess if there is difference in time to development symptoms after milk reintroduction at month 9 and 20 between the active treatment group and the placebo group.

**i.** To assess the changes in exploratory biologic markers including T-regulatory cells, thymic stromal lymphopoietin (TSLP), and complete blood count (CBC) with differential and milk-specific Immunoglobulin level and epigenetic changes between the active treatment group and the placebo group.

### 2.2.4 Secondary efficacy endpoints

The secondary efficacy endpoint measures are:

**a.** The EoE symptom score and global assessment score at the end of each treatment period at 11 and 22 months (improvement in EoE symptom score will be defined as a decrease in total symptom score of two or more from baseline to the end of each treatment period at 11 and 22 months) as well as the change in EoE symptom score from baseline to the end of each treatment period at 11 and 22 months (e.g., the change in EoE symptom score at 11 month = the EoE symptom score at 11 month – (minus) the EoE symptom score at baseline, the change score is the difference) and the EoE frequency and severity symptom scores measured by Pediatric Eosinophilic Esophagitis Symptoms Score (PEESS) at the end of each treatment period at 11 and 22 months as well as the changes in these symptom scores from baseline to the end of each treatment period at 11 and 22 months.

**b.** Mean esophageal eosinophil count which is the average of all of the samples obtained on biopsy at the end of each treatment period at 11 and 22 months.

**c.** The changes in mean and maximum esophageal eosinophil count from baseline to the end of each treatment period at 11 and 22 months.

**d.** The percentages of subjects with ≤ 1 eosinophil/HPF (excellent response), subjects with 2-14 eosinophils/HPF (good response), and subjects with ≥ 15

eosinophils/HPF (poor response) at the end of each treatment period at 11 and 22 months.

**e.** Esophageal endoscopy score at the end of each treatment period at 11 and 22 months and the change in the esophageal endoscopy score from baseline to the end of each treatment period at 11 and 22 months.

**f.** Changes in the eosinophilic esophagitis quality of life score from baseline to the end of each treatment period at 11 and 22 months.

**g.** Changes in the composite score from baseline to the end of each treatment period at 11 and 22 months.

**h.** Time to development symptoms after milk reintroduction at month 9 and 20.

**i.** Changes in exploratory biologic markers, including T-regulatory cells, TSLP, and CBC with differential and milk-specific Immunoglobulin level and epigenetic changes.

### 2.2.5 Safety objectives

The safety objectives are to evaluate the safety of Viaskin® Milk EPIT treatment in children and adolescents with milk-induced EoE. 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.

### 2.2.6 Safety endpoints

The safety endpoints are:

**a.** Local skin tolerance: incidence, severity and duration of local Treatment-Emergent Adverse Event (TEAE) at site of Viaskin® application as reported by subjects in the diary card.

**b.** Potentially drug-related TEAEs.

**c.** Discontinuation due to TEAEs.

**d.** Laboratory data, physical examinations, and vital signs.

**e.** Systemic allergic symptoms and relatedness to Viaskin®.

**f.** Potentially drug-related systemic allergic symptoms.

**g.** SAEs.

### 2.3 Treatments

Subjects will be randomized to receive Viaskin® with milk protein (500 μg of milk proteins) or placebo during the first year in the study. Viaskin® milk contains a dry deposit of natural milk protein formulated without adjuvant. 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® (500 μg of milk proteins).

### 2.4 Procedures

Study subjects, randomization, replacements of the withdrawn subjects, and duration of the study are described.

#### 2.4.1 Study Population

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.** Well documented symptoms suggestive of EoE after ingestion of milk and currently following a strict milk-free diet.

2. Upper endoscopy and biopsy at clinical evaluation during screening showing greater than or equal to 15 eosinophils per HPF isolated to the esophagus meeting the consensus diagnosis of EoE, after milk was re-introduced into the subject's diet (30 ml/day for 1 week to 2 months), while the subject was on a proton pump inhibitor.
3. 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 a milk-free diet, and while the subject is on a proton pump inhibitor.
4. A 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.

### 2.4.2 Randomization and replacement

Approximately 22 eligible subjects to obtain 18 completed subjects will be randomized in a 3:1 ratio into two different treatment groups, (1) to receive EPIT with Viaskin® Milk (500 µg of milk proteins) or (2) placebo (16 subjects in the active Viaskin® Milk group and 6 subjects in the placebo group). 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.

### 2.4.3 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 for the screening period; 11 months for the treatment period; 11 months for open label extension; and a 2-week follow-up visit). 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.

### 2.5 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. Fully eligible subjects will be required to attend 17 study visits as follows:

**Screening period:** Potentially eligible subjects will be enrolled into the study (Visit 1) to confirm Treatment Period study eligibility and obtain a number of study endpoints. The GI group will follow SOC 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.

Visit 1: Informed Consent obtained: milk introduction.

Visit 2: One week to 2 months after milk-introduction. Subjects have a SOC upper endoscopy/biopsy performed to confirm the diagnosis of EoE. Milk is removed from the diet.

Visit 3: Subjects have a second SOC upper endoscopy/biopsy to confirm milk induced EoE performed after a minimum of 6 weeks under milk-free diet.

If a subject has an endoscopy that confirms milk responsive EoE in the preceding 12 months, they will not need a repeat endoscopy to be eligible for the study.

**Treatment period:** There will be seven visits during the treatment period:

Visit 4 (Day 1): This visit corresponds to the first day of treatment and can be performed as soon as the results of the upper endoscopy and biopsy at Visit 3 are available and there is confirmed eligibility into the study.

Visit 5: This corresponds to day 8 of treatment.

Visit 6: This corresponds to month 1 of treatment.

Visit 7: This corresponds to month 3 of treatment.

Visit 8: This corresponds to month 6 of treatment.

Visit 9: This corresponds to month 9 of treatment (milk-reintroduction).

Visit 10: One week to 2 months after milk reintroduction. During this time, subjects will have weekly calls to monitor symptoms. Subjects have a third SOC upper endoscopy/biopsy. This is the end of double-blind treatment. The open-label treatment period will start on that day.

**Open label extension:** There will be six visits during the open-label treatment period:

Visit 11: This corresponds to day 8 after the Visit 10 research biopsy.

Visit 12: This corresponds to month 1 after the Visit 10 research biopsy.

Visit 13: This corresponds to month 3 after the Visit 10 research biopsy.

Visit 14: This corresponds to month 6 after the Visit 10 research biopsy.

Visit 15: This corresponds to month 9 after the Visit 10 research biopsy.

Visit 16: Subjects have a fourth upper endoscopy/biopsy. This is the end of open-label treatment period.

**Last assessment and end of study period:** There will be only one visit during this period.

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

## 3. Statistical Considerations

This section provides a detailed description of the statistical design, study objectives, and sample size determination and power calculation.

### 3.1 Statistical design

This is a randomized, double-blind, placebo-controlled clinical trial with Viaskin® Milk as Treatment 1 and placebo as Treatment 2. Primary and secondary efficacy objectives as well as the safety objectives are presented in Section 2.2.

### 3.2 Sample size determination and power calculation

The primary objective of this study is to determine whether mean maximum eosinophil counts is different in the subjects on the Viaskin Milk group compared to those on the placebo group. 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 22 evaluable subjects with milk-induced EoE confirmed by endoscopy and biopsy. Approximately 20 subjects (15 subjects in the active Viaskin® Milk group and 5 subjects in the placebo group) will be randomized to two treatment groups to obtain 18 completed subjects assuming 10% dropout rate. 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.

### 3.3 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 various imputation techniques (i.e., last observation carried forward (LOCF)) will be utilized to assess the robustness of the data. Analyses of secondary efficacy measures will be based on the intent-to-treat (ITT) population with missing values imputed using the last value carried forward analysis.

## 4. Statistical Analyses

This section provides a detailed description of the statistical analyses and methods, tables, listings, and figures. SAP Table shells are presented in Section 5.1.

The definitions of the analysis populations are listed. The general description of the planned analysis is provided. Descriptive and baseline characteristics will be generated for the purpose of describing the study population. Because the sample size is small, sometimes the most informative way of presenting the data will be through graphs or listing of the raw data.

The primary and secondary efficacy endpoints will be analyzed using the intent-to-treat (ITT) and per protocol populations. The least squares mean and two-sided 95% confidence interval (CI) for the between-treatment differences will be estimated from the models. The Hodges-Lehmann analysis of median differences will be produced for some of the secondary efficacy endpoints. Relative risk (RR) or odds ratio (OR) with 95% CI will be presented for some of the binary endpoints. Longitudinal models will be used to analyze some of the efficacy endpoints. These models will focus on the difference between baseline and end of the double-blind treatment as well as end of

the open-label treatment; measurements taken before the end of the double-blinded treatment will be used to increase the precision of the estimates of the changes from baseline to the both end of the double-blind treatment and the end of the open-label treatment. Sensitivity analyses will be performed to examine the potential outliers and influential points. These measurements will be assessed by visual examination of histograms and normal probability plots of residuals from the models. The methods or statistical tests that will be used in the primary and secondary efficacy analyses and safety analyses are described. Details are provided below.

### 4.1 Analysis populations

The analysis populations are:

- **Safety population:** The safety population is comprised of all subjects who are randomized and received at least one dose of study treatment and all subjects in the control group who did not withdraw or were not withdrawn. This population will be used to assess comparative safety information.
- **Intent-to-treat population:** The intent-to-treat (ITT) population (full analysis set) is comprised of all subjects who are randomized. Subjects in the ITT population will be categorized by their randomized treatment assignment. This population will be used to assess comparative efficacy information.
- **Per protocol population:** The per protocol (PP) population includes 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 (i.e., subjects who have not gone through the third upper endoscopy and biopsy at the end of the double-blind treatment, subjects with a compliance below 80%, etc.). The PP population will be used to perform confirmatory analyses of the primary efficacy evaluation.

## 4.2 Descriptive analyses

Standard descriptive statistics will be used to describe subjects' baseline characteristics and study endpoint measures overall and within each treatment group. Summary statistics such as means, standard deviations, medians, interquartile range and ranges for continuous variables (e.g., age, height, weight, and maximum esophageal eosinophil count) and frequency counts and percentages for categorical variables (e.g., race and ethnicity) will be generated. Medical histories will be summarized by system organ class and preferred term.

Demographic characteristics (*Table 1*), medical history (*Table 2*), vital signs at baseline (day 1), end of the double-blind treatment (visit 10), and end of the open-label treatment (visit 16) (*Table 3*), and both hematology and chemistry laboratory test results at baseline, end of the double-blind treatment, and end of the open-label treatment (*Table 4A and Table 4B*) will be summarized. Transformation (e.g., logarithmic transformation) of some of the continuous variables will be applied if needed.

## 4.3 Subject disposition

Subject disposition will be summarized for the ITT population. Subjects in each study population (ITT, PP, and Safety), subjects who received study medication, and subjects who completed and discontinued the double-blind period as well as the open-label period will be summarized (e.g., frequency counts and percentages) by treatment groups and overall (*Table 5*). The primary reason for discontinuation from the double-blind period and the open-label period will be listed by treatment groups.

## 4.4 Efficacy analyses

The methods for the primary and secondary efficacy analyses are described.

### 4.4.1 Primary efficacy analyses

Descriptive statistics for the maximum esophageal eosinophil count (the primary efficacy endpoint) on all specimens obtained on the biopsy at baseline (Day 1) and end of treatment (Visit 10) as well as the change from baseline to end of treatment will be presented by treatment groups and age groups (4-11 years old and 12-17 years old) (*Table 6*). The primary efficacy endpoint of the maximum esophageal eosinophil count will be analyzed using an analysis of covariance (ANCOVA) models with the treatment group (active versus placebo) and baseline patient's maximum esophageal eosinophil count. The least square means for the treatment groups, difference in least square means between the treatment groups, and a two-sided 95% CI for the difference between treatment groups will be presented (*Table 7*). Analysis of the primary endpoint in the logarithmic scale will be considered. Geometric mean and geometric mean ratio (anti-log of the parameter estimates) with 95% CIs will be reported when analyses are performed in the logarithmic scale of the primary endpoint.

### 4.4.2 Secondary efficacy analyses

Descriptive statistics for the secondary efficacy endpoints will be presented by treatment groups. The following secondary efficacy endpoints will be assessed:

#### 4.4.2.1 Total esophageal endoscopy score

The total score for each subject will be calculated and summary statistics at baseline, end of the double-blind treatment, and end of the open-label treatment as well as the changes from baseline to end of the double-blind treatment and to end of the open-label treatment will be presented by treatment groups (*Table 8*). Hodges-Lehmann estimate with 95% CI for difference of median of the changes in esophageal endoscopy

scores between two treatment groups will be reported. The total score at the end of the double-blind treatment and at the end of the open-label treatment between two treatment groups will be analyzed separately using ANCOVA as described in Section 4.4.1. The least square means for the treatment groups, difference in least square means between the treatment groups, and a two-sided 95% CI for the difference between the treatment groups will be presented (*Table 9*).

#### 4.4.2.2 Eosinophilic esophagitis symptom and global assessment scores

Summary statistics for individual eosinophilic esophagitis symptom score (Abdominal/Chest pain, Vomiting/Regurgitation, and Dysphagia) as well as investigator's eosinophilic esophagitis global assessment score at baseline, end of the double-blind treatment, and end of the open-label treatment as well as changes from baseline to end of the double-blind treatment and to end of the open-label treatment will be presented by treatment groups and overall (*Table 10*). The total EoE symptom score for each subject will be calculated and summary statistics at baseline, end of the double-blind treatment, and end of the open-label treatment, as well as the changes from baseline to end of the double-blind treatment and to end of the open-label treatment will be presented by treatment groups and overall. Improvement in symptom scores will be defined as a decrease in total eosinophilic esophagitis symptom score of two or more from baseline to end of the double-blind treatment and to end of the open-label treatment. Subjects will be categorized based on whether they improved their symptoms in two different ways. First, subjects who improved their symptom scores are considered as responders and subjects who did not improve their symptom scores are considered as non-responders. Second, subjects who improved their symptom scores will be categorized as poor improvement (<30%), good improvement (30-70%), and excellent improvement (>70%). RR or OR along with 95%

CI for the percentage of responders between two treatment groups will be presented. (*Table 11*).

In addition, frequency and severity EoE symptom scores measured by Pediatric Eosinophilic Esophagitis Symptoms Score (PEESS) will be examined. Summary statistics for the frequency and severity EoE symptom scores at baseline, end of the double-blind treatment, and end of the open-label treatment will be reported for each treatment group and overall. The changes in frequency and severity EoE symptom scores from baseline to end of the double-blind treatment and to end of the open-label treatment will be reported and Hodges-Lehmann estimates with 95% CIs for differences of medians of these changes between two treatment groups will be reported (*Table 12*).

#### 4.4.2.3 Percentage of subjects per response rate

The percentage of subjects showing an excellent response (≤ 1 eosinophils/HPF), good response (2-14 eosinophils/HPF), and poor response (≥ 15 eosinophils/HPF) at the end of the double-blind treatment and at the end of the open-label treatment as well as RR (i.e., the percentage of subjects showing excellent response in the treatment group divided by the percentage of subjects showing excellent response in the placebo group) along with 95% CIs between two treatment groups will be presented (*Table 13*).

#### 4.4.2.4 Eosinophilic esophagitis quality of life score

Summary statistics for the EoE quality of life score at baseline, end of the double-blind treatment, and end of the open-label treatment will be reported for each treatment group and overall. The changes in quality of life score from baseline to end of the double-blind treatment and to end of the open-label treatment as well as the Hodges-

Lehmann estimates along with 95% CIs for difference of medians of these changes between the two treatment groups will be reported (*Table 14*).

#### 4.4.2.5 Composite score

Summary statistics for the composite score at baseline, end of the double-blind treatment, and end of the open-label treatment will be reported for each treatment group and overall. The changes in composite score from baseline to end of the double-blind treatment and to end of the open-label treatment as well as the Hodges-Lehmann estimates along with 95% CIs for differences of medians of these changes between the two treatment groups will be reported (*Table 15*).

#### 4.4.2.6 Development of symptoms

Time to development of symptoms after milk reintroduction at month 9 and 20 will be described across two treatment groups.

#### 4.4.2.7 Exploratory biologic markers

The Hodges-Lehmann estimates for median differences for continuous variables and RRs for categorical variables along with 95% CIs of the changes in exploratory biologic markers, including T-regulatory cells, TSLP, CBC with differential, and milk-specific immunoglobulin level, as well as epigenetic changes between the active treatment group and the placebo group will be reported.

### 4.5 Safety analysis

AEs, laboratory tests (hematology and chemistry), and vital signs will be listed. No formal statistical analysis of safety endpoints will be performed. The details of the safety analysis are provided below.

### 4.5.1 Adverse events

All AEs will be listed/described and reported by treatment groups, subject, start date, severity, grade, causality, action taken, stop date, outcome, and absence of serious AE (T*able 16A and Table 16B*). All AEs will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The number of subjects who experienced at least one AE as well as the number of AEs will be summarized by system organ class and treatment group (*Table 17A and Table 17B*). The Summary of AEs (total number of subjects with AEs, total number of AEs, number of AEs per subject, severity of AEs, any serious AEs, AEs leading to discontinuation and death, ongoing AEs, and outcome) by treatment group will be presented (*Table 18*).

TEAEs will be defined as any AEs, regardless of relationship to study drug, which occur during the 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® Milk. TEAE will be considered drug-related if relationship information is missing. An overall summary of TEAEs (the number and percentage of subjects with any TEAE, total number of subjects with potentially drug-related TEAE, total number of TEAEs, total number of local TEAE, number of TEAEs per subject, severity of TEAEs, any serious TEAE, any TEAE leading to discontinuation and death) by treatment groups will be provided (*Table 19A and Table 19B*).

The number of subjects with adverse events on local skin reactions will be summarized (Table 20)

### 4.5.2 Laboratory assessments

Summary of both hematology and chemistry laboratory values categorized based on common toxicity criteria grade will be presented by treatment groups. All laboratory data will be listed and values that are out of normal range will be indicated (*Table 21*).

### 4.5.3 Vital signs

Observed vital sign values and changes from baseline to visits will be summarized by treatment groups. 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 22*).

## 5. Appendices

### 5.1 Statistical Analysis Plan Table shells

Table 1. Demographic Characteristics

| | All | Viaskin® milk | Placebo | |
|---|---|---|---|---|
| Age, year | | | | |
| n | | | | |
| n missing | | | | |
| Mean ± SD | | | | |
| Median (IQR) | | | | |
| Range | | | | |
| 4-11 years old, n (%) | | | | |
| 12-17 years old, n (%) | | | | |
| Gender, n (%) | | | | |
| Male | | | | |
| Female | | | | |
| Ethnicity, n (%) | | | | |
| Hispanic or Latino | | | | |
| Neither Hispanic nor Latino | | | | |
| Race, n (%) | | | | |
| American Indian or Alaska Native | | | | |
| Asian | | | | |
| Native Hawaiian or other Pacific Islander | | | | |
| Black or African American | | | | |
| White | | | | |
| Does not know | | | | |
| Refuse | | | | |

Values will be expressed as frequency counts (percentages) unless indicated.
SD, Standard deviation; IQR, Interquartile range

**Table 1 specification** Repeat with ITT population and per protocol (PP) population separately as Table 1A and Table 1B, respectively.

Table 2. Medical History by System Organ Class and Preferred Term

| | All | Viaskin® milk | Placebo | |
|---|---|---|---|---|
| Constitutional | | | | |
| Ears, Nose, Mouth, Throat | | | | |
| Cardiovascular | | | | |
| Respiratory | | | | |
| Gastrointestinal | | | | |
| Genitourinary | | | | |
| Integumentary | | | | |
| Musculoskeletal | | | | |
| Neurological | | | | |
| Hematologic | | | | |
| Lymphatic | | | | |
| Allergic | | | | |
| Immunologic | | | | |
| Endocrine | | | | |
| Asthma | | | | |
| Allergic Rhinitis | | | | |
| Food Allergy | | | | |
| Atopic Dermatitis | | | | |
| Other | | | | |

Values will be expressed as frequency counts (percentages) [n (%)].

**Table 2 specification**

Repeat with ITT population and PP population separately as Table 2A and Table 2B, respectively.

Table 3. Summary Statistics for Vital Signs

| | All | Viaskin® milk | Placebo | |
|---|---|---|---|---|
| Height, cm | | | | |
| Baseline # | | | | |
| Visit 10 # | | | | |
| Visit 16 # | | | | |
| Weight, kg | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Blood pressure, mmHg | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Pulse rate, beats/min | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Respiratory rate, breaths/min | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Temperature, °C | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |

# Baseline, Visit 10, and Visit 16 correspond to day 1, end of the double-blind treatment and end of the open-label treatment, respectively.
Values will be expressed as n, n missing, mean ± SD, median (IQR), and range.

Table 4A. Summary Statistics for Laboratory Results (Hematology)

| | All | Viaskin® milk | Placebo | |
|---|---|---|---|---|
| RBC count, MIL/μL | | | | |
| Baseline # | | | | |
| Visit 10 # | | | | |
| Visit 16 # | | | | |
| WBC count, Thou/μL | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Hemoglobin, g/dL | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Hematocrit, % | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Platelet count, Thou/μL | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Segmented neutrophils, cells/μL | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Lymphocytes, cells/μL | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Monocytes, cells/μL | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |

| | | | | |
|---|---|---|---|---|
| Eosinophils, cells/ μL<br>Baseline<br>Visit 10<br>Visit 16 | | | | |
| Basophils, cells/μL<br>Baseline<br>Visit 10<br>Visit 16 | | | | |

# Baseline, Visit 10, and Visit 16 correspond to day 1, end of the double-blind treatment and end of the open-label treatment, respectively.
Values will be expressed as n, n missing, mean ± SD, median (IQR), and range.

Table 4B. Summary Statistics for Laboratory Results (Chemistry)

| | All | Viaskin® milk | Placebo | |
|---|---|---|---|---|
| Total protein, g/dL | | | | |
| Baseline # | | | | |
| Visit 10 # | | | | |
| Visit 16 # | | | | |
| Blood urea nitrogen, mg/dL | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Creatinine, mg/dL | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| ALP (Alkalin phosphatase), U/L | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| ALT (Alanine aminotransferase), U/L | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| AST (aspartate aminotransferase), U/L | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Total bilirubin, mg/dL | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |

# Baseline, Visit 10, and Visit 16 correspond to day 1, end of the double-blind treatment, and end of the open-label treatment, respectively.
Values will be expressed as n, n missing, mean ± SD, median (IQR), and range.

**Table 4 (4A and 4B) Specification**

Laboratory results (Hematology and Chemistry) will also be summarized in the "Other" unit(s) if there is/are "Other" unit(s).

Table 5. Subject Disposition

| | All | Viaskin® milk | Placebo |
|---|---|---|---|
| Randomized, n (%) | | | |
| Yes | | | |
| No | | | |
| Study population, n (%) | | | |
| Safety | | | |
| Intent-to-treat | | | |
| Per protocol | | | |
| Received study medication, n (%) | | | |
| Yes | | | |
| No | | | |
| Completed double-blind period, n (%) | | | |
| Yes | | | |
| No | | | |
| Discontinued double-blind period, n (%) | | | |
| Yes | | | |
| No | | | |
| Completed open-label period, n (%) | | | |
| Yes | | | |
| No | | | |
| Discontinued open-label period, n (%) | | | |
| Yes | | | |
| No | | | |

Values will be expressed as frequency counts (percentages).

Table 6. Descriptive Statistics for Maximum Esophageal Eosinophil Count (Primary Efficacy Endpoint)

| | Viaskin® milk (n=xx) | | | Placebo (n=xx) | | |
|---|---|---|---|---|---|---|
| | Baseline | Visit 10 | Change | Baseline | Visit 10 | Change |
| 4-11 years old<br>n<br>n missing<br>Mean ± SD<br>Median (IQR)<br>Range | | | | | | |
| 12-17 years old<br>n<br>n missing<br>Mean ± SD<br>Median (IQR)<br>Range | | | | | | |
| 4-17 years old (All)<br>n<br>n missing<br>Mean ± SD<br>Median (IQR)<br>Range | | | | | | |

SD, Standard deviation.
Visit 10 is the end of treatment. Change = Visit 10 – Baseline.

**Table 6 specification**

Repeat with ITT population and PP population separately as Table 6A and Table 6B, respectively.

Table 7. Maximum Esophageal Eosinophil Count Analysis at the End of Double-blind Treatment (Primary Efficacy Analysis, ANCOVA models)

| | Least square means | 95% CI |
|---|---|---|
| Viaskin® milk | xx.xx | - |
| Placebo | xx.xx | - |
| Difference (Viaskin® milk – Placebo) | xx.xx | (xx.xx, xx.xx) |

Number of observations used: xxx
Least square means from the analysis of covariance (ANCOVA) model including treatment group and baseline maximum esophageal eosinophil count as covariates will be reported. A two-sided 95% confidence interval (CI) for the difference in least square means between two treatment groups will be reported.

**Table 7 specification**
Repeat with ITT population and PP population with LOCF separately as Table 7A and 7B, respectively.

Table 8. Summary Statistics for Total Esophageal Endoscopy Score (Secondary Efficacy Endpoint)

| | All | Viaskin® milk | Placebo | Median Difference (95% CI) # |
|---|---|---|---|---|
| Total esophageal endoscopy score | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Change from baseline to visit 10 | | | | xx (xx, xx) |
| Change from baseline to visit 16 | | | | xx (xx, xx) |

Values will be expressed as n, n missing, mean ± SD, median (IQR) range.
# Hodges-Lehmann estimate with 95% CI for median differences between two treatment groups will be reported.

**Table 8 specification**
Repeat with ITT population and PP population separately as Table 8A and Table 8B, respectively.

Table 9A. Total Esophageal Endoscopy Score Analysis at the End of the Double-blind Treatment (Secondary Efficacy Analysis, ANCOVA Models)

| | Least square means | 95% CI |
|---|---|---|
| Viaskin® milk | xx.xx | - |
| Placebo | xx.xx | - |
| Difference (Viaskin® milk – Placebo) | xx.xx | (xxxx,xx.xx) |

Number of observations used: xxx.
Least square means from the analysis of covariance (ANCOVA) model including treatment group and total esophageal endoscopy score at baseline as covariates will be reported. A two-sided 95% confidence interval (CI) for the difference in least square means between two treatment groups will be reported.

Table 9B. Total Esophageal Endoscopy Score Analysis at the End of the Open-label Treatment (Secondary Efficacy Analysis, ANCOVA Models)

| | Least square means | 95% CI |
|---|---|---|
| Viaskin® milk | xx.xx | - |
| Placebo | xx.xx | - |
| Difference (Viaskin® milk – Placebo) | xx.xx | (xx.xx, xx.xx) |

Number of observations used: xxx.
Least square means from the analysis of covariance (ANCOVA) model including treatment group and total esophageal endoscopy score at baseline) as covariates will be reported. A two-sided confidence interval (CI) for the difference in least square means between two treatment groups will be reported.

**Table 9 specification**
Repeat with ITT population and PP population separately as Table 9A-1 and Table 9A-2 as well as Table 9B-1 and Table 9B-2, respectively.

Table 10. Summary Statistics for Eosinophilic Esophagitis Symptom and Global Assessment Scores (Secondary Efficacy Endpoints)

| | All | Viaskin® milk | Placebo | |
|---|---|---|---|---|
| Eosinophilic esophagitis symptom score | | | | |
| Baseline | | | | |
| 0 (None) | | | | |
| 1 (Mild) | | | | |
| 2 (Moderate) | | | | |
| 3 (Severe) | | | | |
| 4 (Very severe) | | | | |
| Visit 10 | | | | |
| 0 (None) | | | | |
| 1 (Mild) | | | | |
| 2 (Moderate) | | | | |
| 3 (Severe) | | | | |
| 4 (Very severe) | | | | |
| Visit 16 | | | | |
| 0 (None) | | | | |
| 1 (Mild) | | | | |
| 2 (Moderate) | | | | |
| 3 (Severe) | | | | |
| 4 (Very severe) | | | | |
| Change from baseline to visit 10 | | | | |
| -4 (Very severe to None) | | | | |
| -3 | | | | |
| -2 | | | | |
| -1 | | | | |
| 0 (No change) | | | | |
| 1 | | | | |
| 2 | | | | |
| 3 | | | | |
| 4 (None to Very severe) | | | | |
| Change from baseline to visit 16 | | | | |
| -4 (Very severe to None) | | | | |
| -3 | | | | |
| -2 | | | | |
| -1 | | | | |

Table 10. Summary Statistics for Eosinophilic Esophagitis Symptom and Global Assessment Scores (Secondary Efficacy Endpoints)

| | All | Viaskin® milk | Placebo | |
|---|---|---|---|---|
| 0 (No change) | | | | |
| 1 | | | | |
| 2 | | | | |
| 3 | | | | |
| 4 (None to Very severe) | | | | |

Values will be expressed as frequency counts (percentages).

**Table 10 specifications**

Repeat with each individual eosinophilic esophagitis symptom scores (Abdominal/Chest pain, Vomiting/Regurgitation, and Dysphagia) as well as the investigator's global assessment scores on ITT population and PP population separately as Table 10-1A, Table 10-1B, Table 10-2A, Table 10-2B, Table 10-3A, Table 10-3B, Table 10-4A, and Table 10-4B, respectively.

Table 11. Summary Statistics for The Total Eosinophilic Esophagitis Symptom Score (Secondary Efficacy Endpoint)

| | All | Viaskin® milk | Placebo | |
|---|---|---|---|---|
| Total eosinophilic esophagitis symptom score #<br>Baseline<br>Visit 10<br>Visit 16<br>Change from baseline to visit 10<br>Change from baseline to visit 16 | | | | |
| Improvement in eosinophilic esophagitis total symptom score at visit 10 *<br>Yes (Responders), n (%)<br>No (Non-responders), n (%) | | | | |
| Improvement in eosinophilic esophagitis total symptom score at visit 10 ** | | | | |
| Poor improvement (<30%), n (%)<br>Good improvement (30-70%), n (%)<br>Excellent improvement (>70%), n (%) | | | | |
| Improvement in eosinophilic esophagitis total symptom score at visit 16 *<br>Yes (Responders), n (%)<br>No (Non-responders), n (%) | | | | |
| Improvement in eosinophilic esophagitis total symptom score at visit 16 ** | | | | |
| Poor improvement (<30%), n (%) | | | | |

Table 11. Summary Statistics for The Total Eosinophilic Esophagitis Symptom Score (Secondary Efficacy Endpoint)

| | All | Viaskin® milk | Placebo | |
|---|---|---|---|---|
| Good improvement (30-70%), n (%) | | | | |
| Excellent improvement (>70%), n (%) | | | | |

# Values will be expressed as n, n missing, mean ± SD, median (IQR), and range. Hodges-Lehmann median differences between two treatment groups will be reported.
* Improvement in total eosinophilic esophagitis symptom scores is defined as a decrease in total symptom scores of two or more from baseline to end of the double-blind treatment (visit 10) and from baseline to end of the open-label treatment (visit 16). If change in total symptom score (Visit 10 – baseline or Visit 16 - baseline) is 2 or greater than 2, subject is responder; if not, subject is non-responder. Values will be expressed as frequency counts (percentages).
** Improvement will be reported as Poor, Good, and Excellent as FDA requested.
Relative risk with 95% CI of the improvement between two treatment groups will be presented.

**Table 11 specification**

Repeat with ITT population and PP population separately as Table 11A and Table 11B, respectively.

Table 12. Summary Statistics for Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS) (Secondary Efficacy Endpoint)

| | All | Viaskin® milk | Placebo | Median Difference (95% CI) # |
|---|---|---|---|---|
| Frequency Symptom Score | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Change from baseline to visit 10 | | | | |
| Change from baseline to visit 16 | | | | |
| Severity Symptom Score | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Change from baseline to visit 10 | | | | |
| Change from baseline to visit 16 | | | | |
| Frequency and Severity Symptom Score (Total score) | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Change from baseline to visit 10 | | | | |
| Change from baseline to visit 16 | | | | |

Values will be expressed as n, n missing, mean ± SD, median (IQR), and range.
# Hodges-Lehmann estimate with 95% CI for median differences between two treatment groups will be reported.

**Table 12 specifications**

Repeat with ITT population and PP population separately as Table 12A and Table 12B, respectively.

Table 13A. Summary Statistics for Response rate at the End of the Double-blind Treatment (Secondary Efficacy Endpoint)

| | All | Viaskin® milk | Placebo | Relative Risk (95% CI) |
|---|---|---|---|---|
| Response rate, n (%) | | | | |
| Excellent (≤ 1 eosinophils/HPF) | | | | |
| Good (2-14 eosinophils/HPF) | | | | |
| Poor (≥ 15 eosinophils/HPF) | | | | |

Values will be expressed as frequency counts (percentages).

Table 13B. Summary Statistics for Response rate at the End of the Open-label Treatment (Secondary Efficacy Endpoint)

| | All | Viaskin® milk | Placebo | Relative Risk (95% CI) |
|---|---|---|---|---|
| Response rate, n (%) | | | | |
| Excellent (≤ 1 eosinophils/HPF) | | | | |
| Good (2-14 eosinophils/HPF) | | | | |
| Poor (≥ 15 eosinophils/HPF) | | | | |

Values will be expressed as frequency counts (percentages).

**Table 13 specification**

Repeat on ITT population and PP population separately as Table 13A-1 and Table 13A-2 as well as Table 13B-1 and Table 13B-2, respectively.

Table 14. Summary Statistics for Eosinophilic Esophagitis Quality of Life Score (Secondary Efficacy Endpoint)

| | All | Viaskin® milk | Placebo | Median Difference (95% CI) # |
|---|---|---|---|---|
| Quality of life score | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Change from baseline to visit 10 | | | | xx (xx, xx) |
| Change from baseline to visit 16 | | | | xx (xx, xx) |

Values will be expressed as n, n missing, mean ± SD, median (IQR), and range..
# Hodges-Lehmann estimate with 95% CI for median differences between two treatment groups will be reported.

**Table 14 specifications**
Repeat with ITT population and PP population separately as Table 14A and Table 14B, respectively.

Table 15. Summary Statistics for Composite score (Secondary Efficacy Endpoint)

| | All | Viaskin® milk | Placebo | Median Difference (95% CI) # |
|---|---|---|---|---|
| Quality of life score | | | | |
| Baseline | | | | |
| Visit 10 | | | | |
| Visit 16 | | | | |
| Change from baseline to visit 10 | | | | xx (xx, xx) |
| Change from baseline to visit 16 | | | | xx (xx, xx) |

Values will be expressed as n, n missing, mean ± SD, median (IQR), and range.
# Hodges-Lehmann estimate with 95% CI for median differences between two treatment groups will be reported.

Composite score = Maximum Eosinophils per HPF + 10*EREFS + 2*PEESS +5* (Investigator assessment of EoE symptom activity)

**Table 15 specifications**

Repeat with ITT population and PP population separately as Table 15A and Table 15B, respectively.

Table 16A. Detailed Listing for All Adverse Events by MedDRA System Organ Class

| MedDRA System Organ Class | Treatment Group | Subject ID | Adverse Event Description | Start Date | Severity | Grade | Causality | Action Taken | Stop Date | Outcome | Serious AE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

Adverse events were classified into SOC and PT using Version XX.0 of MedDRA.
The following coding will be used:
Severity: 1=Mild, 2=Moderate, 3=Severe, 4=Life-threatening, and 5=Death.
Grade: 1, 2, 3, and 4.
Causality: 1=Unlikely related, 2=Possibly related, and 3=Probably related.
Action taken: 0=None, 1=Prescribed medication, 2=Non-medication treatment, 3=Hospitalization or prolongation, 4=Discontinued treatment.
Outcome: 1=Ongoing (no change), 2= Recovering/resolving (improving), 3=Worsened, 4=Recovered/resolved with no sequelae, 5= Recovered/resolved with sequelae (chronic stable) 6=Death.

Table 16B. Detailed Listing for All Adverse Events by MedDRA Preferred Term

| MedDRA Preferred Term | Treatment Group | Subject ID | Adverse Event Description | Start Date | Severity | Grade | Causality | Action Taken | Stop Date | Outcome | Serious AE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

Adverse events were classified into SOC and PT using Version XX.0 of MedDRA.
The following coding will be used:
Severity: 1=Mild, 2=Moderate, 3=Severe, 4=Life-threatening, and 5=Death.
Grade: 1, 2, 3, and 4.
Causality: 1=Unlikely related, 2=Possibly related, and 3=Probably related.
Action taken: 0=None, 1=Prescribed medication, 2=Non-medication treatment, 3=Hospitalization or prolongation, 4=Discontinued treatment.
Outcome: 1=Ongoing (no change), 2= Recovering/resolving (improving), 3=Worsened, 4=Recovered/resolved with no sequelae, 5= Recovered/resolved with sequelae (chronic stable) 6=Death.

Table 17A. Adverse Events by System Organ Class (Number of subjects)

| | Viaskin® milk | Placebo |
|---|---|---|
| Number of subject with adverse events | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

Adverse events were classified into SOC and PT using Version XX.0 of MedDRA.

Table 17B. Adverse Events by System Organ Class (Number of adverse events)

| | Viaskin® milk | Placebo |
|---|---|---|
| Total number of adverse events | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

Adverse events were classified into SOC and PT using Version XX.0 of MedDRA.

Table 18. Summary of Adverse Events by Treatment Group

| | All | Viaskin® milk | Placebo |
|---|---|---|---|
| Number of subjects (%) with AEs | | | |
| Number of AEs | | | |
| Number of AEs per subject<br>0<br>1<br>2 + | | | |
| Number of systemic allergic symptoms | | | |
| Potentially drug-related<br>Yes<br>No | | | |
| Severity of AEs<br>Mild<br>Moderate<br>Severe<br>Life-threatening<br>Death | | | |
| Serious AEs (SAEs)<br>Yes<br>No | | | |
| Number of potentially drug-related SAEs | | | |
| AE leading to discontinuation<br>Yes<br>No | | | |
| AE leading to death<br>Yes<br>No | | | |
| Ongoing<br>Yes<br>No | | | |
| Outcome<br>Unchanged<br>Worsened<br>Recovered/resolved with no sequelae<br>Recovered/resolved with sequelae<br>Death | | | |

Table 19A. Treatment-Emergent AEs (TEAEs)* by Treatment Groups (Number of subjects (%))

| | All | Viaskin® milk | Placebo |
|---|---|---|---|
| TEAEs | | | |
| Potentially drug-related TEAE | | | |
| Severity of TEAE<br>Mild<br>Moderate<br>Severe<br>Life-threatening<br>Death | | | |
| Serious TEAE | | | |
| TEAE leading to discontinuation | | | |
| TEAE leading to death | | | |
| Number of TEAEs<br>0<br>1<br>2<br>3 + | | | |
| Ongoing<br>Yes<br>No | | | |
| Outcome<br>Unchanged<br>Worsened<br>Recovered/resolved with no sequelae<br>Recovered/resolved with sequelae<br>Death | | | |

* Treatment-emergent AE is defined as any AE, regardless of relationship to study drug, which occur during AE collection period of study drug or ant event already present that worsens in either intensity or relationship to study drug following exposure to Viaskin®.

Table 19B. Treatment-Emergent AEs (TEAEs)* by Treatment Groups (Number of TEAE)

| | All | Viaskin® milk | Placebo |
|---|---|---|---|
| Number of TEAEs | | | |
| Number of potentially drug-related TEAE | | | |
| Number of severity of TEAE<br>Mild<br>Moderate<br>Severe<br>Life-threatening<br>Death | | | |
| Number of serious TEAE | | | |
| Number of TEAE leading to discontinuation | | | |
| Number of TEAE leading to death | | | |
| Number of TEAEs per subject<br>0<br>1<br>2<br>3 + | | | |
| Number of local TEAE | | | |
| Number of severity of local TEAE<br>Mild<br>Moderate<br>Severe<br>Life-threatening<br>Death | | | |
| Outcome<br>Unchanged<br>Worsened<br>Recovered/resolved with no sequelae<br>Recovered/resolved with sequelae<br>Death | | | |

* Treatment-emergent AE is defined as any AE, regardless of relationship to study drug, which occur during AE collection period of study drug or ant event already present that worsens in either intensity or relationship to study drug following exposure to Viaskin®.

Table 20. Summary Statistics of Local Skin Reactions (Adverse Events)

| | All | Viaskin® milk | Placebo | |
|---|---|---|---|---|
| Number of patients with reactions | | | | |
| 0 | | | | |
| 1 | | | | |
| 2 | | | | |
| 3 | | | | |
| 4 | | | | |

Values will be expressed as frequency counts (percentages) unless indicated.

Table 21. Summary of Laboratory Abnormalities based on CTC Grade by Visit and Treatment Groups

| | Viaskin®Milk | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | Visit 1 | Visit 8 | Visit 10 | Visit 16 | Visit 1 | Visit 8 | Visit 10 | Visit 16 |
| **Hematology** | | | | | | | | |
| RBC Count | | | | | | | | |
| WBC Count | | | | | | | | |
| Hemoglobin | | | | | | | | |
| Hematocrit | | | | | | | | |
| Platelet Count | | | | | | | | |
| Segmented Neutrophils | | | | | | | | |
| Lymphocytes | | | | | | | | |
| Monocytes | | | | | | | | |
| Eosinophils | | | | | | | | |
| Basophils | | | | | | | | |
| **Chemistry** | | | | | | | | |
| Total Protein | | | | | | | | |
| Blood Urea Nitrogen | | | | | | | | |
| Creatinine | | | | | | | | |
| ALP | | | | | | | | |
| ALT | | | | | | | | |
| AST | | | | | | | | |
| Total Bilirubin | | | | | | | | |

Values (abnormalities) will be expressed as frequency counts (percentages). Number of subject evaluated at each visit will be reported.
Treatment groups will be compared using Fisher's exact test.
ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase.

Table 22. Summary of Clinically Relevant Abnormalities in Vital Signs by Visit and Treatment Groups

| | Viaskin® Milk | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | Temperature | Pulse | SBP | DBP | Temperature | Pulse | SBP | DBP |
| Visit 1 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |
| Visit 2 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |
| Visit 3 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |
| Visit 4 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |
| Visit 5 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |
| Visit 6 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |
| Visit 7 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |

Table 22. Summary of Clinically Relevant Abnormalities in Vital Signs by Visit and Treatment Groups

| | Viaskin® Milk | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | Temperature | Pulse | SBP | DBP | Temperature | Pulse | SBP | DBP |
| Visit 8 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |
| Visit 9 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |
| Visit 10 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |
| Visit 11 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |
| Visit 12 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |
| Visit 13 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |
| Visit 14 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |

Table 22. Summary of Clinically Relevant Abnormalities in Vital Signs by Visit and Treatment Groups

| | Viaskin® Milk | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | Temperature | Pulse | SBP | DBP | Temperature | Pulse | SBP | DBP |
| Visit 15 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |
| Visit 16 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |
| Visit 17 | | | | | | | | |
| Abnormal, n (%) | | | | | | | | |
| Number of subjects evaluated | | | | | | | | |

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.
Criteria for abnormalities:
Temperature: < 35 ˚C and a decrease from pre-dosing of at least 1 ˚C or >38.5 ˚C and an increase from pre-dosing of at least 1 ˚C.
Pulse: > 120 beats/minute or an increase from pre-dosing of > 20 beats/minute, or < 50 beats/minute or a decrease from pre-dosing of > 20 beats/minute.
SBP: > 140 mmHg or an increase from pre-dosing of > 40 mmHg, or < 90 mmHg or a decrease from pre-dosing of > 30 mmHg.
DBP: > 90 mmHg or an increase from pre-dosing of > 30 mmHg, or < 50 mmHg or a decrease from pre-dosing of > 20 mmHg.

## 5.2 Consort diagram

**Figure 1: Consort Diagram**