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Sustained milk consumption after 2 years post-Milk Epicutaneous immunotherapy for Eosinophilic Esophagitis

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To the Editor:

Eosinophilic Esophagitis (EoE) is an allergic disease of the esophagus without any curative therapy. Typical symptoms of EoE are feeding difficulties, vomiting, abdominal pain and dysphagia and vary by age, with a diagnosis confirmed on esophageal biopsy with > 15 eosinophils/high power field (eos/hpf).<sup>1</sup>

The three treatment options for pediatric EoE<sup>2</sup> are: 1) high dose proton pump inhibitors which is effective in 50%; 2) topical swallowed steroids, which is effective in inducing EoE remission in 50-90% of patients; 2) dietary elimination of the causative allergen/s which is effective in 50-70% of patients with selective food elimination, and 95% with elemental diets<sup>3</sup>. Cow milk (CM) is the most common food allergen causing disease in up to 65% of patients.<sup>4</sup> When either treatment is discontinued, inflammation and symptoms recur.<sup>3</sup>

Epicutaneous immunotherapy (EPIT) is an investigational immunotherapy using low dose allergen exposure through the skin to induce desensitization. In the randomized controlled clinical trial, *Study of Efficacy and Safety of Viaskin® Milk for CM-induced EoE (SMILEE Study)*, 20 pediatric participants with CM-induced EoE were randomized to receive EPIT with Viaskin® Milk (n=15) or placebo (n=5)(appendix). After CM-induced EoE was confirmed, EPIT therapy was applied daily for 9 months during a CM-free period, followed by CM-containing diet for 2 months. At 11 months in the intent to treat population, there was no significant difference between placebo and active therapy. But, in the pre-defined per-protocol population (7 patients-Viaskin® Milk, 2 patients- placebo), Viaskin® Milk treated subjects had a significant lower number of eos/hpf on biopsy. Endoscopy, symptoms and histologic findings correlated. After the blinded phase, 19 subjects were enrolled in open-label extension (additional 11 months of therapy). At the end of the open-label phase, 6/19 subjects had < 6 eos/hpf (32% response rate); 3/19 subjects had 7-14 eos/hpf for total response rate of 47%.<sup>5</sup>

In this manuscript, we continue to follow all 19 subjects who completed the open-label extension (currently 2 years after the end of Viaskin® Milk therapy) to understand whether CM continued in their diet without symptoms (Figure 1). Medication use, milk consumption and standardized symptom scores were collected during routine clinical care (see appendix). Four of 5 subjects who had <6 eos/hpf after milk introduction were able to continue with approximately 2 servings of CM/day without any symptoms on the 2 symptom scales (Table 1). One subject had an upper endoscopy and biopsy had 0 eosinophils. Two subjects, who had 6-14 eos/hpf during the

study, continued to tolerate CM, including one subject who continued to have 6-14 eos/hpf on repeat endoscopy. In addition, 4 subjects who had significant symptoms ingesting CM and had > 15 eos/hpf during the initial SMILEE study were able to add CM back into their diet without having symptoms, as either baked CM (n=2) or regular CM with concomitant swallowed steroids therapy (n=2).

The follow-up of this pilot study for the use of EPIT for milk-induced EoE suggests that the treatment effect can persist for 2 years after stopping therapy; six out of 7 patients in the responder and partial responder groups remain completely symptom-free while consuming an average of 480 ml/day of CM. In contrast to the current therapies of diet elimination or swallowed topical steroids where symptoms return when therapy is stopped, EPIT has suggests persistent effectiveness. These findings align with EPIT's proposed mechanism of action, by directly targeting and reprogramming the immune response to allergen.<sup>3</sup> EPIT may induce true tolerance, as is observed in murine models, where Foxp3(+) CD25(+) CD4(+) T regulatory cells are induced and can transfer tolerance.<sup>6</sup> Further longer-term studies are needed to examine this possibility and confirm these unique findings.

Reference:

1. Spergel JM, Dellon ES, Liacouras CA, et al. Summary of the updated international consensus diagnostic criteria for eosinophilic esophagitis: AGREE conference. *Ann Allergy Asthma Immunol.* 2018;121:281-284.
2. Spergel JM, Brown-Whitehorn TA, Muir A, Liacouras CA. Medical algorithm: Diagnosis and treatment of eosinophilic esophagitis in children. *Allergy.* 2020;75:1522-1524.
3. Nhu QM, Aceves SS. Medical and dietary management of eosinophilic esophagitis. *Ann Allergy Asthma Immunol.* 2018;121:156-161.
4. Kagalwalla AF, Amsden K, Shah A, et al. Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr.* 2012;55:711-716.
5. Spergel JM, Elci OU, Muir AB, et al. Efficacy of Epicutaneous Immunotherapy in Children With Milk-Induced Eosinophilic Esophagitis. *Clin Gastroenterol Hepatol.* 2020;18:328-336 e327.
6. Dioszeghy V, Mondoulet L, Dhelft V, et al. The regulatory T cells induction by epicutaneous immunotherapy is sustained and mediates long-term protection from eosinophilic disorders in peanut-sensitized mice. *Clin Exp Allergy.* 2014;44:867-881.

7. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. *Gut*. 2013;62:489-495.

Sincerely,

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Table 1

| Responder Status to Viaskin Patch after milk introduction and treatment | <b>Complete responders<br/>(<math>&lt; 6</math> eos/hpf)</b> | <b>Partial Responders<br/>(6-14 eos/hpf)</b> | <b>Non Responders<br/>(<math>&gt; 15</math> eos/hpf)</b>                                                                   |
|-------------------------------------------------------------------------|--------------------------------------------------------------|----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| N                                                                       | 6                                                            | 3                                            | 10                                                                                                                         |
| Eos/hpf at the end of EPIT therapy                                      | 0.2 + 0.4                                                    | 9.3 + 1.2                                    | 53.8 + 46.5                                                                                                                |
| Time from last application of Patch (yrs; mean + SD)                    | 2.0 + 0.2                                                    | 2.0 + 0.1                                    | 2.1 + 0.3                                                                                                                  |
| Current Milk consumption (servings/day; mean + SD)                      | 2.1 + 0.4                                                    | 2.75 + 0.4                                   | 2 subject on baked milk with nl bx<br>2 subjects on milk on swallowed steroids-nl bx<br>3 off milk<br>1-Biological therapy |
| Current Symptoms Score (0-9)                                            | 4 - none<br>1 -Symptom Score of 2                            | 2-none                                       |                                                                                                                            |
| Esophageal biopsy (eos/hpf)                                             | 0<br>N=1                                                     | 10<br>N=1                                    | 2                                                                                                                          |
| EREFS                                                                   | 0                                                            | 2                                            |                                                                                                                            |
| Lost to Follow-up                                                       | 1                                                            | 1                                            |                                                                                                                            |

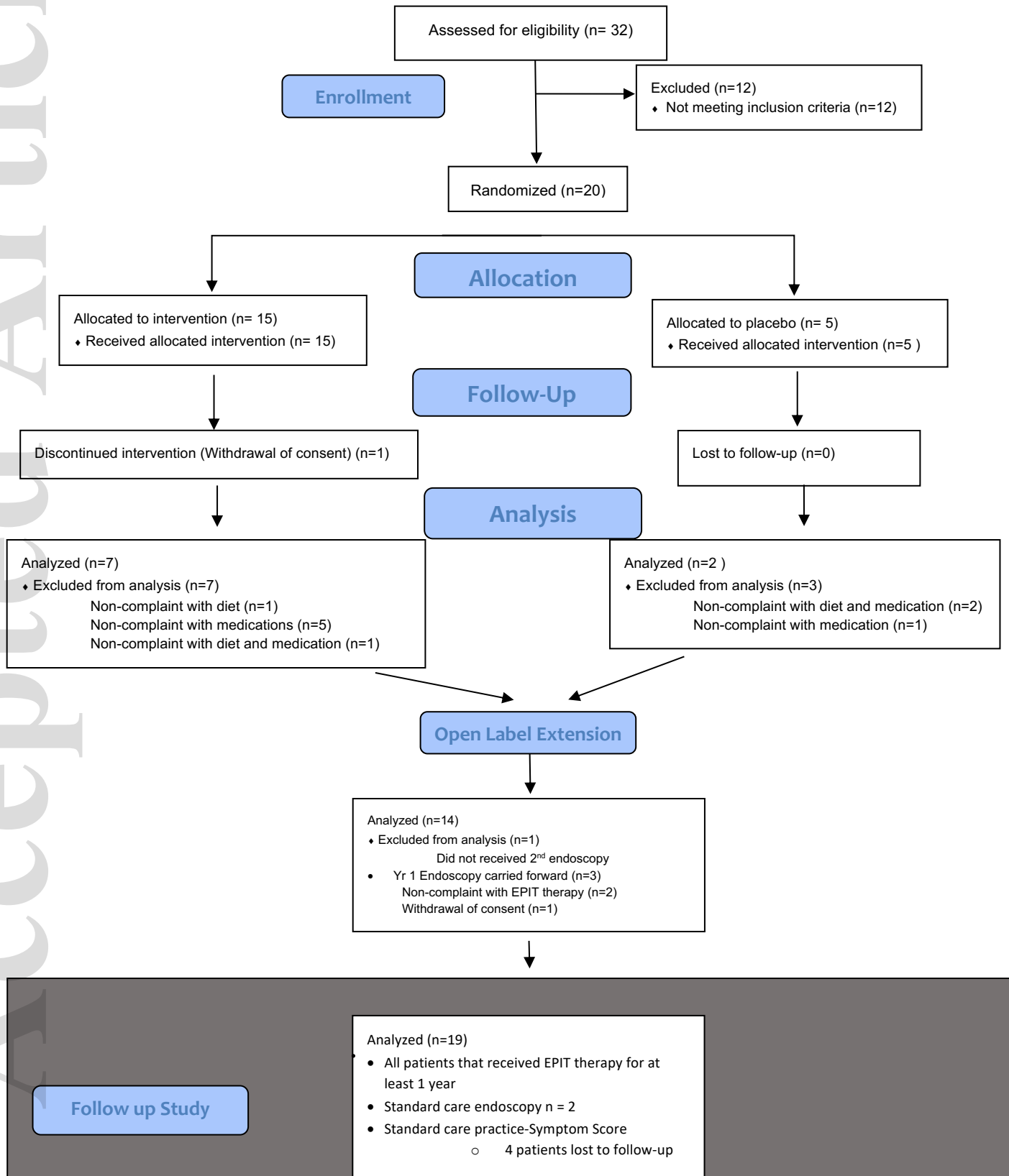
Eos/hpf-eosinophils per high power field; NI bx-normal biopsy; yrs-years, SD-standard deviation, EREFS-Validated endoscopy visual score (Edema, rings, exudate, furrow and strictures)<sup>7</sup>

Figure 1: Consort Diagram

Figure 1 Legend: Consort diagram of original trial and current follow-up studies. The paper focuses on follow-up standard of care aspect of the study. (Area highlighted)

Figure E1

## CONSORT Flow Diagram



## Appendix

### Study Design

A double-blind, placebo-controlled, individually randomized, parallel group phase 2A randomized trial to study the efficacy and safety of Viaskin<sup>®</sup> Milk, an allergen extract of milk administered using the Viaskin<sup>®</sup> epicutaneous delivery system (DBV Technologies<sup>®</sup>, Paris, FR) in subjects from 4 to 17 years old with a milk induced EoE (Figure 1) (Study of Efficacy and Safety of Viaskin<sup>®</sup> Milk for milk induced EoE: SMILEE Study) was conducted at Children's Hospital of Philadelphia (CHOP). Subjects were recruited from the CHOP Center for Pediatric Eosinophilic Diseases. The screening period had two esophagogastroduodenoscopy's (EGD) with biopsies - the first was on a 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  $\geq 15$  (eosinophils/high power field (eos/hpf) and an EGD with biopsy on a milk-free diet for 2 months showed  $< 15$  eos/hpf, then the subjects were eligible for participation in the study. Eligible subjects were randomized in a 3:1 ratio into two different treatment groups to either receive epicutaneous immunotherapy (EPIT) with Viaskin<sup>®</sup> Milk (500  $\mu$ g of milk proteins) or placebo (both supplied from DBV Technologies, Paris, FR), respectively. The Viaskin<sup>®</sup> patch is a 30mm titanium patch-coated film that is attached to skin with adhesive backing. The subjects were monitored for symptoms and adverse events at regularly scheduled visits. After 9 months of EPIT treatment, milk was reintroduced into the diet at equivalent amounts and duration as the screening period with minimum of 240 ml of milk daily of 2 months. In addition, medications remained identical during the study period (same dose of PPI at 1-2 mg/kg BID, inhaled and intranasal corticosteroids for asthma and allergic rhinitis, respectively). All subjects had standard EoE therapy with no change in diet or medications. An end of study EGD with biopsies was performed after the milk-reintroduction period. After the 2<sup>nd</sup> endoscopy, all patients were started on open label active product. The subjects were allowed to continue on milk, if they had less 10 eos/hpf; otherwise,

the subjects removed milk from their diet. After 9 months of open label therapy, milk was reintroduced

Participants were excluded if they had IgE mediated milk allergy (positive skin test or specific IgE to milk using standard techniques)<sup>1</sup>, were pregnant or breastfeeding, were 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 gastritis, gastroenteritis or colitis were also excluded. Parents or legally authorized representatives for participants under 17 years of age signed a written informed consent form using standard GCP (Good Clinical Practice) procedures. 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, CHOP) and data management and statistical analyses were done by independent party (Westat®, Rockville, MD). The clinical trial was done under Children's Hospital of Philadelphia IRB (protocol#13-010148) and IND #16518 and collection of routine follow-up data was approved by Children's Hospital of Philadelphia IRB protocol (#07-005420).

All patients regardless of being in intent to treat or per-protocol analysis were eligible to enroll in the open-label extension as long as they had research endoscopy at the end of the double-blind phase. With amendment (noted in Spergel et al<sup>2</sup>), diet and medication compliance were monitored and corrected during the study.

### **Diagnosis of Eosinophilic Esophagitis**

The diagnosis of EoE was confirmed by performing an esophagogastroduodenoscopy (EGD) and biopsy showing  $\geq 15$  eos/hpf after at least a two-month period of high dose PPI therapy (1-2 mg/kg dose BID).<sup>3</sup> EGDs and biopsies were done under general anesthesia or sedation as determined by the gastroenterologists. Biopsies were obtained, fixed in formalin,

and paraffin embedded using standard methods. Maximum eosinophil counts per high power (eos/hpf, 400X) field from 4 µm H&E stained sections were determined by a blinded pathologist.

### **Symptom monitoring:**

Patient symptoms were tracked using two different measures as standard of care: 1) individual patient symptoms of vomiting, abdominal pain and dysphagia (none-0 to severe-3 for total score of 0-9); 2) a validated pediatric symptom scale for both parents and children (Pediatric Eosinophilic Esophagitis Symptom Score Version 2 (PEESS®)-Parent and Child).<sup>4</sup> The PEESS® is a 20 question survey asking patient symptom intensity and frequency on a 5 point scale (0 to 4) for each question for the preceding month. This information was collected at each follow-up visits and we have incorporated these questionnaires into our standard of care.

**Standard of Care endoscopy:** Endoscopy were completed as standard of care for either new onset symptoms or change of medications and diet. Proton pump inhibitor (PPI) use was unchanged as diet was consistent. (One patient had repeat endoscopy after adding foods and stopping PPIs was not induced in this analysis).

**Medication use:** Medication use and compliance with medication were verified with patient and their parents on each routine clinical visit.

**Milk consumption:** Milk consumption was asked by a registered dietician during routine visits and averaged over a three standard diet record. Serving size is defined by Food Drug Administration as 240 ml.

### **Appendix References:**

1. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol*. 2002;109(2):363-368.
2. Spergel JM, Elci OU, Muir AB, et al. Efficacy of Epicutaneous Immunotherapy in Children With Milk-Induced Eosinophilic Esophagitis. *Clin Gastroenterol Hepatol*. 2020;18(2):328-336 e327.
3. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128(1):3-20 e26; quiz 21-22.
4. Franciosi JP, Hommel KA, DeBrosse CW, et al. Development of a validated patient-reported symptom metric for pediatric eosinophilic esophagitis: qualitative methods. *BMC Gastroenterol*. 2011;11:126.