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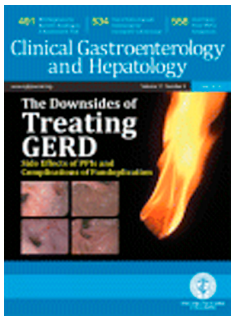

Efficacy of Epicutaneous Immunotherapy in Children with Milk-Induced Eosinophilic Esophagitis

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Title: Efficacy of Epicutaneous Immunotherapy in Children with Milk-Induced Eosinophilic Esophagitis

Short Title: DBPC Trial of EPIT for Milk induced EoE

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Abbreviations:
Adverse events-AE; Analysis of Covariance-ANCOVA; Confidence Interval- CI; Double-Blind-DB; Eosinophils-Eos; Eosinophilic Esophagitis-EoE; Esophagogastroduodenoscopy-EGD; Esophageal Endoscopic Reference Score-EREFS; Epicutaneous Immunotherapy-EPIT; evaluable population –EP; Gastrointestinal-GI; High power field-hpf; Immunoglobulin E-IgE; Intent to Treat-ITT; Interleukin-IL; Medical Dictionary for Regulatory Activities-MedDRA; Open label-OL; Oral immunotherapy-OIT; Pediatric Eosinophilic Esophagitis Symptom Score-PEESS; Per Protocol-PP; Proton pump inhibitor-PPI; Quality of Life- QOL; Serious Adverse Events-SAE; Standard Deviation-SD; The Children's Hospital of Philadelphia-CHOP; United States Federal and Drug Administration-FDA

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The study sponsor (DBV Technologies) had no role in analysis or interpretation of data. They provided the Viaskin Patch. Final study design was done by JMS and AC.

Writing Assistance: None

Author Contributions: JMS-developed the protocol, designed the study, interpreted the data, draft the manuscript and obtained funding (JMS had no role in data acquisition); OUE-provided statistical analysis; ABM, CAL, TBW, MOL- had a role in acquisition of data, drafting manuscript, and analysis of results; BJW-performed all pathology analysis and helped in drafting the manuscript; DB-acquisition of the data, performed all regulatory roles including IND submission and reviewed the manuscript, and AC-PI for the clinical trial, reviewed all data and analysis the data and provided study supervision.

Abstract:

Background & Aims: Eosinophilic esophagitis (EoE) is caused by an immune response to specific food allergens. There are no approved therapies beyond avoidance of the allergen(s) or treatment of inflammation. Epicutaneous immunotherapy (EPIT) reduces features of eosinophilic gastrointestinal disease in mice and pigs. We performed randomized, placebo-controlled study to determine the safety and efficacy of EPIT with Viaskin milk in children with milk-induced EoE.

Methods: In a double-blind study, 20 children (4–17 years old) with milk-induced EoE were randomly assigned to groups given EPIT with Viaskin milk (n=15) or placebo (n=5) for 9 months during a milk-free period, followed by milk-containing diet for 2 months with EPIT. Then, subjects underwent upper endoscopy analysis, biopsies were collected, and maximum esophageal eosinophil counts were determined and was the primary endpoint. After upper endoscopy, patients were given open-label EPIT for 11 months (open-label phase). The subjects were allowed to consume milk if they had maximum values of fewer than 10 eosinophils/high-power field (eos/hpf); otherwise, they remained on a milk-free diet until the last 2 months of the open-label phase.

Results: In the intent to treat population, there was no significant difference between the Viaskin milk group in mean eos/hpf (50.1 ± 43.97 eos/hpf) vs the placebo group (48.20 ± 56.98 eos/hpf). However, in the per-protocol population (7 patients given Viaskin milk and 2 patients given placebo), patients given Viaskin milk patients had a significantly lower mean eos/hpf count (25.57 ± 31.19) than patients given placebo (95.00 ± 63.64) (p=0.038). At the end of the open-label phase, 9 of 19 evaluable subjects had mean values of fewer than 15 eos/hpf (47% response). The number of adverse events did not differ significantly between the Viaskin milk and placebo groups; there was 1 serious adverse event in the placebo group.

Conclusions: In a pilot study of pediatric patients with EoE given EPIT with Viaskin milk or placebo for 11 months, we found no significant difference between groups for the maximum eosinophil count at the end of the study. However, findings from a per-protocol analysis indicate that Viaskin milk can reduce eos/hpf. At study completion, 47% of patients who continued open-label Viaskin milk for an additional 11 months had mean values of fewer than 15 eos/hpf. ClinicalTrials.gov no: NCT02579876

KEY WORDS: immune regulation, food allergy, inflammation, esophagus

Key Words: Epicutaneous Immunotherapy, food allergy, Eosinophilic Esophagitis, clinical trial

Introduction:

Eosinophilic Esophagitis (EoE) is a food-based disease of the esophagus with a current prevalence of 1/2000 in the United States.[1] The typical symptoms of EoE are feeding difficulties and failure to thrive in infants and abdominal pain in children. Dysphagia appears to be more common in older children and adults.[2] Because of these diverse and non-specific symptoms, EoE can be diagnosed only by esophageal biopsy with the finding of greater than or equal to 15 eosinophils/high power field (eos/hpf) using peak value as the primary diagnostic feature.[3, 4]

Unlike other food allergies, EoE is probably not immunoglobulin E (IgE) mediated based on mouse and clinical evidence.[5] Therefore, current investigational studies, such as oral immunotherapy (OIT) for IgE-mediated food allergy, are not successful for EoE. In fact, OIT seems to induce EoE in about 5-10% of the patients.[6] EoE appears to be a T-cell mediated disease as Th2-cytokines, especially interleukin (IL)-13, are associated with esophageal eosinophilia.[2] We recently identified antigen-specific T-cell activation in peripheral blood in milk-sensitive EoE population[7] making T-cells an attractive therapeutic target.

There are two current management options for pediatric EoE. 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, formulation and medication used. However, when steroids are stopped, inflammation and symptoms reoccur.[8] In addition, long-term data on safety and efficacy is not available and potential growth retardation and adrenal suppression are possible.[9] The second treatment option is dietary elimination of the causative antigen(s). The two basic approaches for elimination diets are removal of foods based on testing or removal of the most common food allergens, both with similar rates of remission (50-70%).[10] These diet restrictions are often difficult to follow and may lead to growth or nutritional deficiencies as well as decreased quality of life. When diet is not followed, symptoms and eosinophilia return. Therefore, a novel approach to the treatment of EoE that is focused on the cause of disease is needed. This strategy would be the first to treat the underlying cause of the inflammation - - cell activation in response to food antigen.[7]

For EoE, Mondoulet and colleagues have developed a mouse model based on repeat exposure to peanut. The mice developed profound eosinophilic inflammation in the gastrointestinal (GI) tract (predominantly in the esophagus).[11] Using a similar model, they have also found similar inflammation in piglet model of eosinophilic gastrointestinal disease.[12] They were able to further show that epicutaneous immunotherapy (EPIT) to peanut prevents the development of EoE in both mouse and piglet models. [11, 12] In addition, epicutaneous desensitization has been successfully used to desensitize children with cow's milk-induced and peanut IgE-mediated reactions in phase 2 and 3 clinical trials with excellent safety profile.[13, 14] It is also known that milk is the most common food causing EoE.[10] Therefore, based on these successful models in mice and pigs, we conducted a pilot phase 2A clinical study using EPIT in children with milk-induced EoE, with the goal of reducing esophageal eosinophilia to normal levels after reintroduction of the causative allergen, milk.

Methods:

Study design and Participants

The double-blind (DB), placebo-controlled, individually randomized, parallel group phase 2A trial with an open label extension to study the efficacy and safety of Viaskin Milk, an allergen extract of milk administered epicutaneously using the Viaskin epicutaneous delivery system (DBV Technologies, Paris, FR) in subjects from 4 to 17 years old with a milk induced EoE (Figure 1) (Study of Efficacy and Safety of Viaskin Milk for milk induced EoE: SMILEE Study) was conducted at The Children's Hospital of Philadelphia (CHOP). The diagnosis of EoE was confirmed with an esophagogastroduodenoscopy (EGD) and biopsy showing greater than or equal to 15 eos/hpf after at least two-month period of high dose PPI (1-2 mg/kg dose BID).[15] The screening period had two EGDs with biopsies with the first one on milk-containing diet (minimum of 240 ml a milk a day) and the second on a milk-free diet. Patients completed a daily diary to measure milk consumption. If the upper endoscopy and biopsy on a milk-containing diet showed greater than or equal to 15 eos/hpf and EGD with biopsy on milk-free diet for 2 months showed less than 10 eos/hpf, then subjects were eligible for participation in the study. Eligible

subjects were 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 (both supplied from DBV Technologies, Paris, FR). Viaskin patch is 30mm titanium patch-coated film that is attached to skin with adhesive backing. The subjects were monitored for solicited symptoms and adverse events on regular scheduled visits (Figure 1). After 9 months of EPIT, milk was reintroduced into the diet of the subject at equivalent amounts and duration as the screening period with minimum of 240 ml of milk daily of 2 months. The 9 month treatment period is based on the response in the piglet model.[12] In addition, medications were identical during the two periods (same dose of PPI at 1-2 mg/kg BID, inhaled and intranasal corticosteroids for asthma and allergic rhinitis, respectively). All subjects did not have changes in diet or medications during the trial. The third EGD and biopsy were performed after the milk-reintroduction period. After the third EGD, subjects were enrolled in an 11 month open-label (OL) extension of Viaskin Milk, which was applied daily. The subjects continued milk if there EGD and biopsy had less 10 eos/hpf; otherwise, they excluded milk until last 2-month period, where the subjects had equivalent amounts of milk introduced into their diet until the end of study where the final EGD and biopsy were performed (Figure 1).

Randomization, masking and exclusion criteria are noted in supplemental section and protocol. Determination of per protocol patients were done by 3 individuals blinded to endoscopy results and adverse events. This completed trial is registered with ClinicalTrials.gov, NCT02579876.

Outcome Measures and Procedures:

EGDs and biopsies were done by general anesthesia or sedation as determined by the gastroenterologists. Six biopsies were obtained, fixed in formalin, and paraffin embedded using standard methods. Maximum eosinophil counts per high power (400X) field from 4 µm H&E stained sections were determined by a blinded pathologist. Objective measure of endoscopy (endoscopy score) was measured by using validated scale (Esophageal Endoscopic Reference Score: EREFS).[16] Patient symptoms were measured by four different measures: investigator global assessment scale of

0 to 3 (none-0 to severe -3); individual symptoms of vomiting, abdominal pain and dysphagia (none-0 to severe-3 for total score of 0-9); validated pediatric symptom scale for both parents and children (Pediatric Eosinophilic Esophagitis Symptom Score Version 2 (PEESS®)-Parent and Child).[17] In addition, Quality of Life (QOL) was measured by validated EoE QOL measures for children and parents.[18] Patients' symptoms and adverse events were assessed at each visit (see complete protocol at 10.5281/zenodo.1205510.). Adherence to diet was measured by daily diet record during the on-milk periods. Adherence to therapy (Viaskin patch) was assessed by both daily records and counting the number of patches returned.

Primary and Secondary Endpoints:

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, after milk reintroduction. Exploratory secondary endpoints are listed in the supplemental section.

Statistical Analysis:

The intent-to-treat (ITT) population was defined as all subjects randomized and received one application of study treatment. The per protocol (PP) population included subjects who do not have pre-defined major deviations from the protocol, including no change in PPI dose, equivalent milk consumption between screening and end of study period and meeting all inclusion and exclusion criteria. The evaluable population (EP) was all subjects that had an endoscopy after any Viaskin therapy, the last endoscopy and biopsy was carried forward. The primary and secondary efficacy endpoints were analyzed using the ITT, PP and EP populations. The primary efficacy endpoint of the maximum esophageal eosinophil count was examined using the analysis of covariance (ANCOVA) models with treatment group and baseline patient's maximum esophageal eosinophil count and baseline total esophageal endoscopy score, respectively. The least squares (LS) means for the treatment groups, difference in the LS means between the treatment groups, and two-sided 95%

confidence interval (CI) for the between-treatment differences were presented. Statistical analysis for secondary endpoints, baseline characteristics and sample size calculation are detailed in supplemental section.

All authors had access to the study data and reviewed and approved the final manuscript.

Results:

Between November 11, 2015, and December 20, 2016, 32 participants were screened with 20 eligible participants enrolled and randomized (Figure E1). The 12 screen failures are detailed in the supplemental section. The 20 randomized subjects in 3 to 1 ratio (Viaskin Milk to placebo), were similar in respect to age, gender and ethnicity (Table E1). The baseline eosinophil counts for the on-milk EGD were similar in both groups and off-milk EGDs eosinophils counts were similar in both treatment groups (Table E1). Both Viaskin Milk and placebo groups had fewer EoE symptoms and improved endoscopy scores in the off-milk EGD compared to the on-milk EGD. The placebo treated group had slightly more EoE symptoms on-milk compared to the Viaskin-treated group on-milk based on PEESS and investigator global assessment. One participant did not complete the study due to increased GI symptoms in the Viaskin Milk group at week 29 and this was considered unrelated to study medication and due to anxiety.

Identification of PP patients were determined by 3 physicians blinded to all endoscopies results, visits and therapy and done prior to unmasking treatment assignments. The PP patients had maintained equivalent diet (plus or minus 1 serving size per day) for two on-milk periods; same dose of PPI and >85% compliance with Viaskin patch. Participants were compliant with the daily use of Viaskin patch with an average of 96% (Range 81%-100%). Dietary compliance was poor as 7/20 patients were non-complaint (Table E2 for list of non-compliance with study). There was a high rate of protocol violations with only 9 patients remaining in the per protocol population: 2 patients in the placebo arm and 7 in the Viaskin Milk arm (Figure E1). 5 violations were due to non-adherence to diet therapy as 2 patients in the placebo arm took ¼ less milk and milk-containing products compared

to baseline as they became symptomatic and refused the diet. The opposite occurred in the Viaskin Milk arm as 3 patients took over 4 times the amount of milk at the end of study compared to baseline. Another issue was non-compliance with PPI dosing (2 in the placebo arm and 1 in active). There was also one patient in the active arm that was on swallowed corticosteroids for EoE during the screening endoscopy, a protocol violation at enrollment (Table E2). During the OL phase, compliance was improved with repeated phone calls during the 2-month reintroduction period with no addition protocol violations. However, one subject was discontinued due to refusal to go back on milk-avoidance diet and one subject due to noncompliance of Viaskin patch during the OL phase.

Primary Endpoint

The primary endpoint in ITT population, the two groups were overall similar (the difference in LS means between Viaskin Milk and placebo: 8.6 (95% CI: -35.36, 52.56)). (Table 1). Two placebo patients increased their PPI doses from the baseline to the end of study.[3, 4] In the pre-defined PP population, maximum eosinophil count at the end of the study was significantly lower for the Viaskin Milk (25.57 ± 31.19 eos/hpf) compared to the placebo (95 ± 63.64 eos/hpf) (Table 2). None of the PP on active therapy had worsening of their histological endpoints. The LS means difference between Viaskin Milk (n=7) and placebo (N=2) was -69.37 (95% CI: -117.47, -21.28). For the OL phase, there was a reduction in eos/hpf from baseline to the end of open label [median change (25^{th}, 75^{th} percentiles): -20 (-64, 20), P=0.099]. One active subject had a reduction from year 1 to 2, who did not respond at year 1. Two placebo patients respond after one year of active therapy. The response did not vary based on if a patient was multi-food allergic or milk-only (see supplemental section).

Secondary Endpoints

In the Viaskin Milk DB phase of therapy, 2 subjects had complete normal endoscopies (excellent response: less than 1 eos/hpf) and 2 patients with pre-defined good response between 2-14 eos/hpf compared to none in the placebo for either outcome in PP population. After the open label phase, 2 placebo patients and one active responded with eosinophil counts for total of 9 subjects less than 15 eos/hpf and 6 subjects less than 1 eos/hpf (Figure 2).

We examined symptom scores via three different methods (parent and patient input-PEESS[17]) and investigator assessment of the subject's symptoms. In the ITT population, the symptom score in the Viaskin Milk was similar to that in the placebo group at the end of the study (median (range): 1 (0-5) versus 1 (0-3) (Table 1). The PEESS-patient score was lower in the Viaskin Milk compared to the placebo at the end of the study (median (range): 7 (0, 37) versus 16 (1, 19)). The PEESS-parent was lower in the Viaskin Milk treated group (9; 0-31) compared to the placebo (21; 4-27). The median difference of change in PEESS-parent from baseline to the end of study between the two groups was 8 (95% CI: 1, 16) in favor of Viaskin Milk therapy.

In the PP population on the parent-based PEESS, the change in total score from baseline to end of DB period was lower in the Viaskin Milk group compared to the placebo group (Table 2). For the PP population, the median difference between the two groups in change from baseline and the end of study was 8 (95% CI: 1, 12) in favor of Viaskin Milk therapy. For the patient-derived PEESS, the change in total score in the Viaskin Milk group was nearly identical to that in the placebo group (Table 2). The median difference between the two groups in change from baseline to the end of study was 1 (95% CI: -8, 7). For the investigator assessment of symptoms, there was lower symptoms in the Viaskin Milk group compared to placebo at the end of study (Table 2). The median difference of change in total EoE symptom score from baseline to the end of study between the two groups was 1.5 (95% CI: -3, 6).

In the OL phase, the symptom score after treatment with Viaskin Milk was 1.00 ± 1.00. The PEESS-patient score significantly decreased from baseline to the end of OL (Change from baseline: -9.88 ± 12.26, P=0.004). The PEESS-parent significantly decreased in the Viaskin Milk treated group from baseline to the end of OL (Change from baseline: -14.58 ± 11.77, P=0.0002) (Table 3).

Esophageal inflammation measured by EREFS was similar in the two groups: LS means: 0.61 (95% CI -0.99, 2.22) in ITT group (Table 1). In the PP population, the EGD at the end of study was less severe in the Viaskin Milk group compared to placebo (Table 2). The difference in LS means between two treatment groups for the EREFs at the end of the study was -1.24 (95% CI: -4.83, 2.36)

in favor of Viaskin Milk therapy. At the end of OL phase, the endoscopy score was 1.53 ± 1.47 which was significantly lower than at baseline (Change from baseline: -0.63 ± 1.07, p=0.033) (Table 3).

Quality of life (QOL) was improved in the Viaskin Milk treatment group compared to placebo with greater decrease in QOL score in parents (details in the supplement section) at the end study compared to baseline. A composite score to score each EoE measure equally (symptoms, histology, endoscopy and investigator assessment) showed improvement for all 3 populations: ITT, PP and OL population (see supplemental section for details).

We performed pre-specified sub analysis of the under 12-year age group as this group was found to be more responsive in the previous EPIT.[14] In the ITT population, there was an improvement in primary endpoint and ERFS but not symptom scores (details in the supplemental section).

There was one SAE in the placebo group for vocal cord dysfunction in a subject with asthma leading to a hospitalization at day 2 of the study. The overall rate of AEs was similar in both groups (Table 4) except for a high rate of GI reactions and infection in the Viaskin milk patch. Most of these AEs were thought not be related to study medication (Table 4). For the GI-related AEs, 69 were mild and 4 were moderate (Viaskin Milk-3 and placebo:1). The rate of GI AEs were slightly higher in patch only treatment period-67% (active) versus 40% (placebo) and related GI AE (Active-13% compared 0%-placebo). The general disorders and administration site conditions were all local skin irritation from the Viaskin patch. There was no difference in skin reaction to the patch in the Viaskin Milk group compared to the placebo group when examined in individual skin AEs (Table E3). There was no difference in hematological or chemistry laboratory values seen at baseline or end of DB (Table E4).

Discussion:

This is the first study examining the use of EPIT in children with milk-induced EoE. In the ITT population, there were no differences in the primary or secondary endpoints. There are at least three possibilities for the lack of response 1) lack of efficacy of the therapy; 2) significant protocol violations in both arms or 3) the placebo has some biologic activity. Nevertheless, in the PP population, the

active arm treated with Viaskin Milk patch had lower maximum eosinophils counts on the reintroduction of milk compared to the placebo. None of the PP on active therapy had worsening of their histological, endoscopic or symptom endpoints. There was also improvement in symptoms and endoscopy scores in PP population.

Similar to previous EPIT[14], there was a significant improvement in ITT population for the subjects <12 year of age. The rationale for the improved response to EPIT in this age group may be due to a more pliable immune system with better response to therapy or maybe a factor due to just a small n.

One theory for the failure of response in the ITT population is likely to number of protocol violations in both arms. For example, the patients on the active therapy wanted to ingest more milk, while the patients in the placebo group wanted less making the comparisons difficult. Three patients in the active therapy went on binge milk diets drinking 4-8x the amount of milk compared to baseline. Also, inconsistent use of PPI was an issue due to PPI's effect on esophageal eosinophilia in particular for 2 placebo patients.[3, 4] Other theories is that the therapy is not effective or placebo Viaskin is not true placebo and has biologic activity. The major limitation in the PP population was the small sample size of this pilot study raising the possibility of false positive results.

Nevertheless, a response rate of 47% from baseline in the open label phase, which is similar to EPIT for IgE mediated food allergy[14] suggests that EPIT may be effective for both IgE and non-IgE mediated food allergy.

Overall, the EPIT was safe with no major differences in AEs except for an increase in GI AEs in the active group but noted mostly during the screening period as they added milk into their diet during this period. There was very few treatment-related AEs (Table 4). Overall, the AEs were primarily mild and did not lead to discontinuation except in one subject.

This phase 2A study utilizing EPIT with Viaskin patch shows promise in patients with milk-induced eosinophilic esophagitis broadening the potential role of this therapy for both IgE mediated and non-IgE mediated food allergy. It is thought that EoE is a T-cell mediated disease based on the

lack of success of removing foods found to be positive on IgE testing (skin testing or serum testing). The importance of T-cells was recently confirmed when we examined these milk-sensitive patients and found that their T-cells were triggered in the setting of active disease and could be stimulated by milk antigens.[7] This antigen-specific Th2 cell activity ($CD154^+CD4^+IL5^+$ and $IL13^+$) was not seen in control patients. So, overall EoE appears to be a T-cell dependent disease and EPIT appears be successful for both IgE and T-cell mediated disease. This is an important factor for 5-10% of subjects with IgE mediated food allergy undergoing oral immunotherapy who either develop EoE or EoE is uncovered as they are being treated.[6] With Viaskin EPIT, the possibility of developing EoE would be much less likely as it appears to work on both IgE and non-IgE mediated disease and no patients had worsening of EoE during EPIT.

In conclusion, this is a small pilot study and additional multi-center studies are needed to confirm this finding and the use of EPIT in the treatment of non-IgE mediated food diseases, like EoE.

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330 **Figure Legends**

331

332 Figure 1: Study of Efficacy and Safety of Viaskin Milk for milk induced EoE (SMILEE) Study Diagram:
333 Study visits (V) for the first 3 visits were considered standard of care and could be done at least 2
334 months apart and needed to be on milk containing diet for 2 months and milk-free diet for 2 months.
335 The remaining visits were done at indicated D (days), and M (months). Three
336 esophagogastroduodenoscopy (EGD) were performed as labeled. To qualify for the protocol, the on-
337 milk EGD had ≥15 eosinophils (eos) per high power field (hpf) and off-milk EGD had ≤10 eos/hpf.

338

339 Figure 2: Response to EPIT therapy. The number of patients meeting the secondary endpoint of
340 response to therapy in per protocol (PP) population for the Viaskin Milk and placebo patients at the
341 visit 10 (end of study) EGD and end of open extension. Excellent response is defined as 0-1
342 eosinophil (eos)/hpf. Good response is defined as 2-14 and poor response is defined as >15 eos/hpf.

343 Table 1: Summary Statistics for Primary and Secondary Endpoints for ITT Patients
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	Viaskin Milk (n=15)	Placebo (n=5)	Viaskin Milk (n=15)	Placebo (n=5)
	Visit 10		Change from Baseline	
PRIMARY ENDPOINT				
Maximum Eosinophil Count (eos/hpf)				
Mean (SD)	50.13 (43.97)	48.20 (56.98)	-10.80 (35.73)	-24.20 (63.32)
Median (P25, P75)	34 (10, 83)	50 (1, 50)	-5 (-32, 0)	-62 (-64, 20)
Range	(0, 128)	(0, 140)	(-71, 60)	(-80, 65)
SECONDARY ENDPOINTS				
Total Endoscopy score (EREFS)				
Mean (SD)	1.93 (1.58)	1.60 (1.67)	-0.07 (1.49)	-0.80 (1.30)
Median (P25, P75)	2 (0, 3)	2(0, 2)	0 (-1,1)	-1 (-2, 0)
Range	(0,4)	(0, 4)	(-3,2)	(-2, 1)
Eosinophilic Esophagitis Symptom Score				
Mean (SD)	1.07 (1.49)	1.40 (1.14)	0.33 (1.72)	-0.20 (2.59)
Median (P25, P75)	1(0, 1)	1 (1, 2)	0 (-1, 1)	1 (-3, 2)
Range	(0,5)	(0, 3)	(-2, 5)	(-3, 2)
Pediatric Eosinophilic Esophagitis Symptom Score (PEESS)-Subject (n=13 in Viaskin milk)				
Mean (SD)	11.15 (11.07)	13.20 (7.33)	-5.75 (10.52)	-15.00 (20.70)
Median (P25, P75)	7 (4, 15)	16 (12, 18)	-5 (-12, 1)	-3 (-31, -2)
Range	(0, 37)	(1, 19)	(-27, 14)	(-43, 4)
Pediatric Eosinophilic Esophagitis Symptom Score (PEESS)-Parent				
Mean (SD)	12.53 (10.51)	17.20 (10.57)	-8.20 (12.94)	-14.80 (7.40)
Median (P25, P75)	9 (4, 25)	21 (8, 26)	-4 (-12, 1)	-12 (-18, -11)
Range	(0, 31)	(4, 27)	(-44, 2)	(-26, -7)

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346 HPF-high power field, SD-Standard deviation,
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348 Table 2: Summary Statistics for Primary and Secondary Endpoints for PP Patients
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	Viaskin Milk (n=7)	Placebo (n=2)	Viaskin Milk (n=7)	Placebo (n=2)
	Visit 10		Change from Baseline	
PRIMARY ENDPOINT				
Maximum Eosinophil Count (eos/hpf)				
Mean (SD)	25.57 (31.19)	95.00 (63.64)	-26.86 (22.53)	42.50 (31.82)
Median (P25, P75)	10 (1, 65)	95 (50, 140)	-20 (-49, -5)	43 (20, 65)
Range	(0,75)	(50, 140)	(-62,0)	(20,65)
SECONDARY ENDPOINTS				
Total Endoscopy score (EREFS)				
Mean (SD)	1.43 (1.51)	3.00 (1.41)	-0.14 (1.77)	0.00 (1.41)
Median (P25, P75)	1 (0, 3)	3(2, 4)	0 (-2,1)	0 (-1, 1)
Range	(0,3)	(2, 4)	(-3,2)	0 (-1, 1)
Eosinophilic Esophagitis Symptom Score				
Mean (SD)	0.71 (1.11)	2.00 (1.41)	0.29 (1.25)	-0.50 (3.54)
Median (P25, P75)	0 (0, 1)	2 (1, 3)	0 (0, 0)	-0.5 (-3, 2)
Range	(0,3)	(1, 3)	(-1,3)	(-3, 2)
Pediatric Eosinophilic Esophagitis Symptom Score (PEESS)-Subject				
Mean (SD)	12.20 (8.87)	17.00 (1.41)	-2.25 (6.13)	-2.50 (0.71)
Median (P25, P75)	10 (7, 15)	17 (16, 18)	-2 (-7, 3)	-3 (-3, -2)
Range	(3, 26)	(16, 18)	(-10, 4)	(-3, -2)
Pediatric Eosinophilic Esophagitis Symptom Score (PEESS)-Parent				
Mean (SD)	14.43 (10.42)	14.50 (9.19)	-1.86 (4.02)	-9.00 (2.83)
Median (P25, P75)	10 (7, 25)	14.5 (8, 21)	-1 (-4, 1)	-9.0 (-11, -7)
Range	(2, 31)	(8, 21)	(-10, 1)	(-11, -7)

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351 HPF-high power field, SD-Standard deviation,
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Table 3: Summary Statistics for Primary and Secondary Endpoints for Open Label EP Patients

	Viaskin Milk N=19	Change from Baseline
PRIMARY ENDPOINT		
Maximum Eosinophil Count (eos/hpf)		
Mean (SD)	47.63 (55.43)	-18.21 (49.4)
Median (P25, P75)	20 (0, 95)	-20 (-64, 20)
Range	(0, 159)	(-83, 89)
SECONDARY ENDPOINTS		
Total Endoscopy score (EREFS)		
Mean (SD)	1.53 (1.47)	-0.63 (1.07)
Median (P25, P75)	1 (0, 3)	0 (-2, 0)
Range	(0, 4)	(-2, 1)
Eosinophilic Esophagitis Symptom Score		
Mean (SD)	1.00 (1.00)	0.00 (1.60)
Median (P25, P75)	1(0, 2)	0 (-1, -1)
Range	(0, 3)	(-3, 3)
Pediatric Eosinophilic Esophagitis Symptom Score (PEESS)-Subject (n=16)		
Mean (SD)	9.41 (6.60)	-9.88 (12.26)
Median (P25, P75)	10 (3, 14.5)	-9 (-14, -4)
Range	(0, 21)	(-43, 13)
Pediatric Eosinophilic Esophagitis Symptom Score (PEESS)-Parent		
Mean (SD)	8.68 (6.51)	-14.58 (11.77)
Median (P25, P75)	9 (4, 11)	-12 (-23, -4)
Range	(0, 26)	(-39, 1)

HPF-high power field, SD-Standard deviation,

359 Table 4: **Adverse Events by System Organ Class (Number of subjects), N (%)**

Number of subjects with adverse event(s)	All (n=20)			Viaskin Milk (n=15)			Placebo (n=5)		
	Total	Treatment Emergent[#]	Related[*]	Total	Treatment Emergent[#]	Related[*]	Total	Treatment Emergent[#]	Related[*]
Blood and lymphatic system disorders	3 (15)	0 (0)	0 (0)	2 (13.3)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)
Ear and labyrinth disorders	1 (5)	1 (5)	0 (0)	1 (6.7)	1 (6.7)	0 (0)	0 (0)	0 (0)	0 (0)
Eye Disorders	1 (5)	0 (0)	0 (0)	1 (6.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal Disorders	16 (80)	12 (60)	2 (10)	14 (93.3)	10 (67)	2 (13.3)	2 (40)	2 (40)	0 (0)
General Disorders and administration site conditions	19 (95)	17 (85)	15 (75)	14 (93.3)	12 (80)	12 (80)	5 (100)	5 (100)	3 (60)
Infections and Infestations	16 (80)	11 (55)	0 (0)	13 (86.7)	8 (40)	0 (0)	3 (60)	3 (60)	0 (0)
Injury, poisoning and procedural complications	3 (15)	0 (0)	0 (0)	2 (13.3)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)
Metabolism and nutrition disorders	1 (5)	0 (0)	0 (0)	1 (6.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	3 (15)	3 (15)	0 (0)	2 (13)	2(13)	0 (0)	0 (0)	1 (20)	0 (0)
Nervous system disorders	7 (35)	0 (0)	0 (0)	5 (33.3)	0 (0)	0 (0)	2 (40)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	17 (85)	12 (60)	0 (0)	12 (80.0)	7 (47)	0 (0)	5 (100)	5 (100)	0 (0)
Skin and subcutaneous tissue disorders	2 (10)	1 (5)	1 (5)	2 (13.3)	1 (6.7)	1 (6.7)	0 (0)	0 (0)	0 (0)

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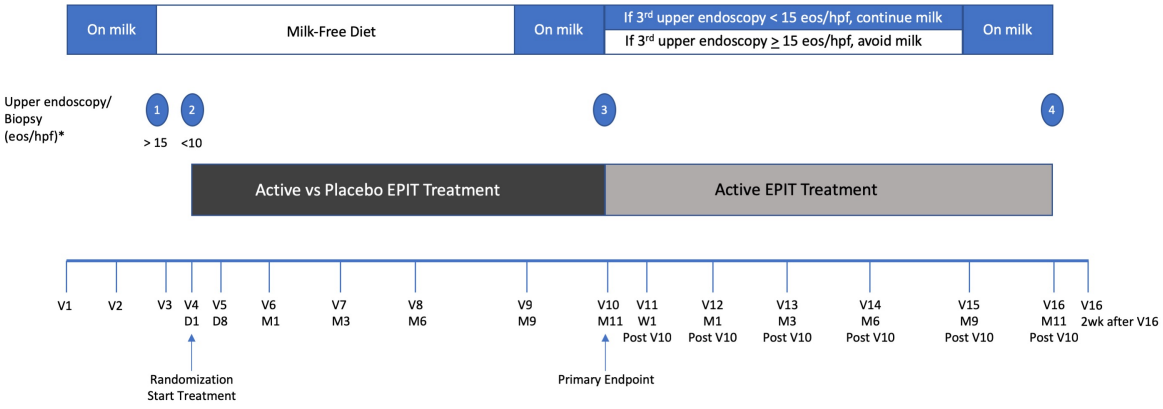
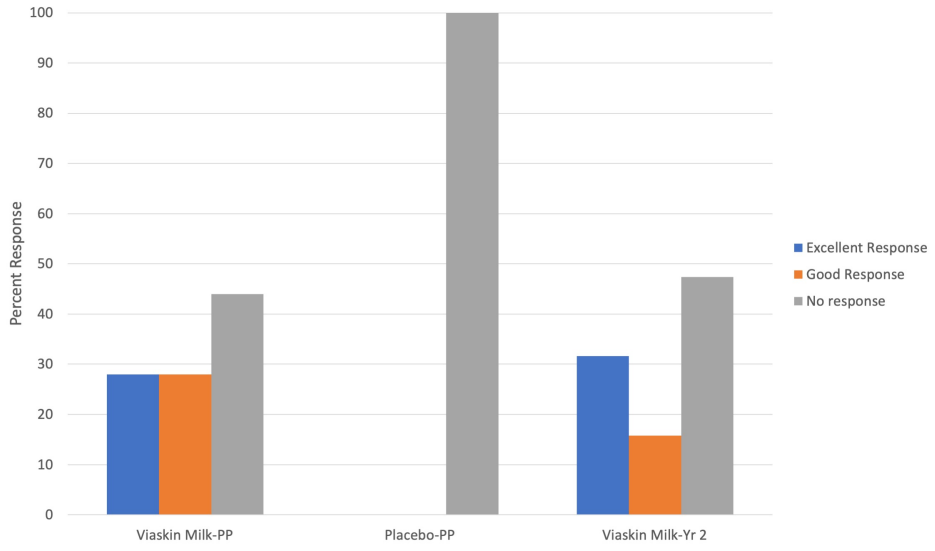
361 #-Adverse Events that occurred when patients when applying patch and not on milk; *All adverse events that were possible, probable and related AE to study medication



* Maximum eosinophils/high power field seen on upper endoscopy



"What You Need to Know"

Need to Know

Background: We performed randomized, placebo-controlled study to determine the safety and efficacy of epicutaneous immunotherapy (EPIT) with Viaskin milk in children with milk-induced EoE.

Findings: In a pilot study of pediatric patients with EoE given EPIT with Viaskin milk or placebo for 11 months, we found no significant difference between groups in the proportions reaching the primary endpoint (eosinophils/high power field) in the intent to treat patients but a reduction in the active patients in the per protocol population compared to placebo. At study completion, 47% of patients who continued open-label Viaskin milk for an additional 11 months had mean values of fewer than 15 eos/hpf.

Implications for Patient Care: Epicutaneous immunotherapy (EPIT) with Viaskin milk can reduce eosinophil counts in about half of children with EoE.