Varying Doses of Epicutaneous Immunotherapy With Viaskin Milk vs Placebo in Children With Cow's Milk Allergy
A Randomized Clinical Trial

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IMPORTANCE No approved treatment exists for allergen-specific immunoglobulin E (IgE)-mediated cow's milk allergy (CMA), a common childhood food allergy.

OBJECTIVE To assess dose, efficacy, and safety of epicutaneous immunotherapy with Viaskin milk in children with IgE-mediated CMA.

DESIGN, SETTING, AND PARTICIPANTS A phase 1/2, 2-part, randomized, double-blind, placebo-controlled dose-ranging clinical trial in children aged 2 to 17 years with IgE-mediated CMA was conducted between November 2014 through December 2017. It took place at 17 trial sites in the US and Canada. Current CMA was confirmed by double-blind, placebo-controlled food challenge at study entry. Part A assessed the short-term safety of 150 μg, 300 μg, or 500 μg of Viaskin milk; part B evaluated the efficacy and safety of the 3 doses vs placebo over 12 months of treatment. Of the 308 screened participants with physician-diagnosed CMA, 198 met eligibility criteria (including an eliciting dose 300 mg or less) and were randomized.

INTERVENTION Safety of Viaskin milk (150-μg, 300-μg, or 500-μg doses) was evaluated over a 3-week period (part A). In part B, 180 additional participants were randomized to receive Viaskin milk at doses of 150 μg, 300 μg, or 500 μg or placebo (1:1:1:1) for 12 months.

MAIN OUTCOMES AND MEASURES The primary outcome was the proportion of treatment responders, defined as a 10-fold or more increase in the cumulative reactive dose of cow's milk protein (reaching at least 144 mg) or a cumulative reactive dose of cow's milk protein at 1444 mg or more at the month 12 double-blind, placebo-controlled food challenge.

RESULTS A total of 95.5% of the randomized participants (mean [SD] age, 8 [4.17] years; 124 of 198 were male [62.6%]) completed treatment. The highest response rate was observed in participants who received Viaskin milk at the 300-μg dose with 24 of 49 responders (49.0%) overall vs 16 of 53 responders (30.2%) in the placebo group (odds ratio, 2.19; 95% CI, 1.91-5.41; P = .09), highest in the 2 to 11 years age group (22 of 38 [57.9%] vs 13 of 40 [32.5%]; P = .04). Most treatment-emergent adverse events were mild or moderate application-site reactions. One participant in the 500-μg Viaskin milk dose group experienced treatment-related anaphylaxis.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, 12 months of daily epicutaneous immunotherapy with a dose of Viaskin milk at 300 μg was associated with a statistically significant treatment response in 2- to 11-year-old children with IgE-mediated CMA. Treatment-related anaphylaxis and treatment-related discontinuation rates were low. Further research is needed to explore Viaskin milk as a viable treatment option for children with IgE-mediated CMA.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02223182
Immunoglobulin (IgE)-mediated cow’s milk allergy (CMA) is one of the most common food allergies in children, with an estimated prevalence of 2% in children 5 years and younger in the US. Approximately 75% of children may outgrow their allergy, though estimates are difficult due to heterogeneity among studies on the natural history of CMA. CMA is a significant health issue and one of the leading causes of fatal anaphylaxis in young children in the United Kingdom and the US. CMA has a high burden of disease, as children with CMA experience a lower health-related quality of life compared with those with other allergies.

The current standard of care is avoidance and readiness to manage unintended exposures, but accidental ingestion reactions are frequent because of the ubiquitous presence of cow’s milk (CM) in Western diets, with up to 40% of children with milk allergy reporting reactions annually. There are no approved treatments available for IgE-mediated CMA; however, a number of therapies are under investigation, including oral, sublingual, and epicutaneous immunotherapy (EPIT) and biological therapies.

EPIT using the Viaskin platform is a novel investigational treatment that harnesses the immunoregulatory potential of the skin by delivering small amounts of the allergen via a condensation chamber applied daily in the form of a patch. EPIT with Viaskin is under investigation for the treatment of peanut allergy in toddlers and children in several phase 3 trials. Animal studies and early clinical pilot data suggest that EPIT with Viaskin milk (DBV135) may be a promising candidate for the treatment of CMA. This study aimed to assess dose, efficacy, and adverse events (AEs) associated with 12 months of daily Viaskin milk among children aged 2 to 17 years with IgE-mediated CMA.

### Methods

#### Trial Design and Participants

This was a 12-month, phase 1/2, 2-part, multicenter, randomized double-blind placebo-controlled clinical trial (eFigure 1 in Supplement 1). Part A assessed the short-term safety of 150-μg, 300-μg, or 500-μg doses of Viaskin milk. Part B evaluated the efficacy and safety of the 3 doses of Viaskin milk vs placebo.

The protocol and informed consent forms were approved by institutional review boards at each site. The protocol and statistical analysis plan are available in Supplement 2 and Supplement 3, respectively. Written informed consent was provided by all participants’ parents/guardians and assent was obtained from children 7 years or younger, per local institutional review boards guidelines. The trial adhered to the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. The 12-month randomized clinical trial phase was conducted between November 2014 and December 2017. Participants were recruited from 17 sites in Canada and the US.

Eligible participants were aged 2 to 17 years at screening with physician-diagnosed CMA and currently following a strict CM-free diet. Other key inclusion criteria were CM-specific IgE levels of 10 kUA per liter or more, a cow’s milk protein (CMP) skin prick test (SPT) with a largest wheal diameter of 6 mm or more, and an eliciting dose of 300 μg or less (approximately 9 mL of CM) based on a double-blind, placebo-controlled CMP challenge.

#### Interventions

In part A, participants were randomized in 3 successive cohorts of 6 participants each to receive Viaskin milk (150-μg, 300-μg, or 500-μg doses) or placebo in a 2:1 ratio. The safety of each Viaskin milk dose vs placebo was evaluated over a 3-week period by the data and safety monitoring board. All participants in part A continued their blinded treatment at the assigned initial dose through month 12.

At the completion of part A (n = 18), additional participants were randomized 1:1:1:1 to receive Viaskin milk at 150-μg, 300-μg, or 500-μg doses or placebo for 12 months. Patches were applied daily at different sites, depending on the age of the participant, as shown in eFigure 2 in Supplement 1. The duration of patch administration is described in eTable 2 in Supplement 1. Patches were identical except that placebo patches were devoid of CMP and held in place by a transparent film dressing.

#### Outcomes

The primary outcome of part A was safety, as assessed by AEs and AEs of special interest (AESIs), which was reviewed by the
data and safety monitoring board for each dose, beginning with 150 μg, prior to treatment initiation with the next highest dose, or placebo, in a blinded fashion.

The primary efficacy outcome of part B was the proportion of treatment responders after 12 months of treatment and a comparison between the proportion at each dose level vs placebo. Treatment response was defined as a 10-fold or more increase in the cumulative reactive dose (CRD) of CMP (reaching 144 mg or more) or a CRD of CMP 1444 mg or more at the month 12 of the DBPCFC.

Secondary efficacy end points included median and mean CRD and change from baseline at month 12, change in severity of symptoms elicited during the DBPCFC, changes from baseline in specific IgE to CM, casein, alpha-lactalbumin, and beta-lactoglobulin, and SPT wheal size to CMP. Data were analyzed by age group (2 to 11 years [children] and 12 to 17 years [adolescents]) and dose allocation. Food-allergy specific health-related quality of life assessments were performed at screening and month 12 data will be presented in a separate manuscript.

AE outcomes included treatment-emergent AEs (TEAEs), serious TEAEs, and AESIs, including severe local cutaneous reactions and systemic allergic TEAEs considered treatment related. Site investigators graded skin reactions from 0 to 4 and assessed the causality/relationship between the study drug and AE, including anaphylaxis, according to the causality criteria (related, probable, possible, unlikely, or not related). All individuals assessing AEs were blinded to study drug assignment. Exploratory end points included enumeration and characterization of reactions triggered by accidental consumption of CM (any form) during the study.

Statistical Analysis

Statistical Power and Sample Size

In the absence of historical experience with Viaskin milk, sample size was determined to provide sufficient power to detect a 35% or more absolute difference on the primary end point, assuming a 50% response rate for participants treated with Viaskin milk, a 15% response rate for participants treated with placebo, and a dropout rate estimate of 15%. Specifically, a sample size of 41 participants per arm was determined to provide 90% power. Thus, 194 participants were planned for randomization (part A, 18 participants; part B, 176 participants).

Statistical Methods

Categorical variables were summarized using patient counts and percentages. The denominator for percentages was the number of participants in the population with available data, unless otherwise stated. Continuous variables were summarized using descriptive statistics. The primary efficacy analysis involved all randomized participants (ie, intention-to-treat). Part A and part B participants were pooled by dose level, as applicable, for the efficacy analyses at month 12. Participants with missing food challenge values at month 12 were counted as nonresponders. Methods of exact logistic regression were used to compare the proportion of treatment responders at month 12 in each dose level to placebo, adjusting for age group, and including the treatment group as fixed effect. P values and odds ratio (ORs) with 95% CIs, were presented.

The primary analysis was repeated on the completers set (full analysis set) and per-protocol population, which excluded participants who discontinued prior to the posttreatment DBPCFC or those with a major protocol deviation. Details on the statistical analysis of the secondary efficacy end points and immunological markers are in the statistical analysis plan (Supplement 3).

The safety set, used for all safety analyses, included all participants who applied at least 1 patch. Participants were analyzed according to treatment received. Safety analyses included AEs, TEAEs, serious AEs, serious TEAEs, local skin reactions as assessed by the participant and investigator, AESIs, and symptoms elicited during the DBPCFC. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

Results

Study Participants

The population for analysis consisted of all 198 randomized participants (mean age, 8 years; 62.6% male), with 53, 49, 49, and 47 participants randomized to receive placebo, Viaskin milk at 150-μg, 300-μg, and 500-μg doses, respectively (Figure 1). Of these, 152 were aged 2 to 11 years (76.8%) and 46 were aged 12 to 17 years (23.2%) at screening.

Baseline characteristics in the treatment and placebo groups are in eTable 3 in Supplement 1. Prevalence of asthma, atopic dermatitis, and other food allergies was high and balanced across groups.

All randomized participants were included in the safety set. A total of 169 participants (85.4%) were included in the per protocol set: 132 participants aged 2 to 11 years (86.8%) and 37 aged 12 to 17 years (80.4%).

Treatment Exposure and Adherence

Median exposure to treatment was 364 days (quarter 1, 361 days; quarter 3, 368 days) and comparable across groups. Treatment adherence was high and comparable between groups (median adherence = 99.3%), and 189 participants completed the trial (95.5%). The percentage of patches not applied per protocol by the participant (main reasons: discomfort, fell off, forgot, investigator’s decision, or personal convenience) was lower in participants randomized to placebo (median 3.9%; quarter 1, 2.5%; quarter 3, 8.3%) compared with those randomized to any active treatment (median 7.0%; quarter 1, 3.6%; quarter 3, 13.9%). Reasons for study discontinuation were AEs (1.5%), withdrawal of consent (1.5%), lost to follow-up (0.5%), noncompliance (0.5%), and sponsor decision (0.5%).

Assessment of Clinical Response

Primary Outcome

A summary of treatment responders at month 12 in the intention-to-treat set is presented in Table 1. After 12 months of treatment, the highest response rate was observed in the Viaskin
milk 300 μg dose group: 24 of 49 participants were responders (49.0%) compared with 16 of 53 placebo participants (30.2%) (OR, 2.19; 95% CI, 0.91-5.41; \(P = .09\)); a difference of 18.3% (95% CI, -0.70 to 35.62). Lower response rates were observed with Viaskin milk doses of 150 μg and 500 μg (36.7% and 36.2%, respectively). A total of 21 of 49 participants reached a CRD of 1444 mg or more at month 12 in the 300 μg Viaskin milk dose group (42.9%) compared with 13 of 53 placebo participants (24.5%). Sensitivity analyses performed on the primary end point were consistent with the primary analysis (eFigure 3 in Supplement 1).

When analyzed according to prespecified age subgroups, children and adolescents, the highest response rates were observed in children who received the 300-μg dose of Viaskin milk (Figure 2); 22 of 38 (57.9%) vs 13 of 40 (32.5%) placebo participants (OR, 2.82; 95% CI, 1.19-6.84; \(P = .04\)), a difference of 25.39% (2-sided 95% CI, 6.86-41.65). Additional subgroup analyses of the primary end point (specific IgE quartiles, filaggrin mutation, and by country) were not informative.

Secondary and Exploratory Outcomes
Increases in CRD were greatest in participants who received Viaskin milk at the 300 μg dose. The median change over 12 months was 300 mg, 400 mg, 93 mg, and 100 mg in the Viaskin milk 150-μg, 300-μg, and 500-μg groups and placebo group, respectively. Similarly, the geometric least-squares...
mean ratio vs placebo was higher in the Viaskin milk 300-μg dose group (2.27; 95% CI, 1.25-4.13; \( P = .01 \)) compared with the Viaskin milk 150-μg dose group (1.48; 95% CI, 0.82-2.67; \( P = .19 \)) and the Viaskin milk 500-μg dose group (1.11; 95% CI, 0.61-2.02; \( P = .74 \)). When changes in the CRD were analyzed according to age, response was greatest for children who received the 300-μg dose of Viaskin milk (eFigure 4 in Supplement 1). Cross-tabulation of changes in ED at month 12 according to age, response was greatest for children who received the 300-μg dose of Viaskin milk (eFigure 4 in Supplement 1).

Changes in specific IgE and IgG4 over time are shown in Figure 3 and eTable 5 in Supplement 1. Specific IgG4 to casein, alpha-lactalbumin, and beta-lactoglobulin increased up to month 12 in the Viaskin milk 150-μg, 300-μg, and 500-μg groups, and all were significantly higher (all \( P < .001 \)) than placebo. Changes were less marked for CM-specific IgE (with no significant trends to the component proteins), and there was an increase in the Viaskin milk 300-μg dose group only from baseline to month 3, followed by a decrease below the month 0 value at month 12. No meaningful changes in CM-SPT were observed. No overt changes in total objective symptom severity scores were observed between baseline and month 12 DBPCFC in any treatment arm or age group.

Accidental Cow’s Milk Consumption (ACMC) Leading to Reactions

During the 12-month treatment period, 77 participants (38.9%) experienced allergic symptoms following ACMC (128 events), with 24.5% reporting symptoms in the Viaskin milk 300-μg group (12 participants; 16 events) compared with 41.5% in the placebo group (22 participants; 39 events), 44.9% in the Viaskin milk 150-μg group (22 participants; 33 events), and 44.7% in the Viaskin milk 500-μg group (21 participants; 40 events). Additionally, no visits to a hospital emergency department following ACMC were seen among all participants treated with the 300-μg dose of Viaskin milk; proportions were 7.5% (4 of 53), 4.1% (2 of 49), 0% (0 of 49), and 2.1% (1 of 47) in the placebo, Viaskin milk 150-μg, 300-μg, and 500-μg groups, respectively (eFigure 5 in Supplement 1). ACMC was higher in adolescents compared with children; however, in both groups, the lowest reported rate of allergic reactions was in the Viaskin milk 300-μg group (eTable 6 in Supplement 1).

AEs

The incidence of TEAEs is shown in eTable 7 in Supplement 1. Nearly all participants (197 of 198 [99.5%]) experienced at least 1 TEAE, with no difference in rates across the groups. TEAEs were mostly mild (192 participants [97.0%]) or moderate (125 participants [63.1%]), with no notable imbalance across groups. Eight participants (4.0%) experienced serious TEAEs outside of DBPCFCs, including 2 anaphylactic reactions after ACMC; none were considered related to treatment.

Treatment-related TEAEs were reported in 142 participants (71.7%), more frequently in participants receiving Viaskin milk than placebo (Table 2); most commonly reported treatment-related TEAEs were application-site reactions (eTable 8 in Supplement 1). Severe treatment-related TEAEs were reported in 8 participants: 4 receiving Viaskin milk at 500 μg (3 with severe application-site reactions, 1 with 2 anaphylactic events deemed probably related to Viaskin milk by the investigator, neither of which were treated with epinephrine), 2 receiving Viaskin milk at 150 μg (severe application-site reaction), and 1 each receiving Viaskin milk at 300 μg and placebo (both severe application-site reactions). Three participants (1.5%) reported a TEAE leading to permanent study discontinuation: 2 receiving Viaskin milk at 300-μg doses (impe-tigo, eczema flare) and 1 receiving Viaskin milk at 500-μg doses (abdominal pain).

In the 2 age subgroups, the frequency and distribution of TEAEs were generally comparable with the overall population. The adolescent group had higher rates of moderate TEAEs, Viaskin milk minus unrelated systemic allergic symptoms and Viaskin milk minus unrelated TEAEs leading to epinephrine administration, were primarily attributed to ACMC.

Discussion

This phase 1/2 study aimed to identify the optimal target population and safe and effective dose of Viaskin milk to investigate in future studies in children with CMA. The Viaskin milk 300-μg 2- to 11-year-old subgroup had a significantly higher proportion of responders, defined by CMA desensitization proven with DBPCFC. All doses of Viaskin milk were associated
with very low rates of serious TEAEs. Local application-site reactions were the most common treatment-related AE, were generally mild or moderate, and did not result in study discontinuation. The high rate of local application-site reactions was expected based upon prior experience with Viaskin peanut. Overall, across the 12 months of the randomized clinical trial, dropout rates were low (4.5%) and compliance with Viaskin milk was high, suggesting tolerability and ease of use.

Quantitative risk-assessment modeling by Remington et al. has demonstrated that increasing the CMPED to 300 mg or 1000 mg in patients with allergy predicts clinically meaningful reductions in the risk of reaction to accidental ingestion (either through contamination or when CM is an unknown ingredient); the ACMC results seen in this study suggest that these quantitative risk assessment data translate clinically, and importantly, are consistent with the surrogate (clinical trial) outcomes seen on DBPCFC.

Although evidence of an effect was observed for the 300-μg dose group, both by comparison with placebo and by change in CRD over the treatment period, there was no definitive difference in response observed in participants who received 150-μg or 500-μg doses of Viaskin milk. The
distribution of baseline characteristics was comparable in measured variables across participants who were randomized to each treatment arm. Therefore, there were no clear differences that could explain these findings. While it is probable that 150-μg dose of Viaskin milk was too low a dose to generate sufficient immunomodulation, the reasons for the response observed in participants who received 500 μg is more difficult to understand. We observed higher month 12 persistence of CMA, this intolerance was not confirmed at study entry by food challenge, and as such, may be an overestimate of this characteristic. It is possible that placebo effect observed in participants treated with the 300-μg dose of Viaskin milk reflects type 1 error.

The observed placebo response rate was higher than anticipated in the study protocol (15%), likely in part due to spontaneous resolution of CMA, particularly in the younger children over the 12-month period. Although 80% of participants reported being unable to tolerate baked milk products, a clinical phenotype which has been associated with persistence of CMA, this intolerance was not confirmed at study entry by food challenge, and as such, may be an overestimate of this characteristic. It is possible that placebo rates would be lower in a study that targeted older children less likely to achieve natural resolution of their CMA.

The number of adolescents in each treatment group was small, making it difficult to draw conclusions related to efficacy in this group. Moreover, patch placement was the inner side of the arms for adolescents, rather than the interscapular area, which may have also altered the response to treatment. Skin biopsy data involving nonallergic adult participants suggest there may be factors in the back (vs the arms, abdomen, or thighs) that make it a more immunologically favorable location to induce desensitization. While higher treatment response in children (back placement) aged 6 to 11 years compared with adolescents and adults (arms) has been also observed in phase 2 peanut EPIT studies, data from both treatment (EPIT and oral immunotherapy) and prevention studies support the idea of greater plasticity of the allergic immune system earlier in life.

To our knowledge, this is the largest study to date of EPIT for IgE-mediated CMA. Results are consistent with peanut allergy clinical trials, suggesting an effect of 1 year of EPIT treatment on increasing the reaction threshold particularly among children, with an encouraging safety profile. While clinical trials, of necessity, rely on the surrogate outcome of a DBPCFC, the ACMC results speak to one of the primary immunotherapy goals for allergic patients/caregivers.

**Limitations**

Limitations of this study include the relatively small sample size, though typical for a phase 1/2 dose-finding study, in each dose group. Some findings may have been due to chance, including the responder rates in the participants who received Viaskin milk at 500 μg. In addition, participants with severe life-threatening anaphylaxis to CM or uncontrolled persistent asthma were not eligible for participation, which could have affected the results and may limit generalizability. However, these exclusions are considered standard in immunotherapy trials that include DBPCFC for ethical and safety concerns and were not related to the potential risks of treatment itself.

**Conclusion**

In this dose-ranging randomized clinical trial of patients with CMA, Viaskin milk at a dose of 300 μg resulted in statistically significant treatment response vs placebo following 12 months of therapy. These findings warrant further clinical trials to explore Viaskin milk as a viable treatment option for children with IgE-mediated CMA.
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