

# ALIMENTARY TRACT

## Efficacy of Epicutaneous Immunotherapy in Children With Milk-Induced Eosinophilic Esophagitis



Jonathan M. Spergel,<sup>\*,‡</sup> Okan U. Elci,<sup>§,||</sup> Amanda B. Muir,<sup>‡,¶</sup> Chris A. Liacouras,<sup>‡,¶</sup> Benjamin J. Wilkins,<sup>#</sup> Deirdre Burke,<sup>\*</sup> Megan O. Lewis,<sup>\*</sup> Terri Brown-Whitehorn,<sup>\*,‡</sup> and Antonella Cianferoni<sup>\*,‡</sup>

<sup>\*</sup>Division of Allergy and Immunology, Children's Hospital of Philadelphia, Pennsylvania; <sup>‡</sup>Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; <sup>§</sup>Westat, Rockville MD; <sup>||</sup>Biostatistics and Data Management Core, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; <sup>¶</sup>Division of Gastroenterology, Hepatology, and Nutrition, Children's Hospital of Philadelphia, Pennsylvania; and <sup>#</sup>Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

### 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 ( $50.1 \pm 43.97$  eos/hpf) vs the placebo group ( $48.20 \pm 56.98$  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 ( $25.57 \pm 31.19$ ) than patients given placebo ( $95.00 \pm 63.64$ ) ( $p = .038$ ). 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](https://www.clinicaltrials.gov) no: NCT02579876

**Keywords:** Immune Regulation; Food Allergy; Inflammation; Esophagus; Epicutaneous Immunotherapy; Eosinophilic Esophagitis; Clinical Trial.

**Abbreviations used in this paper:** AE, adverse events; CI, confidence interval; DB, double blind; EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; EPIT, epicutaneous immunotherapy; GI, gastrointestinal; ITT, intention to treat; LS, least squares; OL, open label; PEESS, Pediatric Eosinophilic Esophagitis Symptom Score; PP, per protocol; PPI, proton pump inhibitor; QOL, quality of life.



Most current article

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1542-3565/\$36.00

<https://doi.org/10.1016/j.cgh.2019.05.014>

Eosinophilic esophagitis (EoE) is a food-based disease of the esophagus with a current prevalence of 1 in 2000 in the United States.<sup>1</sup> 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.<sup>2</sup> Because of these diverse and nonspecific symptoms, EoE can be diagnosed only by esophageal biopsy with the finding of  $\geq 15$  eosinophils/high-power field (eos/hpf) using peak value as the primary diagnostic feature.<sup>3,4</sup>

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

There are 2 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.<sup>8</sup> In addition, long-term data on safety and efficacy is not available and potential growth retardation and adrenal suppression are possible.<sup>9</sup> The second treatment option is dietary elimination of the causative antigen(s). The 2 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%).<sup>10</sup> 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.<sup>7</sup>

For EoE, Mondoulet et al<sup>11</sup> 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). Using a similar model, they have also found similar inflammation in a piglet model of eosinophilic GI disease.<sup>12</sup> They were able to further show that epicutaneous immunotherapy (EPIT) to peanut prevents the development of EoE in both mouse and piglet models.<sup>11,12</sup> 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

## What You Need to Know

### Background

We performed a randomized, placebo-controlled study to determine the safety and efficacy of epicutaneous immunotherapy (EPIT) with Viaskin Milk in children with milk-induced eosinophilic esophagitis (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 per high-power field) in the intention-to-treat patients, but we found a reduction in the active patients in the per-protocol population compared with 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 eosinophils per high-power field.

### Implications for patient care

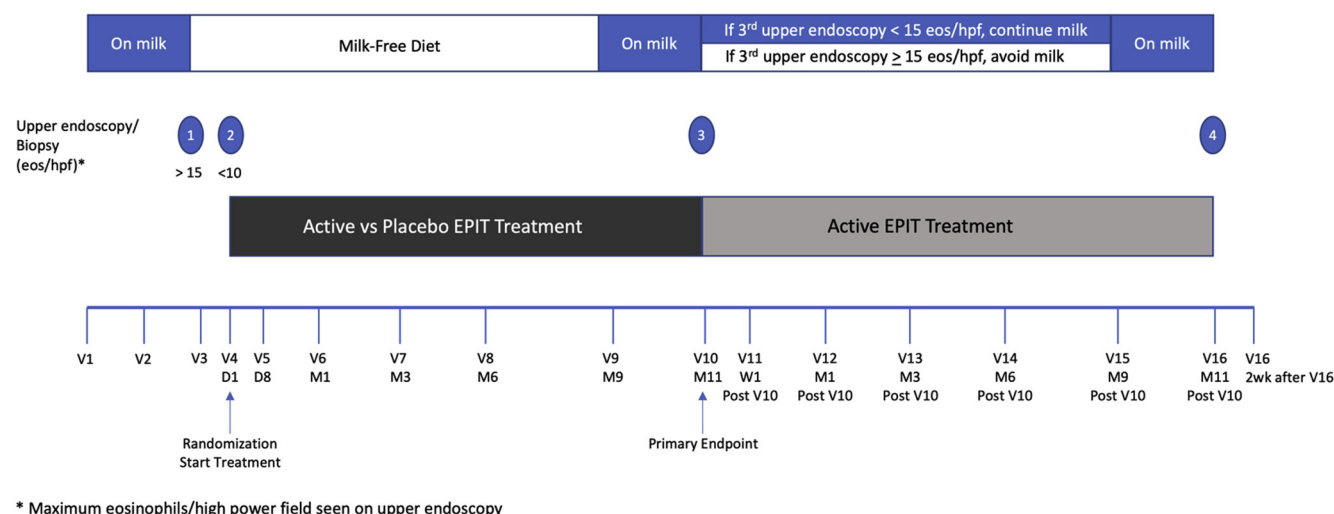
EPIT with Viaskin Milk can reduce eosinophil counts in about half of children with EoE.

profile.<sup>13,14</sup> It is also known that milk is the food that most commonly causes EoE.<sup>10</sup> 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.

## Materials and Methods

### Study Design and Participants

The double-blind (DB), placebo-controlled, individually randomized, parallel-group phase 2A trial with an open-label (OL) 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, France) in subjects from 4 to 17 years of age with a milk-induced EoE (Figure 1) (SMILEE [Study of Efficacy and Safety of Viaskin Milk for milk induced EoE] study) was conducted at the Children's Hospital of Philadelphia. The diagnosis of EoE was confirmed with an esophagogastroduodenoscopy (EGD) and biopsy showing  $\geq 15$  eos/hpf after at least 2-month period of high-dose proton pump inhibitor (PPI) (1–2 mg/kg dose twice daily).<sup>15</sup> The screening period had 2 EGDs with biopsies, with the first one on a milk-containing diet (minimum of 240 mL milk/day) and the second on a milk-free diet. Patients completed a daily diary to



\* Maximum eosinophils/high power field seen on upper endoscopy

**Figure 1.** The SMILEE (Study of Efficacy and Safety of Viaskin Milk for milk induced EoE) study diagram. Study visits (V) for the first 3 visits were considered standard of care and could be done at least 2 months apart and needed to be on a milk-containing diet for 2 months and milk-free diet for 2 months. The remaining visits were done at indicated days (D) and months (M). Three esophagogastroduodenoscopies (EGDs) were performed as labeled. To qualify for the protocol, the on-milk EGD had  $\geq 15$  eosinophils per high-power field (eos/hpf) and the off-milk EGD had  $\leq 10$  eos/hpf.

measure milk consumption. If the upper endoscopy and biopsy on a milk-containing diet showed  $\geq 15$  eos/hpf and EGD with biopsy on milk-free diet for 2 months showed  $< 10$  eos/hpf, then subjects were eligible for participation in the study. Eligible subjects were randomized in a 3:1 ratio, into 2 different treatment groups, to receive epicutaneous immunotherapy (EPIT) with Viaskin Milk (500  $\mu$ g of milk proteins) or placebo (both supplied from DBV Technologies). The Viaskin patch is a 30-mm titanium patch-coated film that is attached to skin with adhesive backing. The subjects were monitored for solicited symptoms and adverse events (AE) 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.<sup>12</sup> In addition, medications were identical during the 2 periods (same dose of PPI at 1–2 mg/kg twice daily, 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 OL extension of Viaskin Milk, which was applied daily. The subjects continued milk if there EGD and biopsy had  $< 10$  eos/hpf; otherwise, they excluded milk until last 2-month period, in which the subjects had equivalent amounts of milk introduced into their diet until the end of study, in which the final EGD and biopsy were performed (Figure 1).

Randomization, masking, and exclusion criteria are noted in [Supplementary Materials](#) and protocol. Determination of per-protocol (PP) patients were done by 3 individuals blinded to endoscopy results and adverse

events. This completed trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT02579876) (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 eos/hpf (400 $\times$ ) field from 4- $\mu$ m hematoxylin and eosin-stained sections were determined by a blinded pathologist. An objective measure of endoscopy (endoscopy score) was measured by using validated scale (Esophageal Endoscopic Reference Score).<sup>16</sup> Patient symptoms were measured by 4 different measures: (1) an investigator global assessment scale ranging from 0 (none) to 3 (severe); (2) patient reported individual symptoms of vomiting, abdominal pain, and dysphagia ranging from 0 (none) to 3 (severe) (total score of 0–9); and a validated pediatric symptom scale for both (3) parents and (4) children (Pediatric Eosinophilic Esophagitis Symptom Score Version 2 [PEESS]–Parent and Child).<sup>17</sup> In addition, quality of life (QOL) was measured by validated EoE QOL measures for children and parents.<sup>18</sup> 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

**Table 1.** Summary Statistics for Primary and Secondary Endpoints for Intention-to-Treat Patients

|                                               | Visit 10              |                   | Change from baseline  |                    |
|-----------------------------------------------|-----------------------|-------------------|-----------------------|--------------------|
|                                               | Viaskin milk (n = 15) | Placebo (n = 5)   | Viaskin milk (n = 15) | Placebo (n = 5)    |
| <b>Primary endpoint</b>                       |                       |                   |                       |                    |
| <b>Maximum eosinophil count, eos/hpf</b>      |                       |                   |                       |                    |
| Mean $\pm$ SD                                 | 50.13 $\pm$ 43.97     | 48.20 $\pm$ 56.98 | -10.80 $\pm$ 35.73    | -24.20 $\pm$ 63.32 |
| Median (IQR)                                  | 34 (10 to 83)         | 50 (1 to 50)      | -5 (-32 to 0)         | -62 (-64 to 20)    |
| Range                                         | (0 to 128)            | (0 to 140)        | (-71 to 60)           | (-80 to 65)        |
| <b>Secondary endpoints</b>                    |                       |                   |                       |                    |
| <b>Total endoscopy score (EREFS)</b>          |                       |                   |                       |                    |
| Mean $\pm$ SD                                 | 1.93 (1.58)           | 1.60 (1.67)       | -0.07 (1.49)          | -0.80 (1.30)       |
| Median (IQR)                                  | 2 (0 to 3)            | 2 (0 to 2)        | 0 (-1,1)              | -1 (-2 to 0)       |
| Range                                         | (0,4)                 | (0 to 4)          | (-3,2)                | (-2 to 1)          |
| <b>Eosinophilic esophagitis symptom score</b> |                       |                   |                       |                    |
| Mean $\pm$ SD                                 | 1.07 $\pm$ 1.49       | 1.40 $\pm$ 1.14   | 0.33 $\pm$ 1.72       | -0.20 $\pm$ 2.59   |
| Median (IQR)                                  | 1 (0 to 1)            | 1 (1 to 2)        | 0 (-1 to 1)           | 1 (-3 to 2)        |
| Range                                         | (0,5)                 | (0 to 3)          | (-2 to 5)             | (-3 to 2)          |
| <b>PEESS-subject (n = 13 in Viaskin milk)</b> |                       |                   |                       |                    |
| Mean $\pm$ SD                                 | 11.15 $\pm$ 11.07     | 13.20 $\pm$ 7.33  | -5.75 $\pm$ 10.52     | -15.00 $\pm$ 20.70 |
| Median (IQR)                                  | 7 (4 to 15)           | 16 (12 to 18)     | -5 (-12 to 1)         | -3 (-31 to -2)     |
| Range                                         | (0 to 37)             | (1 to 19)         | (-27 to 14)           | (-43 to 4)         |
| <b>PEESS-parent</b>                           |                       |                   |                       |                    |
| Mean $\pm$ SD                                 | 12.53 $\pm$ 10.51     | 17.20 $\pm$ 10.57 | -8.20 $\pm$ 12.94     | -14.80 $\pm$ 7.40  |
| Median (IQR)                                  | 9 (4 to 25)           | 21 (8 to 26)      | -4 (-12 to 1)         | -12 (-18 to -11)   |
| Range                                         | (0 to 31)             | (4 to 27)         | (-44 to 2)            | (-26 to -7)        |

EREFS, Esophageal Endoscopic Reference Score; eos/hpf, eosinophils per high-power field; PEESS, Pediatric Eosinophilic Esophagitis Symptom Score.

obtained from the biopsy at the end of double-blind treatment, after milk reintroduction. Exploratory secondary endpoints are listed in the [Supplementary Materials](#).

### Statistical Analysis

The intention-to-treat (ITT) population was defined as all subjects randomized and received 1 application of study treatment. The PP population included subjects who do not have predefined 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 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 evaluable population populations. The primary efficacy endpoint of the maximum esophageal eosinophil count was examined using the analysis of covariance 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 2-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 [Supplementary Materials](#).

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 ([Supplementary Figure E1](#)). The 12 screen failures are detailed in the [Supplementary Materials](#). The 20 randomized subjects in 3:1 ratio (Viaskin Milk to placebo), were similar in respect to age, sex, and ethnicity ([Supplementary Table E1](#)). The baseline eosinophil counts for the on-milk EGD were similar in both groups and off-milk EGD eosinophil counts were similar in both treatment groups ([Supplementary Table E1](#)). Both the Viaskin Milk and placebo groups had fewer EoE symptoms and improved endoscopy scores in the off-milk EGD compared with the on-milk EGD. The placebo-treated group had slightly more EoE symptoms on milk compared with the Viaskin-treated group on milk based on the 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 endoscopy results, visits, and therapy and done before unmasking treatment assignments. The PP patients had maintained equivalent diet

**Table 2.** Summary Statistics for Primary and Secondary Endpoints for Per-Protocol Patients

|                                               | Visit 10             |                   | Change from baseline |                   |
|-----------------------------------------------|----------------------|-------------------|----------------------|-------------------|
|                                               | Viaskin milk (n = 7) | Placebo (n = 2)   | Viaskin milk (n = 7) | Placebo (n = 2)   |
| <b>Primary endpoint</b>                       |                      |                   |                      |                   |
| <b>Maximum eosinophil count (eos/hpf)</b>     |                      |                   |                      |                   |
| Mean $\pm$ SD                                 | 25.57 $\pm$ 31.19    | 95.00 $\pm$ 63.64 | -26.86 $\pm$ 22.53   | 42.50 $\pm$ 31.82 |
| Median (IQR)                                  | 10 (1 to 65)         | 95 (50 to 140)    | -20 (-49 to -5)      | 43 (20 to 65)     |
| Range                                         | (0,75)               | (50 to 140)       | (-62,0)              | (20,65)           |
| <b>Secondary endpoints</b>                    |                      |                   |                      |                   |
| <b>Total endoscopy score (EREFS)</b>          |                      |                   |                      |                   |
| Mean $\pm$ SD                                 | 1.43 $\pm$ 1.51      | 3.00 $\pm$ 1.41   | -0.14 $\pm$ 1.77     | 0.00 $\pm$ 1.41   |
| Median (IQR)                                  | 1 (0 to 3)           | 3 (2 to 4)        | 0 (-2,1)             | 0 (-1 to 1)       |
| Range                                         | (0,3)                | (2 to 4)          | (-3,2)               | 0 (-1 to 1)       |
| <b>Eosinophilic esophagitis symptom score</b> |                      |                   |                      |                   |
| Mean $\pm$ SD                                 | 0.71 $\pm$ 1.11      | 2.00 $\pm$ 1.41   | 0.29 $\pm$ 1.25      | -0.50 $\pm$ 3.54  |
| Median (IQR)                                  | 0 (0 to 1)           | 2 (1 to 3)        | 0 (0 to 0)           | -0.5 (-3 to 2)    |
| Range                                         | (0,3)                | (1 to 3)          | (-1,3)               | (-3 to 2)         |
| <b>PEESS-subject</b>                          |                      |                   |                      |                   |
| Mean $\pm$ SD                                 | 12.20 $\pm$ 8.87     | 17.00 $\pm$ 1.41  | -2.25 $\pm$ 6.13     | -2.50 $\pm$ 0.71  |
| Median (IQR)                                  | 10 (7 to 15)         | 17 (16 to 18)     | -2 (-7 to 3)         | -3 (-3 to -2)     |
| Range                                         | (3 to 26)            | (16 to 18)        | (-10 to 4)           | (-3 to -2)        |
| <b>PEESS-parent</b>                           |                      |                   |                      |                   |
| Mean $\pm$ SD                                 | 14.43 $\pm$ 10.42    | 14.50 $\pm$ 9.19  | -1.86 $\pm$ 4.02     | -9.00 $\pm$ 2.83  |
| Median (IQR)                                  | 10 (7 to 25)         | 14.5 (8 to 21)    | -1 (-4 to 1)         | -9.0 (-11 to -7)  |
| Range                                         | (2 to 31)            | (8 to 21)         | (-10 to 1)           | (-11 to -7)       |

EREFS, Esophageal Endoscopic Reference Score; eos/hpf, eosinophils per high-power field; IQR, interquartile range; PEESS, Pediatric Eosinophilic Esophagitis Symptom Score.

( $\pm 1$  serving size/day) for 2 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 of 20 patients were noncompliant (see [Supplementary Table E2](#) for list of noncompliance with study). There was a high rate of protocol violations, with only 9 patients remaining in the PP population: 2 patients in the placebo arm and 7 in the Viaskin Milk arm ([Supplementary Figure E1](#)). Five violations were due to nonadherence to diet therapy, as 2 patients in the placebo arm took one-quarter less milk and milk-containing products compared with 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 with baseline. Another issue was noncompliance with PPI dosing (2 in the placebo arm and 1 in active). There was also 1 patient in the active arm that was on swallowed corticosteroids for EoE during the screening endoscopy, a protocol violation at enrollment ([Supplementary Table E2](#)). During the OL phase, compliance was improved with repeated phone calls during the 2-month reintroduction period, with no additional protocol violations. However, 1 subject was discontinued due to refusal to go back on a milk-avoidance diet and 1 subject was discontinued due to noncompliance of the Viaskin patch during the OL phase.

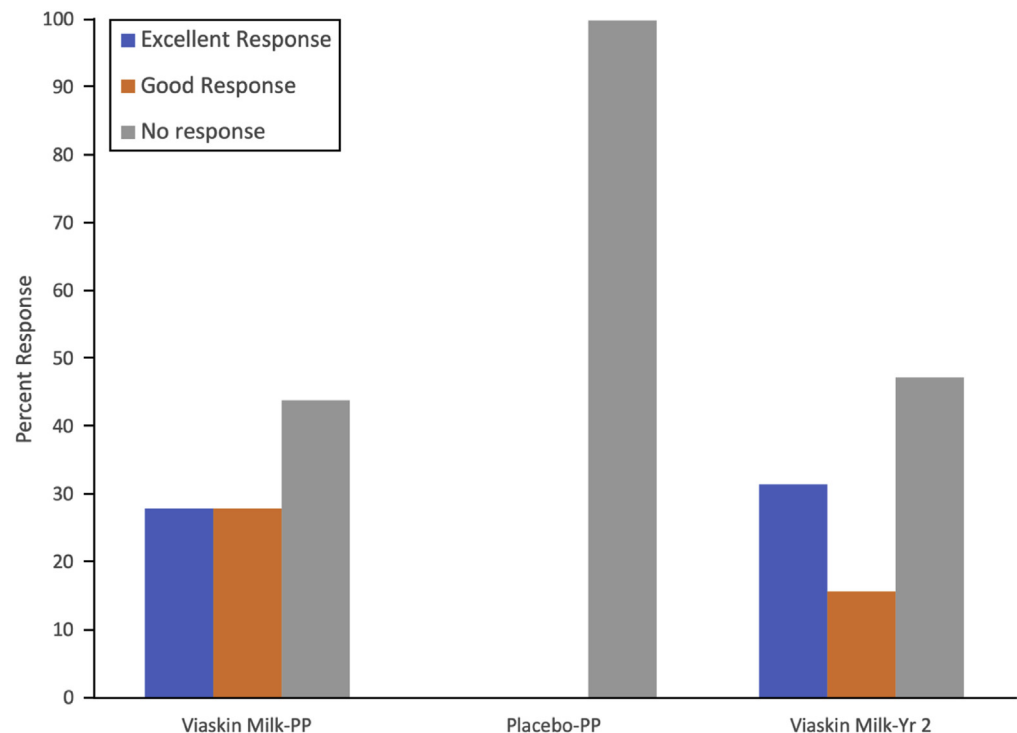
### Primary Endpoint

The primary endpoint in ITT population, the 2 groups were similar overall: the difference in LS means between Viaskin Milk and placebo was 8.6 (95% CI, -35.36 to 52.56) ([Table 1](#)). Two placebo patients increased their PPI doses from the baseline to the end of study.<sup>3,4</sup> In the predefined PP population, maximum eosinophil count at the end of the study was significantly lower for the Viaskin Milk group (25.57  $\pm$  31.19 eos/hpf) compared with the placebo group (95  $\pm$  63.64 eos/hpf) ([Table 2](#)). None of the PP population on active therapy had worsening of their histological endpoints. The LS means difference between Viaskin Milk (n = 7) and placebo (n = 2) groups was -69.37 (95% CI, -117.47 to -21.28). For the OL phase, there was a reduction in eos/hpf from baseline to the end of OL (median change -20 [interquartile range, -64 to 20],  $P = .099$ ). One active subject had a reduction from year 1 to 2, who did not respond at year 1. Two placebo patients respond after 1 year of active therapy. The response did not vary based on if a patient was multifood allergic or milk only (see [Supplementary Materials](#)).

### Secondary Endpoints

In the Viaskin Milk DB phase of therapy, 2 subjects had complete normal endoscopies (excellent response:

**Figure 2.** Response to EPIT therapy. The number of patients meeting the secondary endpoint of response to therapy in the per-protocol (PP) population for the Viaskin Milk and placebo patients at the visit 10 (end of study) esophagogastroduodenoscopy and end of the open-label extension. Excellent response is defined as 0–1 eosinophil per high-power field. Good response is defined as 2–14 eosinophils per high-power field and poor response is defined as >15 eosinophils per high-power field.



<1 eos/hpf) and 2 patients with predefined good response between 2 and 14 eos/hpf compared with none in the placebo for either outcome in PP population. After the OL phase, 2 placebo patients and 1 active patient responded with eosinophil counts, for a total of 9 subjects <15 eos/hpf and 6 subjects <1 eos/hpf (Figure 2).

We examined symptom scores via 3 different methods (PEESS–Parent and PEESS–Patient)<sup>17</sup> 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 1 [range, 0–5] vs 1 [range, 0–3]) (Table 1). The PEESS–Patient score was lower in the Viaskin Milk group compared with the placebo group at the end of the study (median 7 [range, 0–37] vs 16 [range, 1–19]). The PEESS–Parent was lower in the Viaskin Milk–treated group (median 9 [range, 0–31]) compared with the placebo (median 21 [range, 4–27]). The median difference of change in PEESS–Parent from baseline to the end of study between the 2 groups was 8 (95% CI, 1 to 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 with the placebo group (Table 2). For the PP population, the median difference between the 2 groups in change from baseline and the end of study was 8 (95% CI, 1 to 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 2 groups in the change from baseline to the end of study was 1 (95% CI, –8 to 7). For the investigator assessment of

symptoms, there were fewer symptoms in the Viaskin Milk group compared with the placebo group at the end of the study (Table 2). The median difference of change

**Table 3.** Summary Statistics for Primary and Secondary Endpoints for Open-Label Evaluable Population Patients

|                                               | Viaskin milk<br>(n = 19) | Change from<br>baseline |
|-----------------------------------------------|--------------------------|-------------------------|
| <b>Primary endpoint</b>                       |                          |                         |
| <b>Maximum eosinophil count (eos/hpf)</b>     |                          |                         |
| Mean ± SD                                     | 47.63 ± 55.43            | –18.21 ± 49.4           |
| Median (IQR)                                  | 20 (0 to 95)             | –20 (–64 to 20)         |
| Range                                         | (0 to 159)               | (–83 to 89)             |
| <b>Secondary endpoints</b>                    |                          |                         |
| <b>Total endoscopy score (EREFS)</b>          |                          |                         |
| Mean ± SD                                     | 1.53 ± 1.47              | –0.63 ± 1.07            |
| Median (IQR)                                  | 1 (0 to 3)               | 0 (–2 to 0)             |
| Range                                         | (0 to 4)                 | (–2 to 1)               |
| <b>Eosinophilic esophagitis symptom score</b> |                          |                         |
| Mean ± SD                                     | 1.00 ± 1.00              | 0.00 ± 1.60             |
| Median (IQR)                                  | 1 (0 to 2)               | 0 (–1 to –1)            |
| Range                                         | (0 to 3)                 | (–3 to 3)               |
| <b>PEESS–subject (n = 16)</b>                 |                          |                         |
| Mean ± SD                                     | 9.41 ± 6.60              | –9.88 ± 12.26           |
| Median (IQR)                                  | 10 (3 to 14.5)           | –9 (–14 to –4)          |
| Range                                         | (0 to 21)                | (–43 to 13)             |
| <b>PEESS–parent</b>                           |                          |                         |
| Mean ± SD                                     | 8.68 ± 6.51              | –14.58 ± 11.77          |
| Median (IQR)                                  | 9 (4 to 11)              | –12 (–23 to –4)         |
| Range                                         | (0 to 26)                | (–39 to 1)              |

EREFS, Esophageal Endoscopic Reference Score; eos/hpf, eosinophils per high-power field; IQR, interquartile range; PEESS, Pediatric Eosinophilic Esophagitis Symptom Score.

**Table 4.** Adverse Events by System Organ Class

| Number of subjects with adverse event(s)             | All (n = 20) |                                 |                      | Viaskin milk (n = 15) |                                 |                      | Placebo (n = 5) |                                 |                      |
|------------------------------------------------------|--------------|---------------------------------|----------------------|-----------------------|---------------------------------|----------------------|-----------------|---------------------------------|----------------------|
|                                                      | Total        | Treatment emergent <sup>#</sup> | Related <sup>*</sup> | Total                 | Treatment emergent <sup>#</sup> | Related <sup>*</sup> | Total           | Treatment emergent <sup>#</sup> | Related <sup>*</sup> |
| 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)                |

Values are n (%).

#-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

in total EoE symptom score from baseline to the end of study between the 2 groups was 1.5 (95% CI, -3 to 6).

In the OL phase, the symptom score after treatment with Viaskin Milk was  $1.00 \pm 1.00$ . The PEESS-Patient score significantly decreased from baseline to the end of OL (change from baseline:  $-9.88 \pm 12.26$ ;  $P = .004$ ). The PEESS-Parent significantly decreased in the Viaskin Milk treated group from baseline to the end of OL (change from baseline:  $-14.58 \pm 11.77$ ;  $P = .0002$ ) (Table 3).

Esophageal inflammation measured by the Esophageal Endoscopic Reference Score was similar in the 2 groups: the LS means was 0.61 (95% CI -0.99 to 2.22) in the ITT group (Table 1). In the PP population, the EGD at the end of study was less severe in the Viaskin Milk group compared with placebo (Table 2). The difference in LS means between 2 treatment groups for the Esophageal Endoscopic Reference Score at the end of the study was -1.24 (95% CI, -4.83 to 2.36), in favor of Viaskin Milk therapy. At the end of OL phase, the endoscopy score was  $1.53 \pm 1.47$ , which was significantly lower than at baseline (change from baseline:  $-0.63 \pm 1.07$ ;  $P = .033$ ) (Table 3).

QOL was improved in the Viaskin Milk treatment group compared with the placebo group, with a greater decrease in QOL score in parents (details in the Supplementary Materials) at the end study compared with 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 (see Supplementary Materials for details).

We performed prespecified subanalysis of the under-12-years-of-age group, as this group was found to be more responsive in the previous EPIT.<sup>14</sup> In the ITT population, there was an improvement in primary endpoint and ERFs but not symptom scores (details in the Supplementary Materials).

There was 1 serious AE 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 AE was similar in both groups (Table 4), except for a high rate of GI reactions and infection in the Viaskin Milk group. Most of these AE were thought not be related to study medication (Table 4). For the GI-related AE, 69 were mild and 4 were moderate (Viaskin Milk, 3; placebo, 1). The rate of GI AE was slightly higher in patch-only treatment period (67% [active] vs 40% [placebo]) and related GI AE (active 13% compared with 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 with the placebo group when examining in individual skin AE (Supplementary Table E3). There was no difference in hematological or chemistry laboratory values seen at baseline or end of DB phase (Supplementary 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 3 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 the Viaskin Milk patch had lower maximum eosinophil counts on the reintroduction of milk compared with 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,<sup>14</sup> there was a significant improvement in ITT population for the subjects <12 years 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 perhaps a factor owing to a small number of participants.

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 milk, making the comparisons difficult. Three patients in the active therapy went on binge milk diets drinking 4–8× the amount of milk compared with baseline. Also, inconsistent use of PPI was an issue due to PPIs' effect on esophageal eosinophilia in particular for 2 placebo patients.<sup>3,4</sup> 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 OL phase, which is similar to EPIT for IgE-mediated food allergy,<sup>14</sup> 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 AE, except for an increase in GI AE in the active group, which were noted mostly during the screening period, as they added milk into their diet during this period. There was very few treatment-related AE (Table 4). Overall, the AE were primarily mild and did not lead to discontinuation except in 1 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.<sup>7</sup> This antigen-specific Th2 cell activity (CD154<sup>+</sup>CD4<sup>+</sup>IL5<sup>+</sup> and IL13<sup>+</sup>) 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.<sup>6</sup> 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 multicenter studies are needed to confirm this finding and the use of EPIT in the treatment of non-IgE-mediated food diseases, like EoE.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at [www.cghjournal.org](http://www.cghjournal.org), and at <https://doi.org/10.1016/j.cgh.2019.05.014>.

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- Reprint requests**  
Address requests for reprints to: Jonathan M. Spergel, MD, PhD, Children's Hospital of Philadelphia, Division of Allergy and Immunology, Wood Building 3352D, 3401 Civic Center Boulevard, Philadelphia, Pennsylvania 19104. e-mail: [spergel@email.chop.edu](mailto:spergel@email.chop.edu); fax: (215) 590-4529.
- Conflicts of interest**  
These authors disclose the following: Jonathan M. Spergel, Antonella Cianferoni, Megan O. Lewis, and Terri Brown-Whitehorn have consulting agreements and clinical trial grants with DBV Technologies. Jonathan M. Spergel has stock equity with DBV Technologies. The remaining authors disclose no conflicts.
- Funding**  
This work was supported by DBV Technologies (Paris, France) and the Children's Hospital of Philadelphia Eosinophilic Esophagitis Family Fund.

## Supplemental Material

### *Randomization and masking*

Randomization was done with a 3:1 ratio (Viaskin Milk:Placebo) in 4 patient blocks. Four patients >8 years of age were enrolled first per U.S. Food and Drug Administration request. Masking was done with identical-looking Viaskin patches. The randomization list and treatment allocation were done and computer generated by an independent party, eXYSTAT (Paris, France), and they had no other role in the study. Individuals providing care, assessing outcomes, and participants were masked to group assignment. Decisions on per-protocol (PP) patients were done by a group of 3 individuals who were blinded to group assignments and all endoscopy endpoints and were completed before unmasking assignments.

### *Inclusion Criteria*

Subjects were between 4 and 17 years of age at the time of signing the informed consent. They had an upper endoscopy and biopsy at clinical evaluation during screening showing  $\geq 15$  eosinophils per high-power field (eos/hpf) isolated to the esophagus meeting the consensus diagnosis of eosinophilic esophagitis (EoE),<sup>1</sup> after milk was reintroduced into the subject's diet (30 mL/d for 1 week to 2 months), while the subject was on a proton pump inhibitor (PPI). They also needed an upper endoscopy and biopsy at clinical evaluation during screening showing 0–10 eos/hpf isolated to the esophagus after a minimum of 6 weeks under milk-free diet, and while the subject is on a PPI. The subjects need to maintain a constant diet and medication use throughout the trial with the exception of milk as per protocol requirement.

### *Exclusion Criteria*

Participants were excluded if they had IgE-mediated milk allergy (positive skin test or specific IgE to milk using standard techniques), were pregnant or breast-feeding, or were currently taking systemic corticosteroids, tricyclic antidepressants, beta-blockers, or other medications for EoE outside of a PPI. Patients with a history consistent with poorly controlled persistent asthma; comorbid cardiac, autoimmune, infectious gastrointestinal (GI) or pulmonary conditions; or diagnosis of eosinophilic colitis or gastritis were also excluded. Parents or legally authorized representative for participants under 17 years of age signed a written informed consent form using standard Good Clinical Practice procedures. No other concomitant medications or treatments for EoE were allowed, except for a PPI. An independent data and safety monitoring board oversaw the study for safety and risk-benefit assessment.

Monitoring was done by an independent party (Clinical Trial Support Office, Children's Hospital of Philadelphia) and data management and statistical analyses were done by independent party (Westat, Rockville, MD). The study is registered on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02579876) (NCT02579876).

Two changes were implemented in the study protocol to help with recruitment: (1) in the original protocol, the off-milk esophagogastroduodenoscopy (EGD) was first and the on-milk EGD was second, and in the amended protocol either order was permissible; and (2) the maximum count for the off-milk endoscopy was changed from 5 to 10 eos/hpf. The remaining changes were administrative and an open-label extension was added. The full protocol is available on 10.5281/zenodo.1205510.

### *Outcome Measures and Procedures*

The Esophageal Endoscopic Reference Score measured that measures edema, rings, furrows, exudates, and strictures done at each EGD: baseline (visit 2 [V2] and V3), end of double blind (V10), and end of open-label (OL) phase (V16). The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) is a 20-question survey asking patient symptom intensity and frequency on a 5-point scale ranging from 0 to 4 for each question for the preceding month. Therefore, the total score can range from 0 to 80. Quality of life (QOL) and PEESS were evaluated at the time of 4 EGDs during the study, with the first 2 during the screening period EGD on and off the milk-containing diet, the third at the end of the double-blind (DB) phase on the milk-containing diet, and the fourth at the OL phase. Investigator assessment of the subject's symptoms was completed on a 4-point Likert-type scale for 3 separate symptoms (vomiting, abdominal pain, and dysphagia). Post hoc analysis of histology using the Collins-Eosinophilic Esophagitis Histologic Scoring System (EoEHSS)<sup>2</sup> was performed by a single pathologist (B.J.W.) blinded to treatment group.

### *Safety Assessments*

Safety assessments included physical examination and clinical laboratory tests. Adverse events (AE) and serious AE were collected at each visit and reported by treatment groups, subject, start date, severity, grade, causality, action taken, stop date, outcome, and absence of serious AE. Complete blood count with differential and complete metabolic panel were collected at baseline and V10. All AEs were coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities. All efficacy and safety endpoints were agreed on outlined on signed statistical analysis plan on January 5, 2018, before database lock, reviewing any data and data analysis.

### Predefined endpoints

The predefined primary endpoint was difference in the maximum esophageal eosinophil count at the end of treatment between the 2 treatment groups, correcting for baseline differences. Secondary endpoints were studied for both Viaskin Milk and placebo groups, including EoE symptoms score and global assessment score in each treatment group at V10; changes in maximum esophageal eosinophil count from on-milk EGD to V10; the percentages of subjects with  $\leq 1$  eos/hpf (excellent response), subjects with 2–14 eos/hpf (good response), and subjects with  $\geq 15$  eos/hpf (poor response) at V10; difference in esophageal endoscopy score at V10 and changes in esophageal endoscopy score from baseline to V10; changes in the EoE QOL score from baseline to V10; changes in the composite score, which was calculated using 4 measures (eos/hpf, EREFS, PEESS, and investigator assessment of EoE symptom activity), from baseline to V10: [Composite score = Maximum Eosinophils per hpf + 10\*EREFs + 2\*PEESS + 5\*(investigator assessment of EoE symptom activity)].

We also predefined to examine patients under 12 years of age due to improved response to epicutaneous immunotherapy in that population for IgE-mediated food allergies.

### Statistical Analysis

The primary analysis was to test the difference in the maximum esophageal eosinophil count at the end of the treatment between the 2 treatment groups. This test was conducted by calculating the 2-sided 95% confidence interval (CI) for difference in the least squares means between the 2 treatment groups using analysis of covariance. If this 95% CI included zero, then we concluded that there was no difference between the 2 treatment groups. We used standard descriptive statistics, including mean  $\pm$  SD, median (interquartile range [IQR]), and range for continuous variables and frequency counts and percentages for categorical variables, to describe subject's baseline characteristics and study endpoint measures overall and within each treatment group. The secondary endpoint of the total esophageal endoscopy score was examined using the analysis of covariance models with treatment group and baseline patient's maximum esophageal eosinophil count and baseline total esophageal endoscopy score, respectively. The Hodges-Lehmann median analysis to calculate the differences between the 2 treatment groups was performed for the secondary endpoints (total esophageal endoscopy score, total EoE symptom score, PEESS, EoE QOL score). The Hodges-Lehmann estimates with 95% CI for differences of median of the changes in the secondary endpoints were reported. Relative risks along with 95% CI for the percentage of responders showing an excellent response ( $\leq 1$  eos/hpf) and for the percentage of

responders who improved in EoE total symptom score at the end of treatment between the 2 treatment groups were presented. Wilcoxon signed rank test was used for whether within subject median change from baseline to the end of open label study was significantly different than zero. Adverse events summaries used the safety population, defined as all subjects who were randomized and received at least 1 dose of study treatment. We generated all figures, summaries, and statistical analyses using Stata version 15.0 (Stata, College Station, TX).

### Sample Size Calculation

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. Approximately 20 subjects (15 subjects in the active Viaskin Milk group and 5 subjects in the placebo group) were randomized to 2 treatment groups to obtain 18 completed subjects assuming 10% dropout rate. This sample size had 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 SD of 20 using a 2-group *t* test with a 2-sided significance level of .05.

### Results

There were 12 screen failures who did not meet the inclusion or exclusion criteria: 2 due to positive IgE to milk, 7 due to  $<15$  eos/hpf after milk introduction, and 3 due to  $>10$  eos/hpf after milk elimination.

The response for the primary endpoint did not change if the subjects were allergic just to milk (2 of 9 PP patients) or milk only (2 of 4 PP patients) had  $<15$  eos/HPF.

### Secondary Endpoints

QOL was improved in the Viaskin Milk treatment group compared with placebo. A lower score means an improved QOL. In the ITT population for the subjects, the median difference was 1 (95% CI, -12,13). The mean  $\pm$  SD of QOL was lower in Viaskin Milk therapy of  $16.87 \pm 12.06$  compared with  $28.60 \pm 12.03$  in the placebo group at V10. In the PP population, the mean  $\pm$  SD of QOL was lower in Viaskin Milk therapy of  $24.4 \pm 20.68$  was lower compared with  $38.00 \pm 18.38$  in the placebo group at V10. The median difference of change in QOL score from baseline to the end of study between the 2 groups was -2 (95% CI, -33 to 29). There were fewer subjects completing the QOL due to the ages required for the survey. At the end of OL phase, the QOL score was  $23.12 \pm 15.13$  compared with  $28.44 \pm 16.94$  at baseline (change from baseline:  $-5.75 \pm 11.93$ ; *P* = .074).

We created a composite score that weighed the 3 key endpoints (physician, patient, and histology) equally. In the ITT population, the composite score at V10 was lower in Viaskin Milk compared with the placebo (median 98 [IQR, 30 to 155] vs 129 [IQR, 53 to 142]; median difference 61 [95% CI, -48 to 130]). For the PP population, the median change from baseline to V10 was -18 (range, -76 to 12) for Viaskin Milk and was 24.5 (range, 21 to 28) for the placebo. The Hodges-Lehmann median difference between 2 treatment groups was -44.5 (95% CI, -97 to -16). For the OL, the median composite score at V16 was 71 (IQR, 27 to 140), which was lower compared with 138 (IQR, 102 to 183) at baseline (median change from baseline -36 [IQR, -99 to -18];  $P = .002$ ).

For the under-12-years-of-age group, the ITT population (8 in Viaskin Milk and 1 in placebo) had the maximum eos/hpf at V10 for Viaskin Milk (median 48 [range, 0 to 107]); placebo: 140.0. The difference in least-squares means between Viaskin Milk and placebo was -83.68 (95% CI, -160.26 to -7.10). The median change from baseline to the end of study was -13 (range, -71 to 53) for Viaskin Milk and was 65.0 for the placebo. There was a decrease in PEES-Parent score from baseline to the end of study for Viaskin Milk and the placebo (median -5 [-17 to 0] and -11). However, the median endoscopy score at V10 was 2 (range, 0.5 to 3) for the Viaskin Milk group and 2.0 for the placebo group and the median total symptom score was 1 (range, 0 to 5) for the Viaskin Milk group and was 1.0 for the placebo group.

We used the novel pathology endpoints (EoEHSS)<sup>2</sup> in a post hoc analysis. For ITT population, EoEHSS results

were the following Viaskin Milk,  $11.3 \pm 5.8$ ; placebo,  $9.6 \pm 5.2$ . For the PP population, the Viaskin group was  $8.0 \pm 4.6$ , lower than the placebo group,  $13.5 \pm 2.1$ . In an additional post hoc analysis, the response to therapy did not differ in the patients for whom milk was the only cause of their EoE compared with the patients with multiple foods causing their EoE.

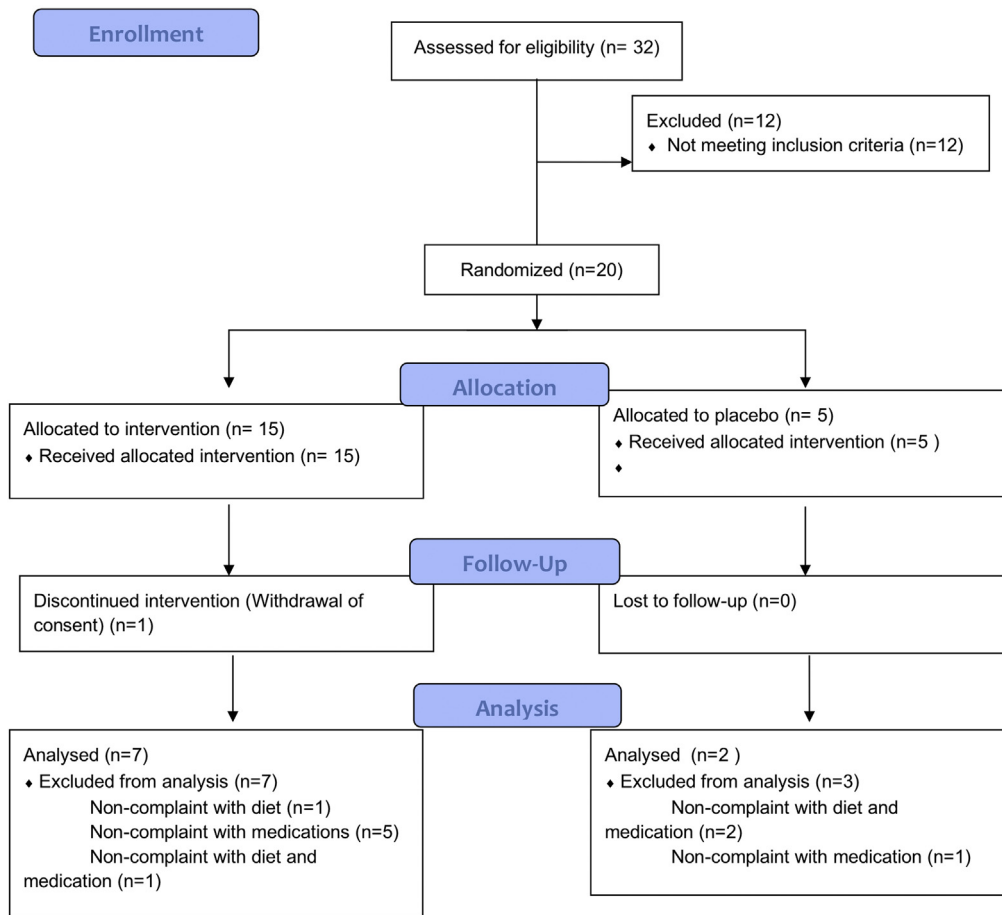
## Acknowledgments

The study was funded by unrestricted grant from DBV Technologies and funds from the Children's Hospital of Philadelphia Eosinophilic Esophagitis Fund. The Viaskin patches were supplied by DBV Technologies.

The authors thank study participants and their family. The authors also thank our study team (A. Hurnton, S. Tilles, R. Saltzman, M. Alfaro, A. Reddy, C. Rooney, J. Wiedmann, S. Guan, P. Mamula, L. Fahey, A. Grossman and Endoscopy suite staff and nurses). The authors thank Mapi Research Trust for the use of PEES and PedsQL-EoE in our study.

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**Supplementary Figure E1.** CONSORT diagram for the clinical trial. The 1 withdrawal was due to increasing gastrointestinal symptoms.

**Supplementary Table E1.** Baseline Demographics

|                                       | Intention to Treat                               |                            | Per Protocol                               |                    |
|---------------------------------------|--------------------------------------------------|----------------------------|--------------------------------------------|--------------------|
|                                       | Viaskin Milk                                     | Placebo                    | Viaskin Milk                               | Placebo            |
| Sex                                   |                                                  |                            |                                            |                    |
| Male                                  | 10 (66)                                          | 5 (100)                    | 4 (57)                                     | 2 (100)            |
| Female                                | 5 (33)                                           | 0                          | 3 (43)                                     | 0                  |
| Caucasian                             | 15                                               | 5                          | 7                                          | 2                  |
| Atopic status                         | 4-AR, 3-AR, AS; 1-AS; 3-AR, AD, AS; 4-FA; 2-none | 2-As, 2-AR, 1-AR, AS, 1-FA | 1-AR, 2-AR, AS; 3-AR, AD, AS; 1-FA; 1-none | 2-As               |
| Subjects with other foods causing EoE | 4                                                | 1                          | 3                                          | 0                  |
| Age, y                                |                                                  |                            |                                            |                    |
| Mean $\pm$ SD                         | 10.46 $\pm$ 2.99                                 | 12.71 $\pm$ 2.03           | 9.56 $\pm$ 3.49                            | 11.02 $\pm$ 2.09   |
| Median (IQR)                          | 10.83 (7.97–12.53)                               | 12.54 (12.50–14.43)        | 8.67 (5.96–12.53)                          | 11.02 (9.55–12.50) |
| Range                                 | (5.86–15.37)                                     | (9.55–14.55)               | (5.86–15.24)                               | (9.55–12.50)       |
| Baseline EGD, eos/hpf on milk         |                                                  |                            |                                            |                    |
| Mean $\pm$ SD                         | 72.40 $\pm$ 29.52                                | 60.93 $\pm$ 49.39          | 52.50 $\pm$ 31.82                          | 52.43 $\pm$ 38.92  |
| Median (IQR)                          | 40 (25–80)                                       | 75 (65–80)                 | 40 (20–80)                                 | 53 (30–75)         |
| Range                                 | (15–178)                                         | (30–112)                   | (30–75)                                    | (20–127)           |
| Baseline EGD, eos/hpf off milk        |                                                  |                            |                                            |                    |
| Mean $\pm$ SD                         | 4.2 $\pm$ 3.69                                   | 1.0 $\pm$ 2.24             | 4 $\pm$ 3.37                               | 0 $\pm$ 0          |
| Median (IQR)                          | 5 (0–6.5)                                        | 0 (0–0)                    | 5 (1.5–4.5)                                | 0 (0–0)            |
| Range                                 | (0–10)                                           | (0–5)                      | (0–10)                                     | (0–0)              |
| Investigator assessment on milk       |                                                  |                            |                                            |                    |
| Mean $\pm$ SD                         | 1.4 $\pm$ 0.89                                   | 1.2 $\pm$ 0.87             | 1.0 $\pm$ 0.89                             | 1.0 $\pm$ 1.41     |
| Median (IQR)                          | 1 (1–2)                                          | 2 (0.5–2)                  | 1 (0–1.75)                                 | 1 (0.5–1.5)        |
| Range                                 | (0–2)                                            | (0–2)                      | (0–2)                                      | (0–2)              |
| Investigator assessment off milk      |                                                  |                            |                                            |                    |
| Mean $\pm$ SD                         | 0.47 $\pm$ 0.64                                  | 0.4 $\pm$ 0.55             | 0.29 $\pm$ 0.48                            | 0 $\pm$ 0          |
| Median (IQR)                          | 0 (0–1)                                          | 0 (0–1)                    | 0 (0–0.5)                                  | 0 (0–0)            |
| Range                                 | (0–2)                                            | (0–1)                      | (0–1)                                      | (0–0)              |
| Endoscopy score on milk (EREFS)       |                                                  |                            |                                            |                    |
| Mean $\pm$ SD                         | 1.93 $\pm$ 1.58                                  | 1.60 $\pm$ 1.67            | 1.43 $\pm$ 1.51                            | 3.00 $\pm$ 1.41    |
| Median (IQR)                          | 2 (1.0–3)                                        | 2 (2.0–3)                  | 2 (0–3)                                    | 3 (3–3)            |
| Range                                 | (0–4)                                            | (2–3)                      | (0–3)                                      | (3–3)              |
| Endoscopy score off milk (EREFS)      |                                                  |                            |                                            |                    |
| Mean $\pm$ SD                         | 0.67 $\pm$ 1.05                                  | 0.4 $\pm$ 0.55             | 0.43 $\pm$ 1.13                            | 0.5 $\pm$ 0.71     |
| Median (IQR)                          | 0 (0–1)                                          | 0 (0–1)                    | 0 (0–0)                                    | 0.5 (0.25–0.75)    |
| Range                                 | (0–3)                                            | (0–1)                      | (0–3)                                      | (0–1)              |
| EoE symptom score on milk             |                                                  |                            |                                            |                    |
| Mean $\pm$ SD                         | 0.73 $\pm$ 1.03                                  | 1.60 $\pm$ 1.82            | 0.43 $\pm$ 0.79                            | 2.50 $\pm$ 2.12    |
| Median (IQR)                          | 0 (0–2)                                          | 1 (0–3)                    | 0 (0–1)                                    | 2.5 (1–4)          |
| Range                                 | (0–3)                                            | (0–4)                      | (0–2)                                      | (1–4)              |
| EoE symptom score off milk            |                                                  |                            |                                            |                    |
| Mean $\pm$ SD                         | 0.20 $\pm$ 0.4                                   | 1.0 $\pm$ 1.22             | 0.14 $\pm$ 0.38                            | 1.50 $\pm$ 2.12    |
| Median (IQR)                          | 0 (0–1)                                          | 1 (0–1)                    | 0 (0–0)                                    | 1.5 (0.75–2.25)    |
| Range                                 | (0–1)                                            | (0–3)                      | (0–1)                                      | (0–3)              |
| EoE PEESS on milk                     |                                                  |                            |                                            |                    |
| Mean $\pm$ SD                         | 17.25 $\pm$ 11.60                                | 28.20 $\pm$ 16.30          | 15.75 $\pm$ 13.82 <sup>a</sup>             | 19.50 $\pm$ 2.12   |
| Median (IQR)                          | 16 (7–28)                                        | 21 (18–32)                 | 16 (4–28) <sup>a</sup>                     | 20 (18–21)         |
| Range                                 | (2–37)                                           | (15–55)                    | (2–30) <sup>a</sup>                        | (18–21)            |
| EoE PEESS off milk                    |                                                  |                            |                                            |                    |
| Mean $\pm$ SD                         | 8.5 $\pm$ 10.26                                  | 7.8 $\pm$ 4.44             | 9.0 $\pm$ 9.12                             | 12.0 $\pm$ 1.41    |
| Median (IQR)                          | 4.5 (2.75–10.75)                                 | 8 (5–11)                   | 7.5 (1.75–14.75)                           | 12 (11.5–12.5)     |
| Range                                 | (0–35)                                           | (2–13)                     | (1–20)                                     | (11–13)            |
| EoE Parent PEESS on milk              |                                                  |                            |                                            |                    |
| Mean $\pm$ SD                         | 20.73 $\pm$ 11.62                                | 32.00 $\pm$ 9.77           | 16.29 $\pm$ 11.22                          | 23.50 $\pm$ 6.36   |
| Median (IQR)                          | 19 (13–29)                                       | 30 (28–39)                 | 18 (6–24)                                  | 23.5 (19–28)       |

**Supplementary Table E1.** Continued

|                          | Intention to Treat |                 | Per Protocol   |                 |
|--------------------------|--------------------|-----------------|----------------|-----------------|
|                          | Viaskin Milk       | Placebo         | Viaskin Milk   | Placebo         |
| Range                    | (3–47)             | (19–44)         | (3–35)         | (19–28)         |
| EoE Parent PEES off milk |                    |                 |                |                 |
| Mean $\pm$ SD            | 8.8 $\pm$ 8.34     | 10.6 $\pm$ 7.64 | 8.0 $\pm$ 3.21 | 7.50 $\pm$ 3.54 |
| Median (IQR)             | 6 (3.5–10.5)       | 710 (5–15)      | 6 (6–9)        | 7.5 (6.25–8.75) |
| Range                    | (0–36)             | (2–21)          | (6–14)         | (5–10)          |

Values are n (%), unless otherwise indicated.

AD, atopic dermatitis; AR, allergic rhinitis; AS, asthma; EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; EREFS, Esophageal Endoscopic Reference Score; FA, IgE-mediated food allergy; IQR, interquartile range; PEES, Pediatric Eosinophilic Esophagitis Symptom Score.

<sup>a</sup>n = 4.

**Supplementary Table E2.** Protocol Violations

| Treatment group reasons not included in per-protocol patients |                                                                                                                |
|---------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| Placebo                                                       | PPI dosing not consistent                                                                                      |
| Placebo                                                       | Diet at beginning of study and at end of study not consistent; PPI dosing not consistent                       |
| Placebo                                                       | Diet at beginning of study and at end of study not consistent                                                  |
| Active                                                        | Did not complete study                                                                                         |
| Active                                                        | Wrong dose of PPI at the end (pharmacy error)                                                                  |
| Active                                                        | Diet at beginning of study and at end of study not consistent                                                  |
| Active                                                        | Diet at beginning of study and at end of study not consistent                                                  |
| Active                                                        | On swallowed steroids at the beginning of study; diet at beginning of study and at end of study not consistent |
| Active                                                        | Diet at beginning of study and at end of study not consistent; PPI dosing not consistent                       |
| Active                                                        | Diet at beginning of study and at end of study not consistent                                                  |
| Active                                                        | PPI dosing not consistent                                                                                      |

PPI, proton pump inhibitor.

**Supplementary Table E3.** Summary of Local Skin Reactions

| Grade    | All (N = 20) | Viaskin Milk (n = 15) | Placebo (n = 5) |
|----------|--------------|-----------------------|-----------------|
| Itching  |              |                       |                 |
| 0        | 20 (100)     | 15 (100)              | 5 (100)         |
| 1        | 19 (95)      | 14 (93.3)             | 5 (100)         |
| 2        | 14 (70)      | 11 (73.3)             | 3 (60)          |
| 3        | 6 (30)       | 5 (33.3)              | 1 (20)          |
| Redness  |              |                       |                 |
| 0        | 20 (100)     | 15 (100)              | 5 (100)         |
| 1        | 18 (90)      | 13 (86.7)             | 5 (100)         |
| 2        | 14 (70)      | 11 (73.3)             | 3 (60)          |
| 3        | 6 (30)       | 5 (33.3)              | 1 (20)          |
| Swelling |              |                       |                 |
| 0        | 20 (100)     | 15 (100)              | 5 (100)         |
| 1        | 12 (60)      | 10 (66.7)             | 2 (40)          |
| 2        | 4 (20)       | 3 (20)                | 1 (20)          |
| 3        | 2 (10)       | 5 (6.7)               | 1 (20)          |

Values are n (%). Inclusion required experiencing at least 1 of the grade levels of local skin reaction.

**Supplementary Table E4.** Chemistry and Hematology

|                                  | Viaskin Milk      |                   | Placebo            |                    |
|----------------------------------|-------------------|-------------------|--------------------|--------------------|
|                                  | Baseline          | Visit 10          | Baseline           | Visit 10           |
| RBC count, MIL/ $\mu$ L          | 4.57 $\pm$ 0.45   | 4.46 $\pm$ 0.28   | 4.78 $\pm$ 0.45    | 4.83 $\pm$ 0.39    |
| WBC, Thou/ $\mu$ L               | 6.34 $\pm$ 1.55   | 6.61 $\pm$ 1.82   | 6.14 $\pm$ 0.99    | 5.90 $\pm$ 0.58    |
| Hemoglobin, g/dL                 | 13.09 $\pm$ 1.27  | 12.81 $\pm$ 1.06  | 13.24 $\pm$ 0.64   | 13.40 $\pm$ 1.18   |
| Platelets, Thou/ $\mu$ L         | 279.5 $\pm$ 49.81 | 283.3 $\pm$ 49.88 | 260.4 $\pm$ 68.62  | 278.0 $\pm$ 69.20  |
| Neutrophils, cells/ $\mu$ L      | 39.33 $\pm$ 7.95  | 36.03 $\pm$ 10.07 | 42.00 $\pm$ 3.52   | 40.92 $\pm$ 9.98   |
| Lymphocytes, cells/ $\mu$ L      | 46.31 $\pm$ 6.88  | 47.12 $\pm$ 8.51  | 39.10 $\pm$ 10.63  | 40.80 $\pm$ 10.71  |
| Eosinophils, cells/ $\mu$ L      | 5.12 $\pm$ 3.51   | 7.14 $\pm$ 2.98   | 7.02 $\pm$ 2.82    | 9.78 $\pm$ 2.97    |
| Total protein, g/dL              | 7.17 $\pm$ 0.27   | 6.91 $\pm$ 0.32   | 7.26 $\pm$ 0.34    | 7.04 $\pm$ 0.09    |
| Blood urea nitrogen, mg/dL       | 10.77 $\pm$ 2.42  | 10.21 $\pm$ 1.72  | 8.67 $\pm$ 1.15    | 9.80 $\pm$ 0.84    |
| Creatinine, mg/dL                | 0.48 $\pm$ 0.09   | 0.49 $\pm$ 0.12   | 0.60 $\pm$ 0.03    | 0.55 $\pm$ 0.09    |
| Alkaline phosphatase, IU/L       | 240.2 $\pm$ 82.80 | 222.0 $\pm$ 50.08 | 303.0 $\pm$ 103.65 | 319.4 $\pm$ 128.11 |
| Alanine aminotransferase, IU/L   | 15.93 $\pm$ 4.18  | 15.43 $\pm$ 4.94  | 19.60 $\pm$ 9.74   | 16.20 $\pm$ 8.14   |
| Aspartate aminotransferase, IU/L | 28.67 $\pm$ 6.52  | 27.29 $\pm$ 7.35  | 25.80 $\pm$ 10.26  | 28.20 $\pm$ 4.15   |
| Total bilirubin, mg/dL           | 0.32 $\pm$ 0.20   | 0.39 $\pm$ 0.29   | 0.34 $\pm$ 0.15    | 0.38 $\pm$ 0.22    |

Values are mean  $\pm$  SD.

RBC, red blood cells; WBC, white blood cells.

**Supplementary Table E5.** Adverse Events in Open-Label Extension Phase

| Adverse event                                        | Total   | Related <sup>a</sup> |
|------------------------------------------------------|---------|----------------------|
| Blood and lymphatic system disorders                 | 3 (15)  | 0 (0)                |
| Ear and labyrinth disorders                          | 1 (5)   | 0 (0)                |
| Eye disorders                                        | 1 (5)   | 0 (0)                |
| Gastrointestinal disorders                           | 16 (80) | 2 (10)               |
| General disorders and administration site conditions | 19 (95) | 15 (75)              |
| Infections and infestations                          | 16 (80) | 0 (0)                |
| Injury, poisoning, and procedural complications      | 3 (15)  | 0 (0)                |
| Metabolism and nutrition disorders                   | 1 (5)   | 0 (0)                |
| Musculoskeletal and connective tissue disorders      | 3 (15)  | 0 (0)                |
| Nervous system disorders                             | 7 (35)  | 0 (0)                |
| Respiratory, thoracic, and mediastinal disorders     | 17 (85) | 0 (0)                |
| Skin and subcutaneous tissue disorders               | 2 (10)  | 1 (5)                |

<sup>a</sup>All AEs that possible, probable and related.