Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults

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Background: Peanut allergy is common, life-threatening, and without therapeutic options. We evaluated peanut epicutaneous immunotherapy (EPIT) by using Viaskin Peanut for peanut allergy treatment.

Objective: We sought to evaluate the clinical, safety, and immunologic effects of EPIT for the treatment of peanut allergy.

Methods: In this multicenter, double-blind, randomized, placebo-controlled study, 74 participants with peanut allergy (ages 4-25 years) were treated with placebo (n = 25), Viaskin Peanut 100 μg (VP100; n = 24) or Viaskin Peanut 250 μg (VP250; n = 25; DBV Technologies, Montrouge, France). The primary outcome was treatment success after 52 weeks, which was defined as passing a 5044-mg protein oral food challenge or achieving a 10-fold or greater increase in successfully consumed dose from baseline to week 52. Adverse reactions and mechanistic changes were assessed.

Results: At week 52, treatment success was achieved in 3 (12%) placebo-treated participants, 11 (46%) VP100 participants, and 12 (48%) VP250 participants (P = .005 and P = .003, respectively, compared with placebo; VP100 vs VP250, P = .48). Median change in successfully consumed doses were 0, 43, and 130 mg of protein in the placebo, VP100, and VP250 groups, respectively (placebo vs VP100, P = .014; placebo vs VP250, P = .003). Treatment success was higher among younger children (P = 0.03; age, 4-11 vs >11 years). Overall, 14.4% of placebo doses and 79.8% of VP100 and VP250 doses resulted in reactions, predominantly local patch-site and mild reactions (P = .003). Increases in peanut-specific IgG_4 levels and IgG_4/IgE ratios were observed in peanut EPIT-treated participants, along with trends toward reduced basophil activation and peanut-specific T_H2 cytokines.

Conclusions: Peanut EPIT administration was safe and associated with a modest treatment response after 52 weeks, with the highest responses among younger children. This, when coupled with a high adherence and retention rate and significant changes in immune pathways, supports further investigation of this novel therapy. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Peanut hypersensitivity, food allergy, immunotherapy, IgE, desensitization, epicutaneous*

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Abbreviations used

CoFAR: Consortium of Food Allergy Research
CPE: Crude peanut extract
DSMB: Data Safety Monitoring Board
EPIT: Epicutaneous immunotherapy
IQR: Interquartile range
kU_A: Kilounits of antibody
OFC: Double-blind, placebo-controlled oral food challenge
OIT: Oral immunotherapy
SCD: Successfully consumed dose
SPT: Skin prick test
VP100: Viaskin Peanut 100 μg
VP250: Viaskin Peanut 250 μg

Peanut allergy is the most common life-threatening food allergy, with an overall prevalence of 0.5% to 1%[1,2] and a 3-fold increase noted from 1997-2008.[2] In addition to being a key culprit in food-induced mortality, peanut allergy is associated with reduced quality of life and health economic effect.[3-5] Currently, there is no US Food and Drug Administration–approved treatment for peanut allergy, with management consisting of a peanut-free diet and access to self-injectable epinephrine.[6] Despite active avoidance, the risk of an adverse reaction from exposure is ongoing.[7,8] For all these reasons, an effective treatment for peanut allergy would be highly desirable.

Recent efforts have focused on development of allergen-specific immunotherapeutic approaches to treat peanut allergy.[9-15] These approaches are designed to alter immunologic responses to induce short-term desensitization (elimination of reactivity while receiving therapy) and longer-term sustained unresponsiveness (elimination of reactivity while off therapy). Subcutaneous immunotherapy has proved to be unsafe for the treatment of peanut allergy.[16,17] Sublingual immunotherapy has been demonstrated to induce modest clinical benefits while being well tolerated.[10,12,18,19] Oral immunotherapy (OIT) has been shown to induce desensitization in most participants and sustained unresponsiveness in a minority, although adverse reactions are common.[9,11,14,20-22]

Epicutaneous immunotherapy (EPIT) is an emerging modality for the treatment of food allergy. Epicutaneous delivery of antigen has shown benefits when used to treat grass pollen allergy in adults.[23,24] Murine studies indicate that epicutaneously applied antigen modulates T_H2 immune responses[25] through antigen-driven activation of dendritic cells with subsequent immune modulation through trafficking to lymph nodes.[26,27] A pilot study of milk EPIT in 19 infants with milk allergy and children showed trends toward clinical efficacy with acceptable safety in participants treated for 3 months.[28] A phase I study of peanut EPIT demonstrated safety and tolerability by using Viaskin Peanut (DBV Technologies, Montrouge, France) during a 2-week treatment period.[15] The purpose of the current study was to further evaluate peanut EPIT delivered by means of Viaskin Peanut, specifically evaluating clinical desensitization, safety, and immunomodulation after 52 weeks of blinded treatment.

METHODS

Study design and participant selection

This multicenter, randomized, double-blind, placebo-controlled, phase II study compared 2 doses of Viaskin Peanut versus placebo in children and young adults with peanut allergy. The primary end point was the proportion of participants with a successful outcome after 52 weeks of blinded treatment, with treatment success defined as either passing a double-blind, placebo-controlled oral food challenge (OFC) with 5044 mg of peanut protein at week 52 or by a 10-fold or greater increase in the successfully consumed dose (SCD) of peanut protein compared with the baseline OFC. Secondary end points included comparison of the 100- and 250-μg Viaskin Peanut doses, safety, and modulation of immune parameters.

Inclusion criteria included the following: (1) 4 to 25 years of age, (2) physician-diagnosed peanut allergy or a convincing clinical history of peanut allergy, (3) positive skin prick test (SPT) response to peanut (wheal size ≥3 mm greater than that elicited by the saline control) or peanut-specific IgE level of greater than 0.35 kilounits of antibody (kU_A)/L, and (4) positive baseline OFC result to a cumulative dose of 1044 mg or less peanut protein. Subjects with a history of severe anaphylaxis (previous hypotension, neurologic compromise, or mechanical ventilation) to peanut were excluded. See Table E1 in this article's Online Repository at www.jacionline.org for detailed inclusion/exclusion criteria.

Enrollment and randomization

Participants were randomly assigned to double-blind peanut EPIT by using Viaskin Peanut 100 μg (VP100), Viaskin Peanut 250 μg (VP250), or placebo (1:1:1) at each of 5 clinical Consortium of Food Allergy Research (CoFAR) sites (75 total participants). The study was blinded through 52 weeks (Fig 1). Enrollment and randomization of younger participants (ages 4-<6 years) was paused after the first 10 participants were enrolled for a predetermined interim Data Safety Monitoring Board (DSMB) safety review after 35 days of dosing.

Study product

The Viaskin Peanut patch used for this study is comprised of an epicutaneous delivery system containing a dry deposit of a formulation of peanut protein extract manufactured by DBV Technologies SA. The peanut extract is an unmodified lyophilized product derived from the extraction and freeze-drying of defatted peanut flour made from raw peanuts. A liquid formulation of the extract is then deposited on the backing of an occlusive chamber by using electrospraying. The Viaskin patch has a diameter of 26 mm, with an inner diameter of 18 mm containing the peanut protein. The matching Viaskin placebo is the same device devoid of any peanut protein but containing excipients included in the active patch.

EPIT dosing protocol

The Viaskin patch, plus optional Tegaderm covering, was placed on the upper arm (age >11 years) or the interscapular space (4-11 years) in a clockwise rotation by using 1 of 6 application sites at 24-hour intervals. Graduated dosing was performed with the same strength patch by increasing the time worn as follows: week 1, 3 h/d; week 2, 6 h/d; and week 3, 12 h/d. This was followed by patch application for 24 h/d beginning on day 22.

Participants were monitored in the research unit on days 1 and 2 for adverse reactions. If significant local reactions (ie, grade 3 or grade 4 skin reactions; see Table E2 in this article's Online Repository at www.jacionline.org for grading criteria) occurred, participants were instructed to remove the patch immediately and contact the study team for further instructions regarding subsequent patch application. For persistent patch-site reactions, the patch was removed, and the participant was instructed to apply the patch for the length of time that it was tolerated for the following 3 days, followed by an increase in duration of patch application every 3 to 4 days until tolerated for a 24-hour period.

Usual medications, including topical corticosteroids and calcineurin inhibitors, were continued but not within 1 inch of the patch site. Oral and topical antihistamines and topical 1% hydrocortisone were approved for the treatment of patch-site reactions, with more potent topical steroids reserved for limited use with more bothersome reactions.

Adherence and safety assessments

Participants were contacted by telephone monthly and returned to the research unit at the start of weeks 2 to 4 and at completion of weeks 12, 24, 36, and 52 to review tolerability of the study drug, adherence, and any adverse events.

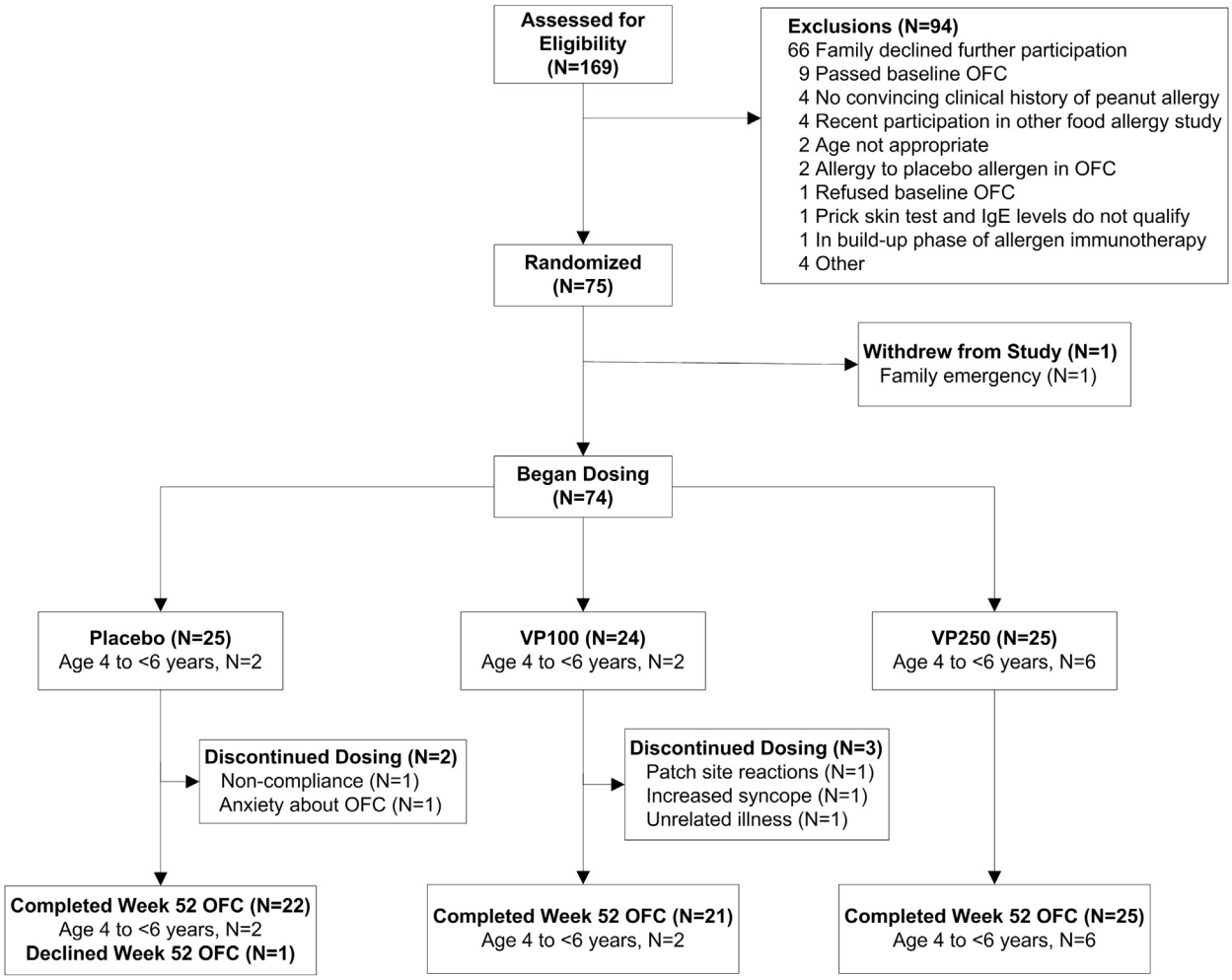

FIG 1. CONSORT diagram. Enrollment and randomization of younger participants aged 4 to less than 6 years was conducted as in the full study population, as indicated. Enrollment was paused after the first 10 participants were enrolled for a predetermined interim DSMB safety review after 35 days (21 days of escalation and 14 days of maintenance) of dosing to ensure tolerability of the study product. Because of completed study enrollment, no further participants in the 4- to less than 6-year-old age range were enrolled after the DSMB review.

Adherence to daily dosing was assessed by using 2 methods. Participants maintained daily diary logs, recording the date and time of patch application and removal during the first 6 months of therapy. Thereafter, dosing logs were only used to record missed doses, doses removed prematurely, or doses associated with adverse symptoms. Dosing logs were reviewed by study personnel at each visit. Participants were also instructed to return all used and unused patches at each visit.

Participants were also monitored for patch-site reactions during scheduled visits and as needed if symptoms were reported. Skin changes at the patch site were scored as grade 0 to 4 by using a standardized scoring system (see Table E2). Symptoms extending outside of the patch site or involving systemic reactions were recorded, and the severity of allergic reactions was reported by using a customized grading system (see Table E3 in this article's Online Repository at www.jacionline.org).

Predetermined rules for potential discontinuation of dosing included occurrence of systemic reactions during any stage of dosing, occurrence of any grade 4 patch-site reaction, more than 3 episodes of grade 3 patch-site reactions, or 2 or more consecutive grade 3 patch-site reactions. Adverse events, serious adverse events, and accidental exposures to peanut were reported throughout the study.

OFCs

At study entry, an OFC was conducted to a cumulative amount of 1044 mg of peanut protein administered in doses every 15 minutes by using a modified PRACTALL Protocol.[29] The OFC was repeated at week 52 to a cumulative dose of 5044 mg of peanut protein (see the Methods section in this article's Online Repository at www.jacionline.org).

SPTs

SPTs using the GREERPick device with peanut extract (Greer Laboratories, Lenoir, NC) and saline and histamine controls were performed at enrollment and 24 and 52 weeks after study entry, as previously described.[10]

In vitro assays

Mechanistic studies were conducted to assess the immunomodulatory effect of peanut EPIT by using serial testing of a variety of immune parameters. Serum peanut-specific IgE and IgG_4 levels were measured by using the ImmunoCAP 250 (Thermo Fisher Scientific, Waltham, Mass). Basophil activation was measured based on CD63 upregulation by using flow cytometry in response to peanut extract stimulation of whole blood.[10]

TABLE I. Baseline characteristics by treatment group*

	Placebo	VP100	VP250	Total
Sex, no. (%)				
Male	16 (64.0)	14 (58.3)	16 (64.0)	46 (62.2)
Female	9 (36.0)	10 (41.7)	9 (36.0)	28 (37.8)
Age (y), median (range)	8.5 (4.8-20.3)	8.4 (4.1-16.6)	7.7 (4.2-14.4)	8.2 (4.1-20.3)
Other allergic disease, no. (%)				
Asthma	12 (48.0)	16 (66.7)	13 (52.0)	41 (55.4)
Atopic dermatitis	12 (48.0)	11 (45.8)	15 (60.0)	38 (51.4)
Other food allergy	20 (80.0)	21 (87.5)	20 (80.0)	61 (82.4)
Atopic dermatitis total score, median (range)	0.0 (0.0-7.0)	0.0 (0.0-7.0)	0.0 (0.0-7.0)	0.0 (0.0-7.0)
Peanut SPT (mm), median (range)	13.5 (3-39.5)	11.8 (4.5-32.0)	12.5 (6.0-25.5)	12.8 (3-39.5)
Peanut IgE (kU_A/L), median (range)	58.0 (0.8-213.0)	84.6 (0.4-213.0)	92.1 (0.52-202.0)	78.2 (0.4-213.0)
Peanut IgG_4 (mg/L), median (range)	1.1 (0.02-7.0)	0.6 (0.03-2.4)	0.5 (0.03-3.0)	0.7 (0.02-7.0)
Peanut IgG_4/IgE ratio,† median (range)	3.8 (0.5-3571.4)	2.5 (0.4-101.6)	3.5 (0.6-74.5)	3.6 (0.4-3571.4)
Total IgE (kU/L), median (range)	360 (21.3-3334)	452 (61.1-5169)	472 (83.5-2143)	452 (21.3-5169)
Peanut IgE/total IgE ratio (%), median (range)	16.9 (0.4-43.7)	12.1 (0.6-59.4)	13.7 (0.4-54.8)	13.9 (0.4-59.4)
Baseline OFC SCD (mg protein), median (range)	44 (0-444)	44 (0-444)	14 (0-444)	44 (0-444)

*There were no statistically significant differences between treatment groups in any baseline characteristics.
†Peanut IgG_4/IgE ratio was calculated by converting IgG_4 levels from milligrams of antibody per liter to nanograms per milliliter and converting IgE levels from kU_A per liter to nanograms per milliliter with the following formula: $(IgG_4 \times 1000) \div (IgE \times 2.4)$.

TABLE II. Week 52 OFC results by treatment group

	Placebo		VP100		VP250		Total	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Treatment success (primary end point)*								
Failure	22	88.0	13	54.2	13	52.0	48	64.9
Success	3	12.0	11	45.8	12	48.0	26	35.1
SCD ≥1044 mg of protein†								
Failure	22	88.0	21	87.5	18	72.0	61	82.4
Success	3	12.0	3	12.5	7	28.0	13	17.6
SCD ≥1044 mg of protein and 10-fold increase from baseline‡								
Failure	23	92.0	22	91.8	21	84.0	66	89.2
Success	2	8.0	2	8.3	4	16.0	8	10.8

Primary end point: The success criterion met was a 10-fold increase in SCD over baseline in all but 1 placebo-treated subject, who had no reaction and passed the week 52 OFC.
*$P = .005$, placebo versus VP100; $P = .003$, placebo versus VP250; $P = .48$, VP100 versus VP250.
†*Post hoc* analysis: $P = .54$, placebo versus VP100; $P = .12$, placebo versus VP250; $P = .12$, VP100 versus VP250.
‡*Post hoc* analysis: $P = .55$, placebo versus VP100; $P = .26$, placebo versus VP250; $P = .27$, VP100 versus VP250.

Peanut-specific T-cell activation and phenotype were assessed by using flow cytometry with CD154 as an activation marker and intracellular staining for IL-4, IL-13, IFN-γ, and IL-10 (see the Methods section in this article's Online Repository).

Ethics

Institutional review boards at each clinical site approved the protocol and consent forms. The study was conducted under a US Food and Drug Administration investigational new drug application and monitored by the National Institute of Allergy and Infectious Diseases DSMB. Written informed consent was obtained from parents/guardians, with assent of those more than 7 years of age.

Statistical analysis

The target sample size of 75 participants (randomized 1:1:1 and stratified by site) was selected to provide 95% power, assuming a 5% success rate for the primary end point in the placebo arm compared with 50% in each of the active arms. Power was determined by using a 1-sided exact unconditional binomial test (Barnard) with an α value of .0125 for each comparison of active to placebo treatment. Alternate success definitions were also compared between the active and placebo arms by using the Barnard test.

TABLE III. Week 52 SCD and change from baseline

	Placebo	VP100	VP250	Total
Week 52 SCD (mg of protein)				
No.	22	21	25	68
Median	14	144	144	144
Minimum	1	44	0	0
Maximum	5044	2044	2044	5044
Change in SCD (mg of protein)*				
No.	22	21	25	68
Median	0	43	130	40
Minimum	−440	−300	−300	−440
Maximum	4600	2040	2040	4600

*$P = .003$ comparing all 3 groups, $P = .014$ for placebo versus VP100, $P = .003$ for placebo versus VP250, and $P = .41$ for VP100 versus VP250.

Continuous variables were contrasted between treatment groups by using the Kruskal-Wallis test, followed by Wilcoxon rank sum tests for pairwise group comparisons. Safety data were contrasted between treatment groups by using the percentage of doses per participant and performed by using the Kruskal-Wallis test, followed by Wilcoxon rank sum tests for pairwise group comparisons.

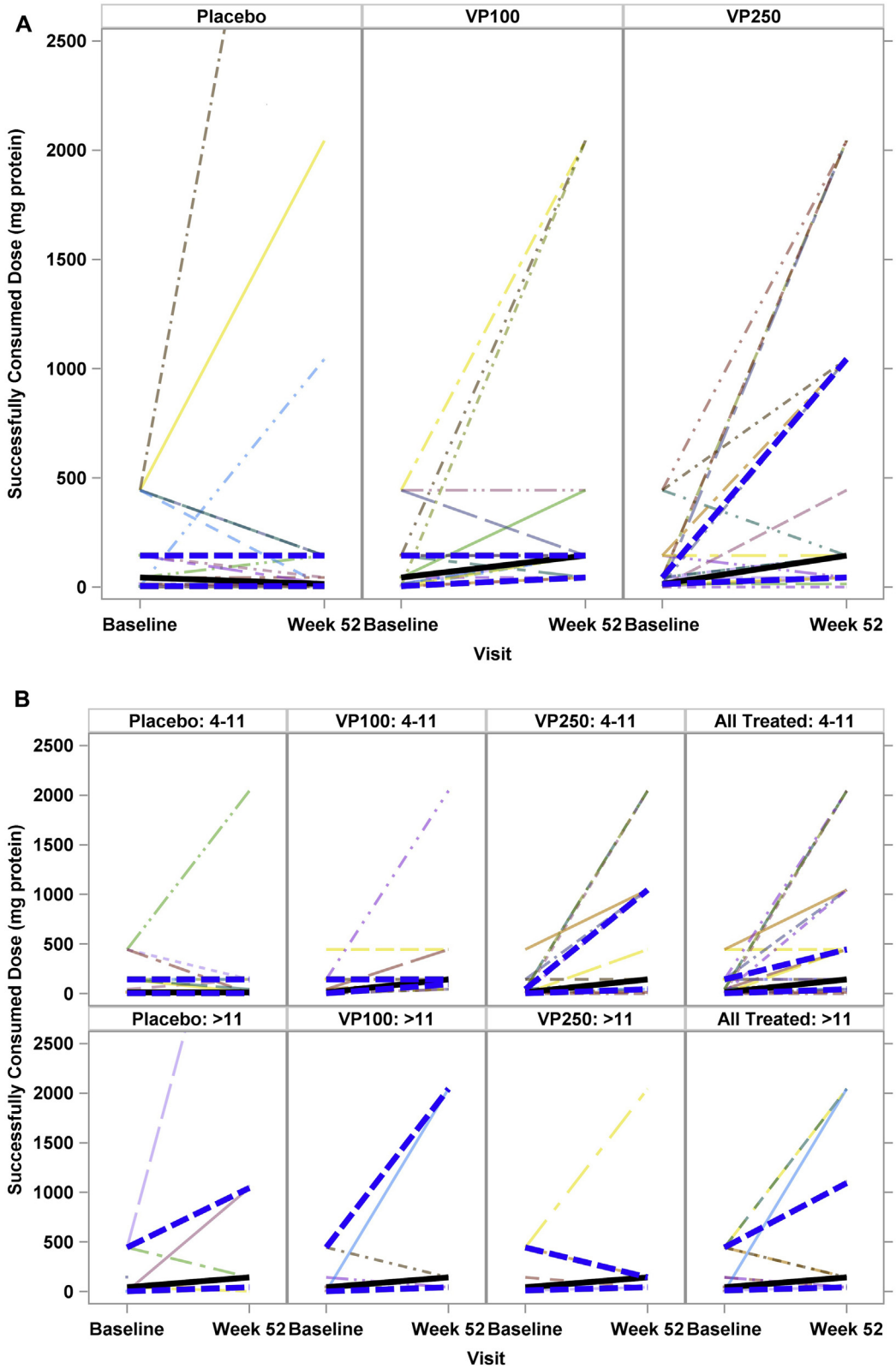

FIG 2. SCD from baseline to the week 52 OFC. **A,** Analysis by treatment group. **B,** Analysis by age and treatment group. *Top panels* represent the 4- to 11-year-old age group. *Bottom panels* represent the greater than 11-year-old age group. *Solid lines* represent median values, and *hatched lines* represent the upper and lower IQR.

TABLE IV. Week 52 OFC results by treatment group and age group

	Treatment group																					
	Placebo						VP100						VP250						All			
	4-11 y		>11 y		All		4-11 y		>11 y		All		4-11 y		>11 y		All		4-11 y		>11 y	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Treatment success																						
Failure	17	94.4	5	71.4	22	88.0	7	41.2	6	85.7	13	54.2	7	38.9	6	85.7	13	52.0	31	58.5	17	81.0
Success	1	5.6	2	28.6	3	12.0	10	58.8	1	14.3	11	45.8	11	61.1	1	14.3	12	48.0	22	41.5	4	19.0
SCD ≥1044 mg of protein																						
Failure	17	94.4	5	71.4	22	88.0	16	94.1	5	71.4	21	87.5	12	66.7	6	85.7	18	72.0	45	84.9	16	76.2
Success	1	5.6	2	28.6	3	12.0	1	5.9	2	28.6	3	12.5	6	33.3	1	14.3	7	28.0	8	15.1	5	23.8
SCD ≥1044 mg of protein and 10-fold increase from BL																						
Failure	18	100.0	5	71.4	23	92.0	16	94.1	6	85.7	22	91.7	14	77.8	7	100.0	21	84.0	48	90.6	18	85.7
Success	0	0.0	2	28.6	2	8.0	1	5.9	1	14.3	2	8.3	4	22.2	0	0.0	4	16.0	5	9.4	3	14.3

TABLE V. Dosing symptoms by treatment group

Dosing symptoms by dose																												
				Patch-site reactions												Non–patch-site symptoms												
		Any reaction		Any patch-site reaction		Grade 2 patch-site reaction		Grade 3 patch-site reaction		Grade 4 patch-site reaction		Reaction extended past patch site		Non–patch-site reaction		Mild symptoms		Moderate symptoms		Severe symptoms		Symptoms >8 h		Treated	
Treatment group	No. of doses	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Placebo	8418	1216	14.4	1200	14.3	128	1.5	0	0.00	0	0.0	133	1.58	17	0.2	17	0.2	0	0.00	0	0.00	982	11.7	106	1.3
VP100	8121	6482	79.8	6479	79.8	1513	18.6	6	0.01	1	0.0	720	8.87	20	0.2	18	0.2	1	0.01	0	0.00	4989	61.4	2218	27.3
VP250	9033	7205	79.8	7203	79.7	2110	23.4	7	0.00	0	0.0	1466	16.23	6	0.1	6	0.1	0	0.00	0	0.00	6397	70.8	2142	23.7

Dosing symptoms by subject																												
	No. of subjects	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Placebo	25	22	88.0	22	88.0	6	24.0	0	0.0	0	0.0	8	32.00	3	12.0	3	12.0	0	0.00	0	0.00	15	60.0	9	36.0
VP100	24	24	100.0	24	100.0	22	91.7	4	16.7	1	4.2	22	91.67	8	33.3	7	29.2	1	4.17	0	0.00	22	91.7	23	95.8
VP250	25	25	100.0	25	100.0	25	100.0	5	20.0	0	0.0	25	100.00	3	12.0	3	12.0	0	0.00	0	0.00	25	100.0	25	100.0

Dosing symptoms by percentage of doses per subject													
	No. of doses, median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Placebo	357 (350-364)	1.6 (0.5-11.9)	1.6 (0.5-7.9)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0.3)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.5 (0-2.8)	0 (0-0.3)
VP100	357 (345-367)	93.9 (73.9-98.3)	92.8 (73.9-98.3)	6.8 (1.6-28.4)	0 (0-0)	0 (0-0)	2.8 (1.2-6.9)	0 (0-0.3)	0 (0-0.3)	0 (0-0)	0 (0-0)	76.7 (22.5-94.5)	8.9 (0.7-53)
VP250	361 (352-370)	96.1 (75.5-98.3)	96.1 (75.5-98.3)	7.4 (1.6-36.8)	0 (0-0)	0 (0-0)	7.6 (1.7-22.6)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	93.6 (27-96.1)	16.2 (4.9-37.7)

Immunologic, activated basophil, and T-cell studies were contrasted between treatment groups over time by using repeated-measures models, accounting for within-participant correlation by using a Toeplitz covariance structure. Log_{10} transformations were applied as needed.

Prespecified exploratory analyses were performed to assess the effect of age on treatment effect by using logistic regression models for binary outcomes and Spearman correlations and linear regression models for continuous outcomes. The primary end point (VP250 vs placebo and VP100 vs placebo) was assessed at the .0125 significance level, mechanistic analyses were assessed at the .01 significance level to control for the multiplicity of analyses, and all other exploratory analyses were assessed at the .05 level. Primary end point *P* values were computed with StatXact (version 10; Cytel, Cambridge, Mass). All other analyses were performed with SAS (version 9.3 or higher; SAS Institute, Cary, NC).

RESULTS

Study population

The CONSORT diagram is represented in Fig 1: 169 participants were screened, 84 had a baseline OFC, 75 were randomized, and 74 received study treatment, with 1 participant withdrawing after randomization but before treatment initiation. The analysis population consists of 74 treated participants (25 in the placebo group, 24 in the VP100 group, and 25 in the VP250 group). As shown in Table I, the majority of participants were male (62.2%), and the median age was 8.2 years (range, 4-20 years). There were no significant differences in baseline demographic characteristics, comorbid atopic diseases, or immunologic measurements across treatment groups. The median baseline peanut SPT response was 12.8 mm, the median peanut IgE level was 78.2 kU_A/L, and the median SCD was 44 mg of peanut protein.

Three placebo-treated participants withdrew/discontinued dosing (2 because of anxiety before the week 52 OFC and 1 because of noncompliance), as did 3 participants from the VP100 group (1 because of grade 3/4 patch reactions, 1 because of non–study-related syncopal episodes, and 1 because of non–study-related illness). All of these participants were considered failures for the primary end point.

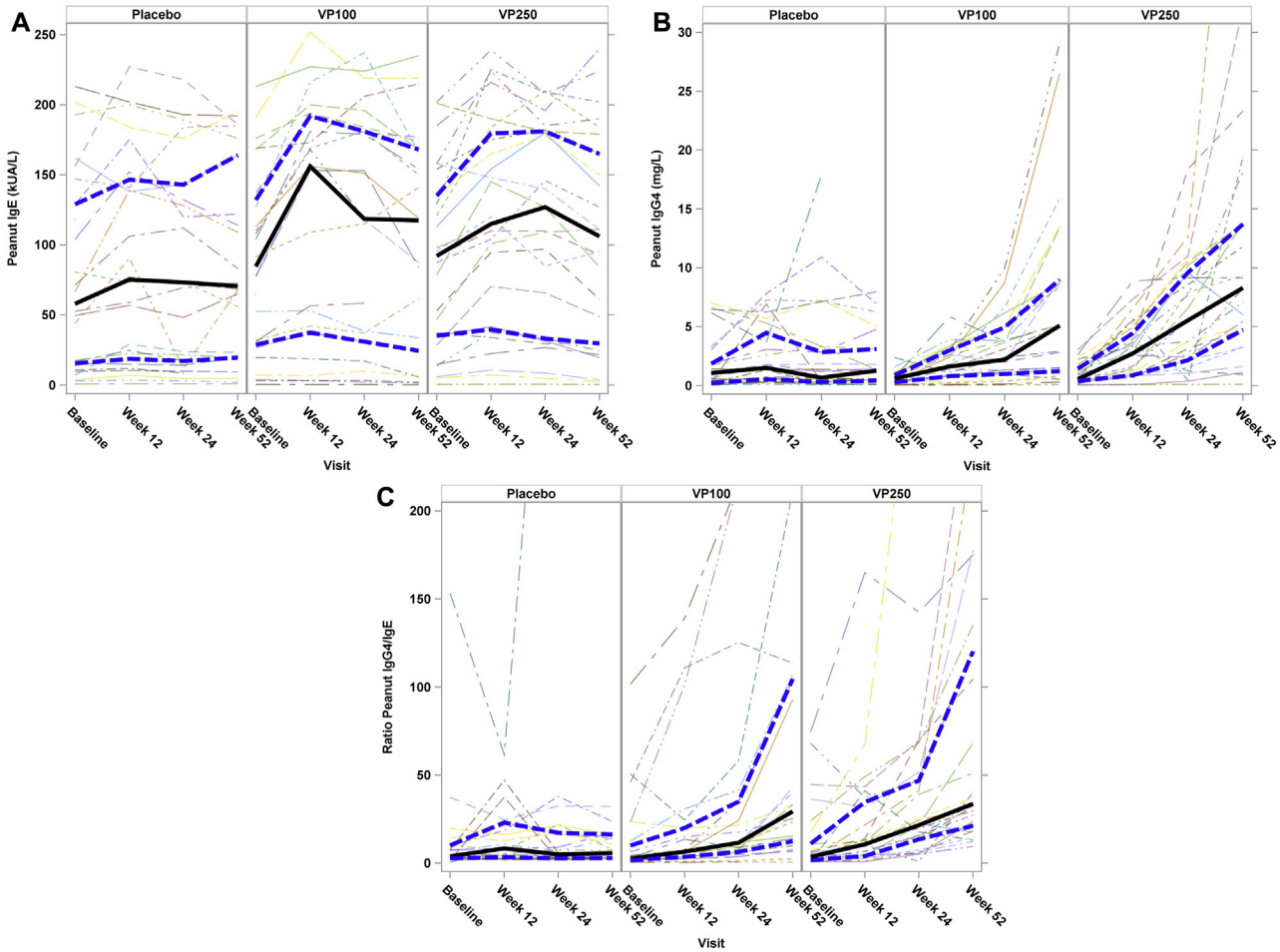

FIG 3. Immune mechanistic assessments over time by treatment group. **A,** Change in peanut-specific IgE levels over time. No significant differences over time were seen between treatment groups ($P = .37$). **B,** Change in peanut-specific IgG_4 levels over time. A significant difference over time was seen between treatment groups ($P < .0001$), with a larger increase noted among the active Viaskin Peanut groups compared with the placebo group. **C,** Change in the peanut IgG_4/IgE ratio over time. A significant difference over time was seen between treatment groups ($P < .0001$), with a larger increase noted among the active Viaskin Peanut groups compared with the placebo group. *Solid lines* represent median values, and *hatched lines* represent the upper and lower IQR.

Efficacy of peanut EPIT

Table II presents results for the primary end point. For the placebo group, 3 (12.0%) participants met the primary end point compared with 11 (45.8%) for the VP100 group and 12 (48.0%) for the VP250 group. Only 1 participant (placebo) passed the week 52 OFC. Comparison of the treatment groups revealed significant differences between the placebo-treated participants and both active treatment arms ($P = .005$ and $P = .003$, respectively), with no difference between the VP100 and VP250 groups ($P = .48$).

Post hoc analyses were undertaken to assess 2 additional efficacy end points (Table II). First, we compared the proportion of participants in each group who had an SCD of at least 1044 mg of protein at the week 52 OFC, which was achieved in 3 (12.0%) placebo-treated participants, 3 (12.5%) VP100-treated participants, and 7 (28.0%) VP250-treated participants (P = not significant for all comparisons). Second, we compared the number of participants who had an SCD of at least 1044 mg of protein plus at least a 10-fold increase in SCD at the week 52 OFC, revealing that only 2 (8.0%) placebo-treated participants, 2 (8.3%) VP100-treated participants, and 4 (16.0%) VP250-treated participants met this stricter definition of success (P = not significant for all comparisons).

Table III shows the SCD for the week 52 OFC, as well as the change in SCD from baseline (Fig 2, *A*). The placebo group had a median change in SCD of 0 mg of protein (interquartile range [IQR], −40.0 to 1.0) compared with median changes of 43 mg of protein (IQR, 0.0 to 140) in the VP100 group and 130 mg of protein (IQR, 30 to 600) in the VP250 group. Median change in SCD was significantly different among the 3 treatment groups ($P = 0.003$, Kruskal-Wallis test), as well as between the placebo and VP100 and VP250 groups (placebo vs VP100, $P = .014$; placebo vs VP250, $P = .003$; VP100 vs VP250, $P = .41$).

As a preplanned exploratory analysis, we assessed the potential effects of age on outcomes (Fig 2, *B*, and Table IV and see Table E4 in this article's Online Repository at www.jacionline.org). We fit a model with the primary end point as the outcome with age as a continuous variable and with age as a dichotomous variable when

comparing participants 11 years or younger with those older than 11 years. Both approaches revealed a statistically significant age-by-treatment interaction, with a successful outcome being more common in younger participants ($P = .03$, dichotomous analysis; $P = .006$, continuous model). In the subgroup of participants 11 years or younger, treatment success was achieved in 1 (6%) placebo-treated child, 10 (59%) VP100-treated children, and 11 (61%) VP250-treated children ($P = .0006$ and $P = .0003$, respectively, compared with placebo; VP100 vs VP250, $P = .98$).

Logistic regression analysis was performed to determine whether any additional baseline factors other than age predicted treatment success (see Table E5 in this article's Online Repository at www.jacionline.org). Only an SCD of less than 44 mg at baseline was statistically associated with a successful outcome ($P = .0001$). This association might only reflect that a lower baseline SCD results in easier attainment of the primary end point; baseline SCD was not significantly correlated with change in SCD from baseline to week 52. Notably, the presence or severity of atopic dermatitis at baseline was not predictive of treatment response.

Safety and adherence

Table V presents dosing symptoms by dose, participant, and percentage of doses per participant for each treatment. Overall, 14.4% of placebo doses resulted in a reaction compared with 79.8% of VP100 and VP250 doses. The majority of reactions were mild and limited to the patch site. Grade 2 or greater patch-site reactions occurred with 1.6% of placebo doses (no grade 3 or 4 reactions) compared with 18.7% of VP100 doses and 23.4% of VP250 doses. One grade 4 patch-site reaction occurred with the VP100 dose in a 12-year-old participant 34 days after enrollment. Reactions extending past the patch site occurred with 1.5% of placebo doses, 8.9% of VP100 doses, and 16.2% of VP250 doses.

Non–patch-site reactions were uncommon, reported in 0.2% of placebo and VP100 doses and 0.1% of VP250 doses. One participant in the VP100 dose group experienced systemic hives that lasted 2 to 4 hours and responded to oral antihistamines. The most commonly reported treatment was topical corticosteroids, followed by oral antihistamines. No epinephrine was used for the treatment of dosing symptoms.

The median percentage of doses per participant with a patch-site reaction was 1.6% for placebo-treated participants compared with 92.8% for VP100-treated participants and 96.1% for VP250-treated participants, whereas for non–patch-site reactions, the median was 0% doses per participant for all groups. The median percentage of doses per participant with a treated reaction was 0% for the placebo group compared with 8.9% for the VP100 group and 16.2% for the VP250 group.

Significant differences were observed for any dosing reaction, patch-site reactions, duration of reaction, doses requiring treatment, and severity of the patch-site reaction. Pairwise group comparisons identified all of the above as being lower in the placebo group compared with the VP100 and VP250 treatment groups. No statistically significant differences were observed between the VP100 and VP250 groups (see Table E6 in this article's Online Repository at www.jacionline.org). Three unrelated severe adverse events were observed during the study: syncopal episodes, abdominal pain, and migraine headache.

Reported compliance with treatment was overall excellent. A total of 26,372 doses were expected, with 25,611 (97.1%) administered: 97.0% in the 4- to 11-year-olds and 97.4% in those older than 11 years.

Immunologic outcomes

Fig 3 shows immunoglobulin results by treatment at baseline and weeks 12, 24, and 52. When assessing global treatment effects over time, significant differences were observed between treatment groups for $\log_{10}$ peanut IgG_4 levels ($P < .0001$) and $\log_{10}$ peanut IgG_4/peanut IgE ratios ($P < .0001$). In particular, participants receiving active treatment had increases in both peanut IgG_4 levels (Fig 3, *B*) and IgG_4/IgE ratios(Fig 3, *C*) when compared with those receiving placebo. No differences over time between treatments were seen for $\log_{10}$ peanut IgE levels ($P = .37$), total IgE levels ($P = .54$), or percentage of peanut IgE ($P = .23$).

Fig 4 shows peanut SPT results by treatment at baseline and weeks 24 and 52. A significant difference was not observed between treatment groups ($P = .17$). However, when the change in SPT response was examined from baseline to week 52, an apparent dose effect was noted, with a reduction in SPT size in the VP250 group (median, −2.5 [IQR, −7.5 to 0.5]; $P = .02$) but not within the VP100 (median, −3.25 [IQR, −7.0 to 3.0]; $P = .07$) or placebo (median, −2.0 [IQR, −5.0 to 1.5]; $P = .27$) groups.

When assessing global treatment effects on peanut-induced basophil activation, significant differences were observed at a stimulant dose of 0.01 μg ($P < .0001$) but not at higher doses. These data are consistent with a shift in threshold of reactivity to peanut rather than a loss of reactivity to peanut. This effect at a dose of 0.01 μg was evident beginning at 12 weeks for both the VP100 and VP250 treatment groups (see Fig E1 in this article's Online Repository at www.jacionline.org).

T-cell studies are summarized in Table E7 in this article's Online Repository at www.jacionline.org. At baseline, 50% and 42% of peanut-responsive $CD154^+CD4^+$ T cells were positive for IL-4 and IL-13, respectively, compared with 3% positive for IFN-γ and 4% positive for IL-10. Statistical analysis for these studies applied a more stringent P value of .01 because of the number of tests performed. No T-cell results reached this level of significance, but a global treatment effect over time on IL-4– and IL-13–producing cells trended toward significance ($P = .059$ and $P = .040$ for IL-4 and IL-13, respectively). Median frequencies of IL-4– and IL-13–producing T cells were lower compared with those in placebo-treated subjects at the VP250 dose but not at the VP100 dose.

Finally, data were analyzed to assess for relationships between baseline age and mechanistic outcomes at week 52. Independent of treatment group, lower age at baseline was correlated with an increasing peanut IgG_4/IgE ratio (rho = −0.31, $P = .010$), as well as with larger decreases from baseline in percentages of $CD63^+$ cells for stimulant levels of 0.1 μg and 0.01 μg (rho = 0.33 and 0.31, respectively; $P \leq .01$). Within groups, for VP100 participants, lower age at baseline correlated with higher week 52 peanut IgG_4 levels (rho = −0.57, $P = .005$) and greater change from baseline to week 52 in peanut IgG_4/IgE ratios (rho = −0.56, $P = .007$). Correlations between baseline age and other mechanistic factors at week 52 were not significant for the other treatment groups.

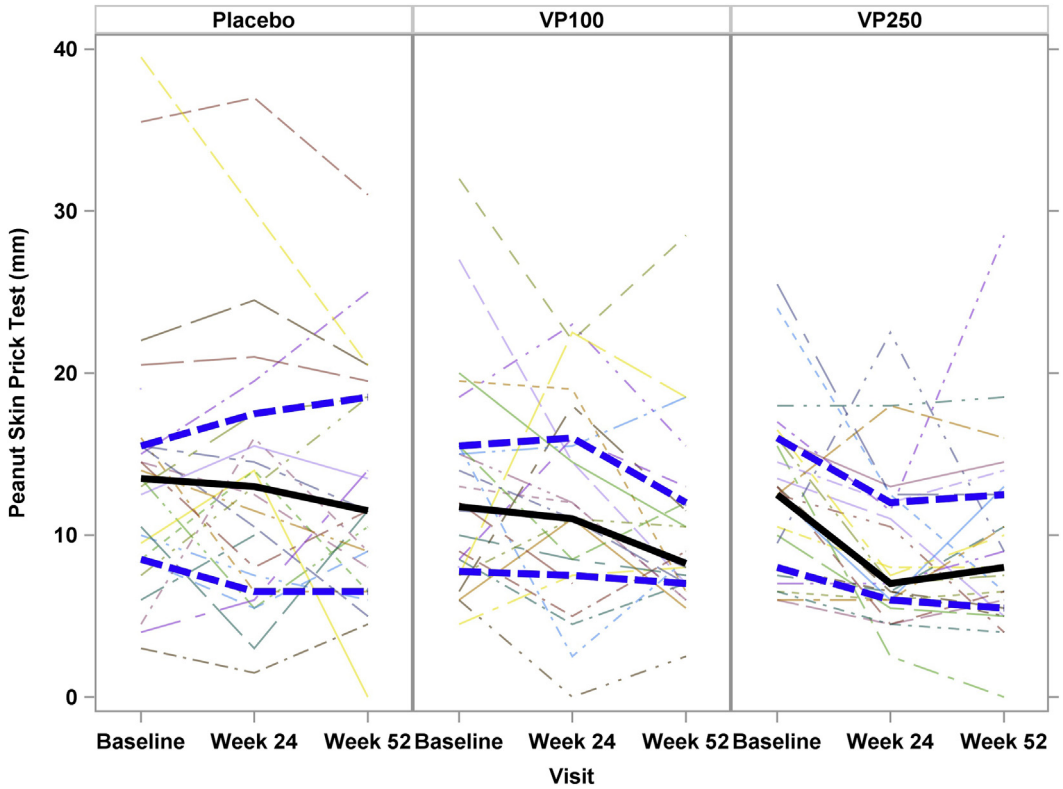

FIG 4. SPT results over time by treatment group. No significant difference was noted among treatment groups over time; however, when examined within a treatment group, a decrease in SPT size was noted in the VP250 group ($P = .02$). *Solid lines* represent median values, and *hatched lines* represent the upper and lower IQR.

DISCUSSION

Exploration for effective treatment options for peanut and other common food allergies remains on the forefront of priorities for clinicians and researchers. EPIT has shown promise in murine studies and early clinical trials as a potential therapeutic option. This multicenter, randomized, controlled trial is the first to comprehensively evaluate the clinical, safety, and immunologic effects of EPIT for the treatment of peanut allergy.

Our findings indicate that peanut EPIT delivered through the Viaskin Peanut patch is safe in our study population of children with peanut allergy, which excluded only children who have experienced severe anaphylaxis. Our findings also indicate that peanut EPIT is potentially effective, with evidence of immune modulation consistent with other forms of immunotherapy. Our findings demonstrate a modest but statistically significant treatment effect, which manifested as a 10-fold or greater increase in OFC SCD from baseline to week 52 among active treatment groups compared with placebo. The effect of treatment was more evident in the younger age group (66% of the VP250 group and 59% of the VP100 group compared with 6% of the placebo group), with little or no effect demonstrated in participants older than 11 years. In addition, we did not demonstrate significant treatment effects when considering other potentially meaningful outcomes in a *post hoc* analysis, such as the proportion of participants achieving an SCD of 1044 mg or greater or those with both a 10-fold increase and an SCD of 1044 mg or greater, and in fact, only 1 subject passed the full 52-week OFC, and that subject was receiving placebo.

The VIPES trial (a phase IIb study with Viaskin Peanut) had similar findings with regard to age, also finding that younger participants achieved more benefit from EPIT when compared with older participants.[30] This suggests that responses to immunotherapy might be more robust in younger patients, as also seen in other studies of both food allergens and aeroallergens.[31,32] Food immunotherapy studies are currently ongoing in younger children, which might help shed further light on this topic, and future studies of EPIT might help to determine whether the poorer responses in older participants are more related to inadequate doses or immunologic differences between younger and older participants.

Adherence to treatment was high in this study, with 97% of expected doses administered through week 52 and only 1 withdrawal caused by local cutaneous grade 3/4 reactions. This finding is similar to the greater than 96% adherence rate reported in the phase I peanut EPIT trial of 100 participants (ages 6-50 years), in which only 3 participants discontinued the trial because of treatment-related reactions.[15]

The safety of peanut EPIT with Viaskin Peanut was extensively evaluated in this trial. Although patch-site reactions were very common and occurred more frequently in the active treatment groups compared with the placebo group, most were mild (≤grade 2). A small proportion of participants (18.9% overall) had non–patch-site reactions that were also mostly mild and responsive to oral antihistamines or topical corticosteroids. No reactions required epinephrine.

It is important to consider these results in the context of other therapies under study for the treatment of peanut allergy. EPIT with Viaskin Peanut was generally well tolerated after 1 year of treatment and induced a modest but statistically significant increase in OFC SCD, with a median increase of 130 mg of protein (approximately 1/2 peanut) in the VP250 group and 43 mg of protein in the VP100 group. In comparison, OIT is associated with more adverse reactions, including anaphylaxis, but has been shown to induce robust changes in challenge thresholds of 5,000 to 10,000 mg.[9,11,14,21,33,34] Sublingual immunotherapy is associated with fewer adverse reactions than OIT, but changes in challenge SCD are also more modest, with our CoFAR study of a similar design demonstrating a change in SCD of approximately 500 mg.[10,12,18] The current EPIT study will extend treatment through 130 weeks, thus providing an important opportunity to assess adherence and clinical efficacy with more extended treatment. This essential balance between safety and efficacy will be of key importance in evaluating these therapies because they move toward clinical use in the coming years.

This is the first study of peanut EPIT to comprehensively evaluate immunologic mechanisms associated with treatment. The immunomodulation noted with active treatment, including increases in peanut-specific IgG_4 levels and IgG_4/IgE ratios, is consistent with changes seen with other forms of food immunotherapy.[11,14,33-36] The trends seen in both basophil and T-cell responses suggest that exposure to peanut through intact skin might modulate T_H2 responses and basophil reactivity. Future analyses at week 130 will determine whether prolonged treatment leads to further downregulation of these responses.

This study is limited by several factors. It is possible that the primary end point, allowing for just a 10-fold change in challenge threshold, was not sufficiently stringent. Exclusion of participants with a prior history of severe anaphylaxis, as in all other food immunotherapy trials that include double-blind, placebo-controlled food challenges in children to date, might influence the results of the study, especially those related to safety and tolerability end points. Although age effects appear to be important, the study was not designed to detect an age effect independent of a treatment effect. The mechanistic studies while using novel T-cell assays were limited in scope based on blood volume. We also acknowledge that blinding of the intervention might have been compromised by the differential rate of patch-site reactions noted between the placebo and active treatment groups. However, because patch-site reactions were seen in all groups, it is unlikely that the patch-site reactions influenced the intervention during the conduct of the blinded portion of the study.

In summary, peanut EPIT with Viaskin Peanut is generally well tolerated and associated with modest but statistically significant clinical and immunologic responses after 52 weeks of active treatment, with the greatest effect noted among the younger participants. Adherence and study retention were high, and although local reactions are common, EPIT appears safe in this study of children with peanut allergy. Additional time on therapy is needed to determine whether the modest clinical changes noted will be enhanced after a longer duration of therapy and will provide clinically meaningful protection from anaphylaxis. These results will be forthcoming, with open-label dosing of participants through 130 weeks in the continuation phase of this study.

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Key messages

- **Peanut EPIT is associated with modest treatment response in children with peanut allergy after 52 weeks of blinded therapy, with a higher response noted among younger children.**
- **The vast majority of children treated with peanut EPIT had mild patch-site reactions; none had serious reactions, and none required epinephrine with dosing.**
- **Immunologic changes were associated with peanut EPIT and were similar to changes noted with other forms of immunotherapy for food allergy.**

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METHODS

OFCs

At study entry, an OFC was conducted with peanut flour to a cumulative amount of 1044 mg of peanut protein administered in doses (1, 3, 10, 30, 100, 300, and 600 mg) every 15 minutes by using a modified PRACTALL Protocol.[E1] The OFC was repeated at week 52 to a cumulative dose of 5044 mg of peanut protein administered in doses (1, 3, 10, 30, 100, 300, 600, 1000, and 3000 mg) per protocol. Lightly roasted peanut flour (Golden Peanut Company, Alpharetta, Ga) was used for peanut OFC, and placebo OFC was conducted with organic oat flour (Arrowhead Mills, Golden, Colo) in equivalent volumes. Each OFC was scored as a pass or failure by an OFC scorer who was blinded to treatment assignment through week 52. Subjects who successfully consumed the total OFC dose were scored as a pass. Inability to tolerate the total OFC challenge dose because of persistent allergic symptoms (eg, hives, wheezing, vomiting, and laryngeal edema) was scored as a failure. Persistent symptoms were defined as those that required treatment for resolution or those that worsened over time. Transient symptoms that resolved completely before the next dose (within 15 minutes) without treatment did not result in termination of the OFC.

T-cell assay methods

Blood samples. Blood samples were obtained as coded specimens in 10-mL sodium-heparin BD Vacutainer tubes (BD Biosciences, San Jose, Calif) at the 5 clinical sites. Whole blood was shipped overnight in temperature-controlled Greenbox shipping containers (ThermoSafe, Arlington Heights, Ill) assembled according to standard operating procedures. Temperature loggers were included to ensure that temperatures were maintained at between 20°C and 30°C. Samples from the Icahn School of Medicine at Mount Sinai clinical site were stored at room temperature and processed the next day to maintain consistency with the other sites.

Cell isolation and stimulation. Whole blood was spun for plasma collection, and PBMCs were isolated by using Ficoll-Paque PLUS (GE Healthcare, Piscataway, NJ), washed, and cultured in AIM V Medium (Thermo Fisher, Grand Island, NY) with 2.5% autologous plasma. Cells (4×10^6) were plated in 1 mL in 24-well culture plates in the presence or absence of 100 μg of crude peanut extract (CPE) or anti-CD3/CD28 stimulation beads (Thermo Fisher) as a positive control. Cells (8×10^6) were used for each of the media and CPE conditions, and 4×10^6 cells were used for anti-CD3/CD28. CPE had been cleaned of endotoxin by using Detoxi-Gel columns (Thermo Fisher). Brefeldin A (BD Biosciences) was added for the last 4 hours of a 6-hour culture with stimulants.

Staining and flow cytometry. Cells were harvested and stained with Live/Dead Fixable Aqua Dead Cell Stain (Thermo Fisher), followed by staining for surface markers: CD3–allophycocyanin-Cy7 (eBioscience, San Diego, Calif); CD4–Brilliant Violet 605 (BV605), CD25-BV650, and CD127-BV785 (from BioLegend, San Diego, Calif); and CCR4–peridinin-chlorophyll-protein complex/Cy5.5, CCR6–phycoerythrin-Cy7, and CXCR5–Alexa Fluor 488 (BD Biosciences). After fixation with 4% paraformaldehyde (Electron Microscopy Sciences, Hatfield, Pa) and permeabilization buffer (eBioscience), intracellular staining was performed with CD154-PE (eBioscience), IFN-γ–Alexa Fluor 700, IL-10–PE-CF594, IL-13–BD Horizon-v450 (all from BD Biosciences), and IL-4–Alexa Fluor 647 (BioLegend). Cells were acquired on a BD LSRFortessa maintained according to standard operating procedures in the Human Immune Monitoring Core at the Icahn School of Medicine at Mount Sinai. Data analysis was performed with FlowJo Software (Ashland, Ore).

REFERENCE

E1. Syed A, Garcia MA, Lyu SC, Bucayu R, Kohil A, Ishida S, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). J Allergy Clin Immunol 2014;133:500-10.

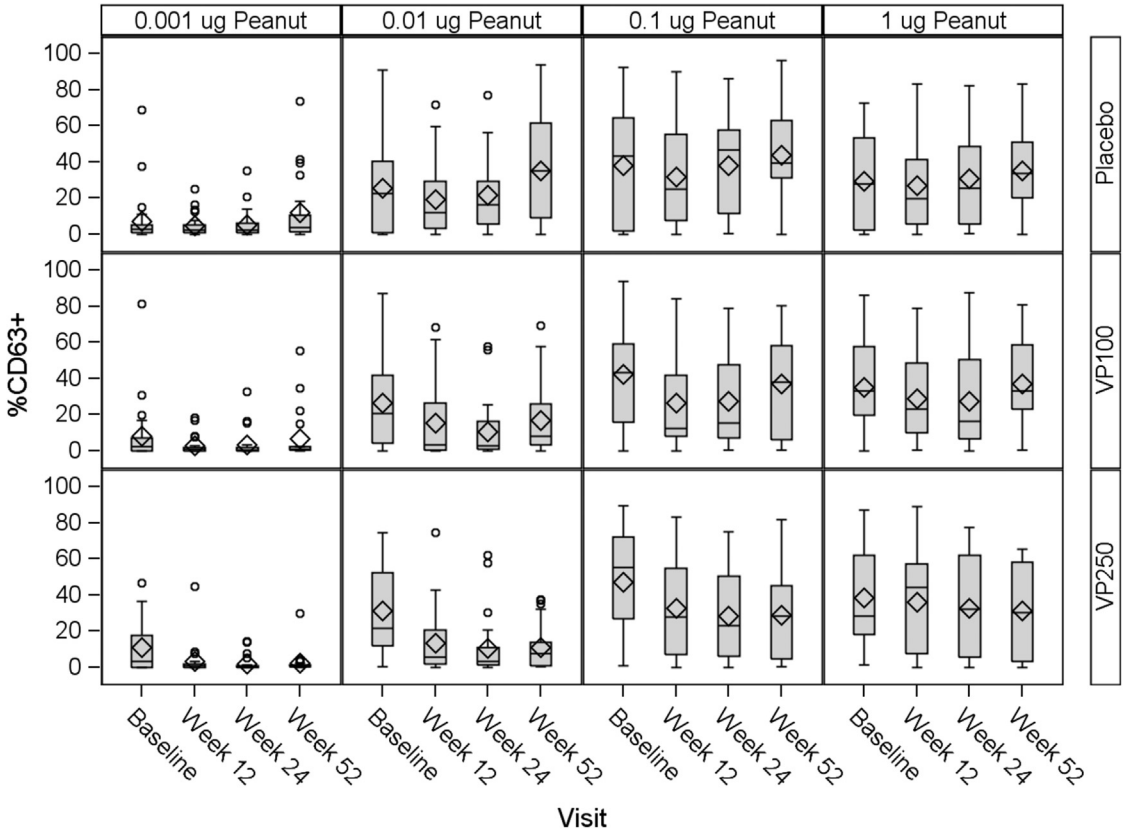

FIG E1. Effect of peanut EPIT on basophil activation (percentage of $CD63^+$ basophils) over time by treatment group. *Top row*, Placebo group; *middle row*, VP100 group; *bottom row*, VP250 group. Cells were stimulated with 0.001 μg/mL peanut extract *(column 1)*, 0.01 μg/mL peanut extract *(column 2)*, 0.1 μg/mL peanut extract *(column 3)*, or 1 μg/mL peanut extract *(column 4)*. Significant differences over time were observed only at a stimulation dose of 0.01 μg of peanut extract ($P < .0001$) when evaluating for a global treatment effect. *Diamonds* represent mean values.

TABLE E1. Inclusion and exclusion criteria

Inclusion criteria

Participants who met *all* of the following criteria were eligible for enrollment as study participants:

- Age 4-25 years, all of either sex and any race and ethnicity at enrollment
- Physician-diagnosed peanut allergy OR convincing history of peanut allergy
- Positive SPT response to peanut (wheal diameter ≥3 mm larger than that elicited by the saline control) OR detectable peanut-specific IgE (ImmunoCAP >0.35 kU_A/L)
- Positive reaction to a cumulative dose of ≤1044 mg of peanut protein in the initial qualifying OFC
- Use of an effective method of contraception by female subjects of childbearing potential to prevent pregnancy and agreement to continue to practice an acceptable method of contraception for the duration of their participation in the study
- Ability to perform spirometric maneuvers in accordance with American Thoracic Society guidelines: children aged 4-11 years who have documented inability to adequately perform spirometry can be enrolled if peak expiratory flow is greater than 80% of predicted value.
- Provision of signed informed consent forms and assent, where indicated

Exclusion criteria

Participants who met *any* of these criteria were *not* eligible for study enrollment:

- History of anaphylaxis to peanut resulting in hypotension, neurological compromise, or requirement for mechanical ventilation
- Participation in a study using an investigational new drug in the last 30 days
- Participation in any interventional study for the treatment of food allergy in the past 6 months
- Pregnancy or lactation
- Current or known allergy to the Viaskin Peanut/Viaskin Placebo patch or excipients
- Current or known allergy to the placebo allergen (oat flour) in OFCs
- Currently in a build-up phase of any allergen immunotherapy
- Severe or poorly controlled atopic dermatitis or greater than a mild flare of active disease at enrollment
- FEV_1 <80% of predicted value or any clinical features of moderate or severe persistent asthma at baseline (as defined by the 2007 National Heart, Lung, and Blood Institute guidelines) and greater than high daily doses of inhaled corticosteroids (>500 μg of fluticasone or equivalent)
- Use of steroid medications in the following manners: history of daily oral steroid dosing for >1 month during the past year, burst of steroid in the past 3 months, or >1 burst oral steroid course in the past year or any use of oral or parenteral steroids for a nonasthma indication within the past 30 days
- Asthma requiring >1 hospitalization in the past year for or >1 emergency department visit in the past 6 months for asthma
- Any previous intubation/mechanical ventilation caused by allergies or asthma
- Use of omalizumab or other nontraditional forms of allergen immunotherapy or immunomodulatory or biologic therapy in the past year
- Use of β-adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium-channel blockers in the past 30 days
- Inability to discontinue antihistamines for skin testing and OFCs
- History of alcohol or drug abuse
- History of cardiovascular disease, uncontrolled hypertension, arrhythmias, chronic lung disease, active eosinophilic gastrointestinal disease, or other medical conditions, including immunologic disorders or HIV infection, which, in the opinion of the investigator, make the participant unsuitable for treatment or at increased risk of anaphylaxis or poor outcome

TABLE E2. Skin reaction grading system

Grade	Skin reaction (clinic assessment)	Skin reaction (participant assessment)
Grade 0	Negative	Normal skin, no reaction
Grade 1A	Only erythema	Redness only
Grade 1B	Erythema, infiltration	Redness and hard or stiff skin
Grade 2 (++)	Erythema, few papules	Redness and a few bumps
Grade 3 (+++)	Erythema, many or spreading papules	Redness with many bumps or spreading bumps
Grade 4 (++++)	Erythema, vesicles	Redness with blisters

TABLE E3. CoFAR grading system for allergic reactions

Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Life-threatening	Grade 5: Death
Transient or mild discomfort (<48 h), no or minimal medical intervention/therapy required. These symptoms can include pruritus, swelling or rash, abdominal discomfort, or other transient symptoms.	Symptoms that produce mild-to-moderate limitation in activity. Some assistance might be needed, but no or minimal intervention/therapy is required. Hospitalization is possible. These symptoms can include persistent hives, wheezing without dyspnea, abdominal discomfort/increased vomiting, or other symptoms.	Marked limitation in activity. Some assistance is usually required; medical intervention/therapy required, and hospitalization is possible. Symptoms can include bronchospasm with dyspnea, severe abdominal pain, throat tightness with hoarseness, and transient hypotension among others. Parenteral medication(s) are usually indicated.	Extreme limitation in activity. Significant assistance is required; significant medical/therapy is required. Intervention is required; hospitalization is probable. Symptoms might include persistent hypotension and/or hypoxia with resultant decreased level of consciousness associated with collapse and/or incontinence or other life-threatening symptoms.	Death

TABLE E4. Week 52 OFC results by treatment group and baseline age

	Treatment group						
	Placebo		VP100		VP250		
	4-11 y	>11 y	4-11 y	>11 y	4-11 y	>11 y	Total
Week 52 SCD (mg of protein)							
Np.	17	5	16	5	18	7	68
Median	14	144	144	144	144	144	144
Minimum	1	4	44	44	0	44	0
Maximum	2044	5044	2044	2044	2044	2044	5044
Change in SCD (mg of protein)*							
No.	17	5	16	5	18	7	68
Median	0	0	71.5	0	130	100	40
Minimum	−440	−300	0	−300	0	−300	−440
Maximum	1600	4600	1900	2040	2040	1600	4600

*When comparing age groups within each treatment group: $P = .67$ for placebo, $P = .59$ for VP100, and $P = .19$ for VP250 participants.

TABLE E5. Logistic regression for baseline factors with treatment success as outcome

	P value, Wald χ^2 test		
	Model with no treatment interaction	Model with significant treatment interaction	
Variable	***P* value**	***P* value for main effect**	***P* value for interaction term**
Age	.0469	.0880	.0057
Sex	.2910	—	—
Allergic rhinitis	.4541	—	—
Atopic dermatitis	.7209	—	—
Asthma (physician's diagnosis)	.9943	—	—
Additional food allergy (unknown = no)	.2651	—	—
AD total score	.2272	—	—
Peanut SPT score	.6301	—	—
Baseline OFC dose at first symptom	.0547	—	—
High vs low baseline OFC SCD*	.0001	—	—
Log_{10} total IgE	.1982	—	—
High vs low peanut IgE†	.6445	—	—
Log_{10} peanut IgG_4	.8053	—	—
Log_{10} peanut IgG_4/IgE ratio	.9417	—	—
Peanut IgE (%)	.2779	—	—
Log_{10} milk IgE	.7291	—	—
Log_{10} egg IgE	.7792	—	—
Peanut, 1 μg	.3156	—	—
Peanut, 0.1 μg	.3722	—	—
Peanut, 0.01 μg	.2922	—	—
Peanut, 0.001 μg	.9826	—	—

*The model using continuous baseline OFC SCD had poor fit, and therefore baseline OFC SCD was divided into high (SCD ≥ 44 mg) and low (SCD < 44 mg) values. The cut point of 44 mg was selected because it was the overall median.

†The model using continuous baseline log_{10} peanut IgE levels had poor fit, and therefore baseline log_{10} peanut IgE levels were divided into high (peanut IgE ≥ 95 kU_A/L) and low (peanut IgE < 95 kU_A/L) values. The cut point of 95 kU_A/L was selected because it was the overall median.

TABLE E6. *P* values from comparisons of percentage of doses per participant with symptoms between treatment groups*

Variable	Placebo vs VP100 vs VP250	Placebo vs VP100	Placebo vs VP250	VP100 vs VP250
Total no. of doses	.2956	.8812	.1518	.2396
Any reaction	<.0001	<.0001	<.0001	.9208
Patch-site reaction	<.0001	<.0001	<.0001	.8579
Reaction extended past patch site	<.0001	<.0001	<.0001	.1139
Non–patch-site reaction	.0771	.0708	1.0000	.0793
Skin symptoms	.2394	.2363	.6836	.1465
Respiratory symptoms	.1210	.1594	1.0000	.1594
Gastrointestinal symptoms	.3529	.3321	1.0000	.3321
Other symptoms	.9975	.9769	1.0000	.9769
Mild symptoms	.1707	.1282	1.0000	.1425
Moderate symptoms	.3529	.3321	1.0000	.3321
Severe symptoms	1.0000	1.0000	1.0000	1.0000
Duration >8 h	<.0001	<.0001	<.0001	.1964
Treated	<.0001	<.0001	<.0001	.5986
Treated with topical steroids	<.0001	.0001	<.0001	.4041
Treated with oral antihistamines	<.0001	<.0001	.0002	.6176
Treated with epinephrine	1.0000	1.0000	1.0000	1.0000
Grade 2 patch-site reaction	<.0001	<.0001	<.0001	.7130
Grade 3 patch-site reaction	.0734	.0424	.0251	.8252
Grade 4 patch-site reaction	.3529	.3321	1.0000	.3321
Grade 2 past patch reaction	<.0001	<.0001	<.0001	.4648
Grade 3 past patch reaction	.0487	1.0000	.0874	.0940
Grade 4 past patch reaction	1.0000	1.0000	1.0000	1.0000

**P* values from comparisons of all 3 treatment groups simultaneously are from the Kruskal-Wallis test. *P* values from pairwise comparisons of treatment groups are from the Wilcoxon rank sum test.

TABLE E7. Medians, lower quartiles, and upper quartiles of peanut-responsive cells per million CD4$^+$ T cells after adjustment for media control or cytokine expression as a percentage of CD154$^+$ cells

	Treatment group															
	Placebo				VP100				VP250				All			
	No.	Median	LQ	UQ	No.	Median	LQ	UQ	No.	Median	LQ	UQ	No.	Median	LQ	UQ
CD4$^+$ cells/10^6																
CD154$^+$																
Baseline	22	185	50	473	21	359	74	475	23	224	79	418	66	225	74	461
Week 24	21	158	45	380	20	126	57	260	19	203	115	289	60	186	54	294
Week 52	21	207	56	404	16	223	66	323	22	77	−16	194	59	151	22	265
IL-4$^+$CD154$^+$																
Baseline	22	128	38	421	21	238	40	351	23	121	44	275	66	150	43	317
Week 24	21	82	11	267	20	84	15	130	19	108	21	150	60	95	15	160
Week 52	21	73	3	188	16	92	13	204	22	46	−6	88	59	62	1	161
IL-13$^+$CD154$^+$																
Baseline	22	121	19	252	21	192	32	329	23	122	41	287	66	134	41	296
Week 24	21	70	29	247	20	75	16	107	19	86	53	141	60	79	24	142
Week 52	21	130	20	189	16	130	29	234	22	61	22	90	59	71	20	165
IFN-γ$^+$CD154$^+$																
Baseline	22	2	−2	8	21	5	1	15	23	2	0	5	66	3	−1	8
Week 24	21	1	−2	4	20	2	0	6	19	1	−3	6	60	1	−2	5
Week 52	21	1	−4	6	16	0	−5	2	22	−2	−11	5	59	0	−7	4
IL-10$^+$CD154$^+$																
Baseline	22	6	1	13	21	9	4	17	23	6	4	14	66	7	2	16
Week 24	21	4	1	11	20	8	1	12	19	15	7	22	60	9	3	15
Week 52	21	7	2	17	16	11	0	18	22	8	0	15	59	7	0	15
CD154$^+$ cells (%)																
IL-4$^+$/CD154$^+$																
Baseline	24	48	25	62	21	54	37	65	23	50	35	62	68	50	32	64
Week 24	21	43	29	56	20	37	20	43	19	41	29	47	60	38	22	49
Week 52	21	42	15	48	16	41	21	54	22	35	24	40	59	38	21	46
IL-13$^+$/CD154$^+$																
Baseline	24	39	12	57	21	47	30	59	23	42	24	56	68	42	21	57
Week 24	21	32	21	50	20	28	11	37	19	32	23	40	60	30	16	41
Week 52	21	36	11	41	16	39	16	47	22	26	16	38	59	34	13	41
IFN-γ$^+$/CD154$^+$																
Baseline	24	2	1	4	21	3	1	4	23	2	1	6	68	3	1	5
Week 24	21	2	1	3	20	3	2	5	19	2	1	4	60	2	1	4
Week 52	21	3	2	5	16	2	1	6	22	4	1	5	59	3	1	5
IL-10$^+$/CD154$^+$																
Baseline	24	4	2	6	21	4	3	5	23	4	3	6	68	4	3	6
Week 24	21	3	2	4	20	5	4	7	19	7	5	9	60	5	3	8
Week 52	21	6	5	8	16	8	4	15	22	9	7	13	59	7	5	12

LQ, Lower quartile; *UQ*, upper quartile.