Original Article

Safety of Epicutaneous Immunotherapy in Peanut-Allergic Children: REALISE Randomized Clinical Trial Results

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What is already known about this topic? In previous phase 2b and 3 clinical trials, epicutaneous immunotherapy (EPIT) with a patch containing 250-μg peanut protein (Viaskin Peanut 250 μg) was well tolerated and statistically superior to placebo in desensitizing peanut-allergic children.

What does this article add to our knowledge? This article provides additional information on the safety profile of EPIT with Viaskin Peanut 250 μg in a setting that approximates potential real-world use.

How does this study impact current management guidelines? The safety data for Viaskin Peanut 250 μg reported herein are consistent with previous phase 2b and 3 studies, which may further support the use of EPIT as a new potential treatment option for peanut allergy.

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Abbreviations used

AEs- Adverse events
DBPCFC- Double-blind placebo-controlled food challenge
EPIT- Epicutaneous immunotherapy
ICH GCP- International Council for Harmonisation Good Clinical Practice
IgE- Immunoglobulin E
IgG4- Immunoglobulin G4
MedDRA- Medical Dictionary for Regulatory Activities
NIAID- National Institute of Allergy and Infectious Diseases
OIT- Oral immunotherapy
psIgE- Peanut-specific IgE
Q1- Quarter 1
Q3- Quarter 3
REALISE- REAL LIfe Use and Safety of EPIT
RDBPCT- Randomized, double-blind, placebo-controlled trial
SAEs- Serious adverse events
SD- Standard deviation
SPT- Skin prick test
TEAEs- Treatment-emergent adverse events
VP250- Viaskin Peanut 250 μg

BACKGROUND: Treatment options for peanut allergy are limited. In previous clinical trials, epicutaneous immunotherapy with a patch containing 250-μg peanut protein (Viaskin Peanut 250 μg [VP250]) was well tolerated and statistically superior to placebo in desensitizing peanut-allergic children.

OBJECTIVE: To examine the safety of VP250 in children, using a study design approximating potential real-world use.

METHODS: REAL LIfe Use and Safety of EPIT (REALISE) is a phase 3 multicenter study consisting of a 6-month, randomized, double-blind, placebo-controlled period followed by open-label active treatment. Children aged 4 to 11 years with physician diagnosis of peanut allergy received daily treatment with placebo (6 months) or VP250 (up to 36 months). Data from the 6-month, randomized, controlled phase of REALISE are reported.

RESULTS: Three hundred ninety-three children were randomized 3:1 to receive VP250 (n = 294) or placebo (n = 99) for 6 months; 284 (72.3%) children had a history of peanut anaphylaxis. According to parent diary, all participants receiving VP250

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and 83.8% receiving placebo reported at least 1 episode of local skin reaction, with frequency decreasing over time. Only 4 participants (1.4%) receiving VP250 discontinued because of adverse events (AEs). Epinephrine was administered for allergic reactions attributed to VP250 in 7 children (2.4%), of whom 5 remained in the study; none involved severe anaphylaxis. Overall, AE rates were similar among participants with and without a history of peanut anaphylaxis.

CONCLUSIONS: In a study designed to mirror real-world use, VP250 was observed to be well tolerated in peanut-allergic children, consistent with previous phase 2b and 3 studies. **(J Allergy Clin Immunol Pract 2021;■:■-■)**

Key words: *Peanut allergy; Food allergy; Epicutaneous immunotherapy (EPIT); Immunotherapy; Real-world setting; Desensitization; Children*

Peanut allergy is common, with increasing global prevalence reported. In the United States, Europe, and Australia, the estimated prevalence of peanut allergy in children is approximately 2%.[1-4] Importantly, peanut allergy resolves in only approximately 20% of children, such that peanut allergy remains a lifelong challenge for the majority.[5-7] Furthermore, concerns about unintentional exposure, unpredictability of severe reactions, and relatively high-risk of anaphylaxis contribute to challenges for patients, families, and health care providers.[8-10]

Epicutaneous immunotherapy (EPIT) is currently under investigation as a novel approach for the treatment of peanut allergy. EPIT aims to induce desensitization by using the unique immune properties of the skin, delivering microgram amounts of allergen. Viaskin Peanut (DBV712) 250 μg (VP250) has undergone evaluation for safety and efficacy in phase 2 and 3 studies.[11-13] In PEPITES (NCT02636699), a phase 3, randomized, double-blind, placebo-controlled trial (RDBPCT) of children with peanut allergy aged 4 to 11 years, VP250 was well tolerated, and a statistically significant difference ($P < .001$) in the primary outcome response rate between the active (35.3%) and placebo (13.6%) groups was observed after 12 months of treatment, with response out to 3 years of treatment in an ongoing open-label trial extension.[13,14]

The phase 3 REAL LIfe Use and Safety of EPIT (REALISE) trial was designed to assess the safety of VP250 in children with peanut allergy under conditions that approximate anticipated real-world use, specifically relying on history as well as supportive testing, and removing the requirement for entry or exit oral double-blind placebo-controlled food challenges (DBPCFCs) that are usually performed in food allergy clinical trials and not in routine clinical practice. Removing the risks associated with entry DBPCFCs allowed for inclusion of children with a past history of severe peanut anaphylaxis, and those unwilling to undergo DBPCFC. We report here the results of the 6-month RDBPCT phase of the REALISE study.

METHODS

The randomized portion of the phase 3 trial was conducted from October 2016 to September 2017 at 32 centers in Canada and the United States. The complete protocol and statistical analysis plans are provided in Appendix E1 and Appendix E2 in this article's Online Repository at www.jaci-inpractice.org, respectively. The study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice (ICH GCP), the ethical principles of the Declaration of Helsinki, and local legal requirements. Parents/legal guardians of participants provided a signed written informed consent, and children of at least 7 years of age (or per local regulations) provided their assent.

Institutional review board and/or independent ethics committee approval was obtained for all study sites. Trial Registration (ClinicalTrials.gov identifier): NCT02916446 (https://clinicaltrials.gov/ct2/show/NCT02916446).

Study design

REALISE comprises 2 parts: a 6-month, double-blind, placebo-controlled treatment period followed by an ongoing open-label, single-arm, active treatment period with VP250 for a total of 3 years of active treatment for all participants (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org).

Participants and randomization

Children aged 4 to 11 years were eligible for participation if they had a physician-diagnosed peanut allergy based on a well-documented medical history of immunoglobulin E (IgE)-mediated reaction after peanut ingestion leading to emergency department visit or physician consultation, a peanut-specific IgE (psIgE) level ≥14 kU/L, and a positive peanut skin prick test (SPT) with a longest wheal diameter ≥8 mm (the combination providing a >95% positive predictive value of clinical peanut allergy). As in current clinical practice, oral food challenges were deferred in this population that was highly likely to be allergic. Children with a history of anaphylaxis to peanut, including severe anaphylaxis (defined as per Table E1 in this article's Online Repository at www.jaci-inpractice.org), were not excluded. At screening, a medical history was obtained, including medical records when available, regarding peanut allergy diagnosis, and frequency and severity of past allergic reactions to peanut. Investigators used National Institute of Allergy and Infectious Diseases[15] criteria to categorize whether children had a past history of anaphylaxis (any severity) to peanut.

Key exclusion criteria included uncontrolled persistent asthma (per Global Initiative for Asthma guidelines),[16] generalized dermatologic disease, and major infectious disease. Eligible participants were randomized by an Interactive Web Response System to receive VP250 or placebo in a 3:1 ratio, with stratification by age to ensure adequate representation of 4- and 5-year-old participants between groups.

Treatments and procedures

Active treatment and placebo patches were identical in size and shape and were applied daily on the interscapular area of the back in 6 sequentially rotating zones (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org). Patches were applied for 6 (±1) hours/d during week 1, 12 (±2) hours/d during week 2, and 24 (±4) hours/d thereafter. Participants were monitored at study sites for adverse reactions for 3 hours at initial patch application, and the remainder of applications were performed at home. Patches that detached within 2 hours of application were discarded and a new patch was reapplied that day. If more than 2 hours elapsed, a new patch was applied the next day. Adjustment of application schedule was allowed based on tolerability and local adverse events (AEs). If a severe local reaction occurred under or near

the application site, the patch was removed, the site cleaned, and if needed, treated with topical corticosteroid, as per the investigator.

Study adherence was assessed at each visit by counting the total number of patches applied since the last visit divided by the number of days in that period of time; participants who were persistently non-study-adherent with patch application were withdrawn from the study at the investigators' discretion.

psIgE and immunoglobulin G4 (IgG4) were assessed at baseline, month 3, and month 6 (Phadia ImmunoCAP system; ThermoFisher Scientific, Waltham, Mass). SPTs were performed using peanut extract plus negative saline control and positive histamine control (SoluPrick solutions; ALK-Abelló, Hørsholm, Denmark) with Duotip II (ALK-Abelló) and measured by the longest wheal diameter and the longest perpendicular wheal diameter at 15 minutes. Filaggrin mutation analysis was performed by Expression Analysis (Q^2 Solutions, Morrisville, NC), specifically for 5 mutations: R501X, 2282Del4, R2447X, S3247X, and 3702delG.

Outcome measures

Safety. Investigators assessed safety at each visit by evaluating AEs and treatment emergent AEs (TEAEs) according to duration, severity, and causal relationship to treatment (related, probable, possible, unlikely, or not related), and those resulting in study discontinuation. Severity of AEs was assessed by the investigator as mild, moderate, or severe. Anaphylaxis was graded 1 (mild), 2 (moderate), or 3 (severe) (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).[15] AEs were coded by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA; version 20.0). Seriousness of AEs was categorized according to ICH GCP criteria. Relevant emergency department records were requested and, if obtained, reviewed by the investigator.

In addition to investigator-reported AEs and assessment of application sites by the investigator at each study visit, parents recorded 3 local skin reactions (itching, swelling, and redness) that were prespecified in the protocol not to be reported as AEs during the first 6-month randomized controlled phase, in daily diaries. Any other local skin reaction or any other type of AE recorded in the diaries was reported by the investigators as an AE. The 3 prespecified local skin reactions were not reported by investigators as AEs unless they were part of another concomitant disease or led to study discontinuation or serious AEs (SAEs). Caregivers photographed any local reactions they were concerned about and/or at the request of the investigator, which were reviewed by the investigator. All diary reported local reactions of itching, swelling, and redness were reported by incidence, severity, and duration. Parents/guardians rated severity as 0 (none), 1 (mild), 2 (moderate), or 3 (severe) based on training at site and descriptions provided in the diaries.

In addition, at each study visit, investigators assessed severity of local skin reactions on a scale grade 0 (negative) to grade 4 (vesicles) and photographs of reactions were taken.

Statistical analyses

The sample size calculation was based on detection of AEs at an annual rate of $\geq$0.024 over the 6-month double-blind period. Three hundred fifty-five participants, with 250 participants in the active treatment and 85 in the placebo arm, were required, allowing for a 15% dropout rate.

Continuous data were summarized by the number of participants/observations with nonmissing data (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum, and maximum, unless otherwise stated. Categorical data were summarized by the number of participants or observations providing nonmissing data at the relevant time point (n), frequency counts, and percentages. Baseline was defined as the last available valid predose assessment; outputs were produced using SAS version 9.3.

The double-blind safety population consisted of all participants who were randomized and received at least 1 dose of study medication. *Post hoc* safety analyses were performed in participants with and without a history of anaphylaxis to peanut.

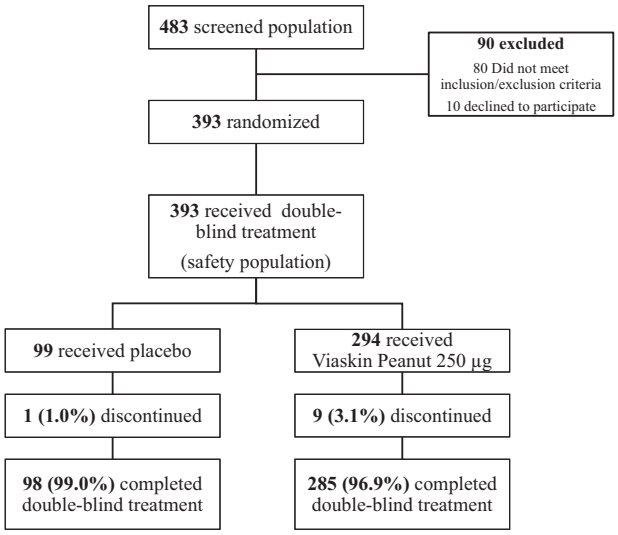

FIGURE 1. Participant disposition.

RESULTS

Participant disposition

The safety population comprised 393 participants, of whom 383 (97.5%) completed the 6-month double-blind treatment (Figure 1). Ten participants (2.5%) withdrew, of whom 9 withdrew from the VP250 arm: 4 (1.4%) due to AEs, 3 (1%) due to consent withdrawal, and 2 (0.7%) were lost to follow-up. Of the 4 participants who withdrew because of AEs, 2 of 393 (0.7%) were due to anaphylaxis, 1 (0.3%) was due to local application site reactions, and 1 (0.3%) was due to urticaria. One (1%) placebo-treated participant was withdrawn because of physician decision (unrelated to adherence to treatment).

Baseline demographics and participant characteristics

Demographic data and participant characteristics were similar between treatment groups (Table I). Median age in both groups was 7.0 years. Overall median psIgE was 91.20 kU_A/L, and median SPT mean wheal size diameter was 11 mm, highly predictive of clinical peanut allergy. The study population was highly atopic (Table I). In addition, 284 participants (72.3%) reported a history of peanut anaphylaxis, with 14 (3.6%) reporting a history of severe anaphylaxis (see criteria in Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Exposure and adherence to treatment

For participants receiving VP250, the median (Q1, Q3) study duration was 194 days (190-199 days) and the median (Q1, Q3) exposure to treatment was 181 days (176-184 days).

TABLE I. Baseline demographic and disease characteristics (double-blind safety population)

Characteristic	Viaskin Peanut 250 μg (n = 294)	Placebo (n = 99)
Male, n (%)	164 (55.8)	65 (65.7)
Age, mean (SD) (y)	7.2 (2.2)	7.2 (2.3)
Age subgroups, n (%)		
4 to <6	92 (31.3)	32 (32.3)
6 to <9	99 (33.7)	31 (31.3)
9 to <12	103 (35.0)	36 (36.4)
Race and ethnicity, n (%)		
White	222 (75.5)	70 (70.7)
Black	6 (2.0)	2 (2.0)
Hispanic	7 (2.4)	2 (2.0)
Asian	27 (9.2)	18 (18.2)
Other	32 (10.9)	7 (7.1)
Peanut allergy history and baseline peanut allergy characteristics		
Age at diagnosis (y)		
Mean (SD)	2.3 (1.61)	2.4 (1.72)
Median (Q1, Q3)	2.0 (1.1-3.0)	1.9 (1.1-3.1)
Time since diagnosis (y)		
Mean (SD)	5.4 (2.52)	5.2 (2.27)
Median (Q1, Q3)	5.3 (3.5-7.2)	4.9 (3.3-7.1)
Baseline peanut-specific IgE (kU/L)		
Mean (SD)	190.5 (212.4)	227.5 (286.9)
Median (Q1, Q3)	91.4 (48.2-274.0)	89.5 (51.4-298.0)
Baseline peanut-specific IgG4 (mg/L)		
Mean (SD)	1.2 (1.7)	1.5 (3.1)
Median (Q1, Q3)	0.7 (0.3-1.4)	0.7 (0.29-1.6)
Baseline wheal diameter		
Median (range) (mm)	11.0 (6.0-31)	11.5 (9.5-15.5)
History of anaphylaxis to peanut, n (%)	206 (70.1)	78 (78.8)
History of severe anaphylaxis to peanut,* n (%)	10 (3.4)	4 (4.0)
History of atopic conditions, n (%)		
Asthma	135 (45.9)	46 (46.5)
Eczema/atopic dermatitis	174 (59.2)	53 (53.5)
Allergic rhinitis	175 (59.5)	55 (55.6)
Allergy(ies) other than peanut	251 (85.4)	82 (82.8)

IgE, Immunoglobulin E; *IgG*, immunoglobulin G; *Q1*, first quartile; *Q3*, third quartile; *SD*, standard deviation.
*Severe anaphylaxis defined as hypoxia, hypertension (more 20% drop in blood pressure) or neurological compromise, cyanosis of SpO_2 ≤92% at any stage, confusion, cardiovascular collapse, loss of consciousness, incontinence, bradycardia, and cardiac arrest.

For those receiving placebo, the median (Q1, Q3) duration of treatment was 194 days (190-201 days) and the median exposure to treatment was 182 days (177-185 days). The median (Q1, Q3) daily duration of patch application was 20.9 hours (18.9-22.0 hours) in those receiving VP250 and 22.5 hours (21.9-22.9 hours) for the placebo group. Days without patch application were relatively infrequent and similar between the VP250 and placebo arms. The mean (SD) and median (interquartile range) percentage of days without patch application was 5.75% (10.4) and 1.71 (0.55, 5.88) in participants receiving VP250 and 5.01% (9.92) and 1.65 (0.54, 5.11) in participants receiving placebo, respectively. A total of 4.2% of VP250 patches and 1.6% of placebo patches were removed before the recommended 24 (±4) hours of application, due to discomfort or personal convenience. Mean adherence to treatment was high overall (98.2%) and in each treatment arm (VP250 = 98.3%; placebo = 97.9%). Of the participants in the study, 97.2% had an adherence to treatment rate of ≥80%. Adherence to treatment remained high over time, with a mean of 97.1% from month 3 to month 6. No participant was withdrawn because of poor adherence to treatment.

Summary of AEs

The majority of participants (n = 349; 88.8%) experienced at least 1 TEAE; most were mild (n = 325; 82.7%) or moderate (n = 145; 36.9%), with a higher percentage of VP250-treated participants (90.5%) versus placebo (83.8%) reporting TEAEs (Table II). The incidence of severe TEAEs was low (1.3% of participants overall) and similar between groups. The most frequently reported TEAEs in VP250-treated participants, regardless of treatment-relatedness, are shown in Table E2 in this article's Online Repository at www.jaci-inpractice.org. Application site reactions reported as TEAEs occurred in 73 (18.6%) participants overall: 64 (21.8%) in the VP250 group and 9 (9.1%) in the placebo group. It should be noted that these local AE rates do not represent all local application site reactions, as itching, redness, and swelling were not reported as AEs, unless they were serious, or led to study discontinuation or had

TABLE II. Summary of adverse events (double-blind safety population)

Category	Viaskin Peanut 250 μg (n = 294) n (%) m* Wilson 95% CI	Placebo (n = 99) n (%) m* Wilson 95% CI
Summary of adverse events		
Any TEAEs	266 (90.5) 1288 86.6; 93.3	83 (83.8) 341 75.4; 89.8
TEAEs considered related to study drug†	94 (32.0) 163 26.9; 37.5	14 (14.1) 20 8.6; 22.4
Study drug–induced local TEAEs‡	64 (21.8) 89 17.4; 26.8	9 (9.1) 10 4.9; 16.4
Systemic allergic TEAEs considered related to study drug	14 (4.8) 15 2.9; 7.8	0 0; 3.7
TEAEs considered unrelated to study drug†	251 (85.4) 1125 80.9; 89.0	78 (78.8) 321 69.7; 85.7
TEAE severity		
Mild	248 (84.4) 1054 79.8; 88.1	77 (77.8) 297 68.6; 84.8
Moderate	118 (40.1) 230 34.7; 45.8	27 (27.3) 43 19.5; 36.8
Severe	4 (1.4) 4 0.5; 3.5	1 (1.0) 1 0.2; 5.5
TEAEs leading to permanent study drug discontinuation	5 (1.7) 8§ 0.7; 3.9	0 0; 3.7
TEAEs leading to temporary study drug discontinuation	44 (15.0) 64 11.3; 19.5	8 (8.1) 12 4.2; 15.1
TEAEs leading to death	0 0; 1.3	0 0; 3.7
Serious TEAEs	3 (1.0) 3 0.4; 3.0	2 (2.0) 2 0.6; 7.1
Serious TEAEs considered related to study drug†	1 (0.3) 1 0.1;1.9	0 0;3.7
Severe TEAEs considered related to study drug	2 (0.7) 2 0.2; 2.5	0 0; 3.7
Severe study drug–induced local TEAEs‡	1 (0.3) 1 0.1; 1.9	0 0; 3.7
Treatment of allergic reactions		
TEAEs leading to an epinephrine intake	16 (5.4) 17 3.4; 8.7	3 (3.0) 3 1.0; 8.5
In TEAEs considered related to study drug†	7 (2.4) 7 1.2; 4.8	0 0; 3.7
In TEAES considered unrelated to study drug	9 (3.1) 10 1.6; 5.7	3 (3.0) 3 1.0; 8.5
TEAEs leading to topical corticosteroid usage	45 (15.3) 55 11.6; 19.9	11 (11.1) 18 6.3; 18.8
TEAEs leading to systemic or inhaled corticosteroid intake	34 (11.6) 42 8.4; 15.7	11 (11.1) 11 6.3; 18.8

TEAE, Treatment-emergent adverse event.
*m indicates the number of events.
†Considered related to the investigational product when reported as possibly related, probably related, or related.
‡Study drug–induced local TEAE is defined as TEAE considered related to study drug with a MedDRA High Level Term equal to "application and instillation site reactions."
§One participant experienced 4 related nonserious induration at patch site TEAEs leading to permanent study drug discontinuation. These TEAEs started during the double-blind, placebo-controlled phase (day 92), but the discontinuation occurred during the open-label period.

potential barrier disruption (see the "Parental local skin reaction assessments" section). Investigators reported any events outside these 3 prespecified reactions (itching, swelling, redness). Overall, the percentage of participants with TEAEs in any category was similar in the 4- to 5-year-old (91.1%) and 6- to 8-year-old (90%) age groups, and slightly lower in the 9- to 11-year-old age group (84.9%). No overt differences in TEAE rates were observed in either group in participants with or without a history of prior peanut anaphylaxis (Table III).

SAEs (Table II) were reported for similar proportions of participants receiving VP250 (1% of participants, 3 events) and placebo (2% of participants, 2 events): 2 participants with anaphylaxis and 1 with bronchospasm (acute asthma exacerbation deemed unrelated to study treatment) receiving VP250 and

TABLE III. Summary of adverse events by the history of peanut anaphylaxis (double-blind safety population)

Summary of adverse events	Viaskin Peanut 250 μg (n = 294)						Placebo (n = 99)					
	Yes (n = 206)			No (n = 88)			Yes (n = 78)			No (n = 21)		
History of anaphylaxis	n	%	m*	n	%	m*	n	%	m*	n	%	m*
Any TEAEs	181	87.9	873	85	96.6	415	66	84.6	255	17	81	86
TEAEs considered related to study drug†	65	31.6	106	29	33	57	13	16.7	17	1	4.8	3
Study drug–induced local TEAEs‡	42	20.4	57	22	25	32	9	11.5	10	0	0	0
Systemic allergic TEAE considered related to study drug†	10	4.9	10	4	4.5	5	0	0	0	0	0	0
Anaphylactic reaction reported by the investigator	9	4.4	9	3	3.4	3	0	0	0	0	0	0
TEAEs considered unrelated to study drug	168	81.6	767	83	94.3	358	61	78.2	238	17	81	83
TEAE severity												
Mild TEAEs	170	82.5	707	78	88.6	347	60	76.9	222	17	81	75
Moderate TEAEs	82	39.8	164	36	40.9	66	21	26.9	32	6	28.6	11
Severe TEAEs	2	1	2	2	2.3	2	1	1.3	1	0	0	0
TEAEs leading to permanent study drug discontinuation	3	1.5	6	2	2.3	2	0	0	0	0	0	0
TEAEs leading to temporary study drug discontinuation	34	16.5	45	10	11.4	19	6	7.7	9	2	9.5	3
TEAEs leading to death	0	0	0	0	0	0	0	0	0	0	0	0
Serious TEAEs	2	1	2	1	1.1	1	2	2.6	2	0	0	0
Serious TEAEs considered related to study drug†	1	0.5	1	0	0	0	0	0	0	0	0	0
Severe TEAEs considered related to study drug	1	0.5	1	1	1.1	1	0	0	0	0	0	0
Severe study drug–induced local TEAEs‡	1	0.5	1	0	0	0	0	0	0	0	0	0
Treatment of allergic reactions												
TEAEs leading to epinephrine administration	10	4.9	10	6	6.8	7	3	3.8	3	0	0	0
In TEAEs considered related to study drug†	5	2.4	5	2	2.3	2	0	0	0	0	0	0
In TEAEs considered unrelated to study drug	5	2.4	5	4	4.5	5	3	3.8	3	0	0	0
TEAEs leading to topical corticosteroid administration	31	15	39	14	15.9	16	8	10.3	14	3	14.3	4

Percentages are based on the number of participants in each subgroup (n).
TEAE, treatment-emergent adverse event.
*m indicates the number of events.
†Considered related to the investigational product when reported as possibly related, probably related, or related.
‡Study drug–induced local TEAE is defined as TEAE considered related to study drug with a MedDRA High Level Term equal to application and instillation site reactions.

1 each of postprocedural hemorrhage and seizure in participants receiving placebo.

TEAEs leading to permanent discontinuation (Table II) were experienced by 4 (1%) participants over this 6-month study duration, all in the VP250 group, including 2 participants with moderate anaphylactic reactions, 1 participant with an application site reaction, and 1 participant with urticaria. A fifth participant experienced application site induration that started on day 92 of the double-blind period and discontinued during the open-label period. None of these participants had a history of severe anaphylaxis to peanut.

TEAEs deemed related to treatment

TEAEs deemed treatment-related by the site investigator (related, probable, or possible) occurred in 108 (27.5%) participants: 32% in VP250 and 14.1% in placebo-treated participants (Table II). Similar proportions of participants across the 3 age groups experienced ≥1 related TEAE (4-5 years, n = 34/124 [27.4%]; 6-8 years, n = 34/130 [26.2%]; 9-11 years, n = 32/139 [23%]). There was a trend toward a reduction in VP250-induced local TEAEs with age: 27.2% in 4-5 years, 17.2% in 6-8 years, and 15.5% in 9-11 years. Similar rates of treatment-related TEAEs were observed in each treatment group regardless of the history of peanut anaphylaxis (Table III). VP250-induced local TEAEs occurred in 20.4% of participants with a history of anaphylaxis and 25% of those without a history of anaphylaxis.

Local skin reactions

Parental local skin reaction assessments. Application site reactions of erythema, pruritus, and swelling were recorded in the participants' diaries over the 6-month period. By this report, all (100%) participants in the VP250 group and 83.8% in the placebo group had local skin reactions. On a scale from 0 (none) to 3 (severe), most local skin reactions were reported as a maximum of grade 2 (42.3%) or grade 3 (45.2%). There were more frequent grade 3 reactions reported in VP250 (54.9%) than in placebo participants (10.8%) (Figure 2; Table E3, available in this article's Online Repository at www.jaci-inpractice.org). The mean number of days with local skin reaction was greater in VP250 participants (141.5 days) than placebo (39.6 days). Severity of local skin reactions declined over time in the VP250 group, with grade 3 reactions reported by 42.1% of participants in month 1 and 18.9% during month 6 (Figure 2).

Investigator local skin reaction assessments at study visits. Investigators assessed local skin reactions at all study visits and reported local skin reactions in 97.6% of participants receiving VP250 and 50.5% receiving placebo. Most participants had local skin reactions of maximum grade 1 (38.9%) or 2 (34.4%). Grade 3 reactions were reported in 15.6% of participants receiving VP250 and 1% of participants receiving placebo. Grade 4 (vesicular) reactions were reported in 3 (1%) participants receiving VP250 participants, none of whom

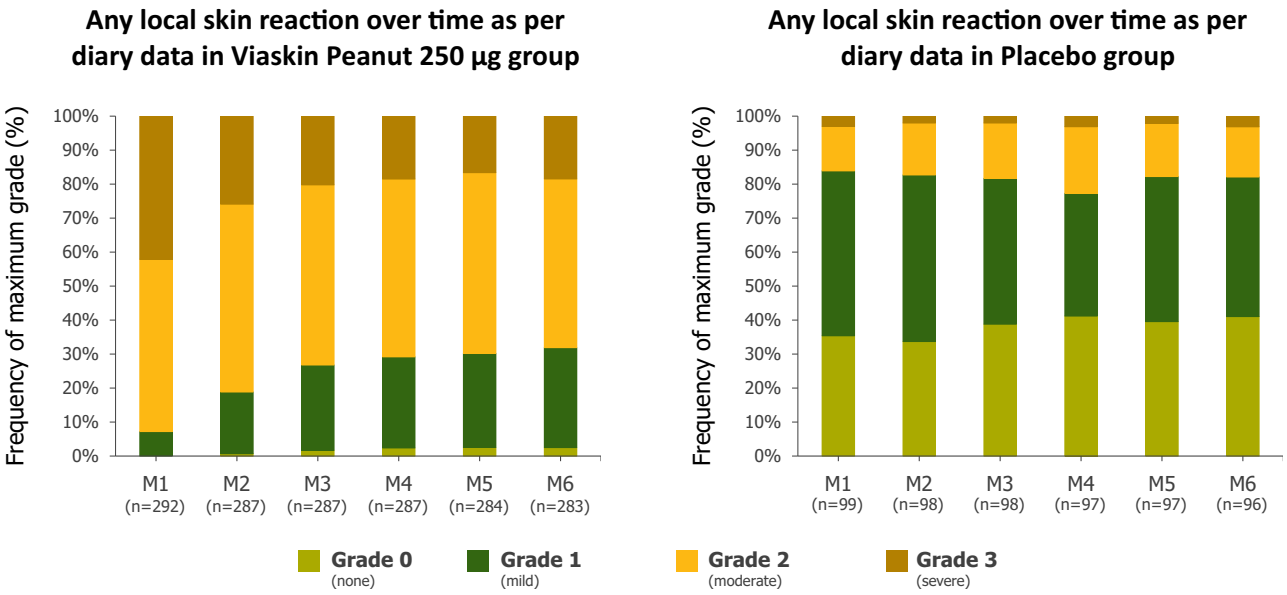

FIGURE 2. Distribution of diary-reported prespecified local skin reactions by severity from month 1 through month 6. *M*, Month.

had a history of severe anaphylaxis, and none resulted in permanent discontinuation.

Filaggrin mutations

Optional filaggrin gene mutation testing was performed in 268 of 393 (68.2%) participants. Of those tested, 41 (15.3%) had mutations detected, of which 39 (95.1%) were heterozygous, with similar proportions in each treatment arm.

The highest ever reported severity of local skin reactions in participants receiving VP250 tended to be higher in participants with, rather than without, mutations (grade 1 = 0%, grade 2 = 35.5%, grade 3 = 64.5% vs grade 1 = 5.2%, grade 2 = 38.2%, and grade 3 = 56.6%, respectively). This trend was less obvious for participants with and without mutations in the placebo group, but those receiving placebo had a greater proportion of participants with grade 2 as highest reported severity, compared to grade 1, with very similar but (not unexpectedly) low rates of grade 3 reactions reported (grade 1 = 30%, grade 2 = 60%, grade 3 = 10% vs grade 1 = 42.6%, grade 2 = 44.7%, and grade 3 = 12.8%, respectively). The limited number of participants with mutations in the filaggrin gene (n = 41) precluded any firm conclusions based on these trends.

Anaphylaxis and use of epinephrine

Twenty-seven anaphylactic reactions were reported by investigators in 27 (6.9%) participants, of whom 24 (8.2%) were receiving VP250 and 3 (3%) placebo (Table E4, available in this article's Online Repository at www.jaci-inpractice.org). Twelve (4.1%) anaphylactic reactions were considered related to VP250; none were severe, according to predefined criteria (Table E1, available in this article's Online Repository at www.jaci-inpractice.org), and 7 of 12 (2.4%) were treated with epinephrine. Rates of anaphylactic reactions considered related to VP250 were similar between participants with and without a history of anaphylaxis to peanut (4.4 % [9 of 206] and 3.4% [3 of 88], respectively) (Table III).

Two participants discontinued permanently because of VP250-related anaphylactic reactions, assessed as moderate in severity: a 6-year-old boy, 31 days after the start of VP250 treatment, and a 10-year-old girl, 9 days after the start of treatment. TEAEs (irrespective of relatedness to treatment) leading to epinephrine administration were reported in 16 (5.4% [17 episodes]) VP250-treated and 3 (3% [3 episodes]) placebo-treated participants.

psIgE and IgG4 levels

In participants receiving VP250, median psIgE transiently increased at month 3 and then declined toward baseline at month 6, whereas median peanut-specific IgG4 increased over time. There were no appreciable changes in the placebo group in either parameter (Figure E3, available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

Findings from the REALISE clinical trial confirmed that EPIT with VP250 is safe and well tolerated in a physician-diagnosed population of peanut-allergic children who were highly allergic, with approximately three-quarters of participants with prior anaphylaxis to peanut, along with high rates of other allergic conditions. These findings support the overall safety of VP250 with a study design approximating real-world clinical care. Almost all parents of participants receiving VP250 reported local application reactions of itching, swelling, and redness in the study diary. Not unexpectedly, TEAEs deemed treatment-related were higher (32%) in participants receiving VP250 compared with placebo (14.1%). However, the vast majority of local application site reactions were mild to moderate in severity and declined over time. Reassuringly, rates of TEAEs were similar in participants regardless of whether they had a history of peanut anaphylaxis, and no new or concerning safety signals were observed in participants with a history of anaphylaxis. Permanent discontinuations due to TEAEs were low, and mean adherence

to treatment was high in both groups, even though local application site reactions reported by parents (in the participant diary) were common. Rates of anaphylaxis were higher in those participants who received treatment compared with placebo, including those reactions deemed related to treatment. Among anaphylaxis events deemed possibly, probably, or related to treatment, there were no cases of severe anaphylaxis, with the majority being assessed as moderate and one-quarter as mild. These were managed with either no, or a single dose, of epinephrine without any sequelae.

EPIT with VP250 has been shown to be efficacious and well tolerated in phase 2 (OLFUS-VIPES) and 3 (PEPITES) controlled clinical trials,[11-13] with quantitative risk analysis modeling suggesting reductions in the risk of reaction to accidental peanut ingestion through contamination in packaged food products and restaurant meals.[17,18] The current phase 3 study, REALISE, aimed to expand the short- and long-term safety database of EPIT with VP250 under conditions more closely representative of usual clinical practice, with diagnosis made by clinical history and very high probability biomarkers rather than DBPCFC. In fact, despite differences in study inclusion requirements, the study population of REALISE and PEPITES were similar in terms of median age at study entry (7 years in both studies), proportion of male participants (58.3% vs 61.2%), asthma (45.5% vs 47.5%), eczema (57.8% vs 61.2%), and ongoing (other) food allergy (59.8% vs 58%), but differed in that REALISE did not exclude individuals with a history of severe anaphylaxis and the baseline mean peanut-sIgE was higher in the REALISE population (199.8 vs 152 kU/L). This suggests that the REALISE population was at least as sensitized (on the basis of peanut-sIgE) as those children who participated in the phase 3 clinical trial, which included DBPCFC, providing additional reassurance for safety in this highly sensitized population.

The safety results of this study are also consistent with those reported in the double-blind, placebo-controlled studies of VP250,[12,13] although direct comparisons cannot be made because of differences in study design and DBPCFC entry requirements in PEPITES and OLFUS-VIPES. Nevertheless, the rates of all TEAEs considered related to study drug were lower in the present study, although rates of discontinuation were similarly low in the phase 2 and 3 studies.[12,13]

As new and potential therapies for peanut allergy emerge, shared decision-making requires thorough conversations between providers and patients/caregivers around concepts such as benefit:risk profiles. A recent comprehensive systematic review and meta-analysis of oral immunotherapy (OIT) for peanut allergy suggested that OIT was associated with a high rate of allergic and anaphylactic reactions compared with either avoidance or placebo treatment,[19] with a calculated risk ratio of 1.92 for SAEs and 3.12 for anaphylaxis based on 12 clinical trials. Daily treatment with VP250 (roughly 1/1000 peanut daily) involves >1000-fold less exposure to peanut protein, compared with maintenance peanut OIT, which typically involves daily ingestion of 300 mg (roughly 1 peanut daily).[20] Clinical trials with VP250 have not required any treatment interruptions or modifications based on activity/exercise, intercurrent illness, hot water exposure, fasting, or menstruation.

The exploratory end points of psIgE and IgG4 levels over the course of the study were of a similar trajectory and magnitude to those observed in previous EPIT studies, consistent with the hypothesis that immunotherapy achieves its efficacy at least in part by immunomodulation, as shown by increasing IgG4 levels over time. The increase in allergen-specific IgG4 has been well described in other forms of specific immunotherapy, including subcutaneous, sublingual, and oral.

One limitation of this study was the small number of patients enrolled with a history of severe peanut anaphylaxis, precluding definitive conclusions about safety in this subgroup compared to the overall participant population. In addition, although the definition of severe anaphylaxis for this study was based on well-known and accepted criteria, and investigators were specifically trained in the use of these criteria, the history of anaphylaxis and severe anaphylaxis was not validated by actual DBPCFC, but by investigators during the screening process (using medical records and emergency department records where available to complement history). A large proportion of participants who were enrolled had a history of peanut-induced anaphylaxis (mild/moderate), allowing for a thorough assessment of this group, which represented the vast majority of children within the greater population with peanut allergy. Within the analyses conducted, no clinically meaningful differences were seen between the overall population and the subgroup with a history of severe anaphylaxis. The current study reports the 6-month, randomized, blinded phase of the REALISE study; however, more information on longer-term safety, in addition to that gained from the ongoing open-label extension of PEPITES (PEOPLE) study,[14] will help to further expand knowledge on the long-term safety and compliance of VP250.

In conclusion, REALISE was designed to replicate real-world conditions without a DBPCFC and therefore had no efficacy assessment. The results of the safety analysis of the double-blind phase of REALISE demonstrate the safety, tolerability, and high adherence to treatment associated with the use of VP250, supporting its use as an immunotherapeutic agent for the management of peanut allergy.

It is clear that peanut allergy poses an ongoing challenge, as it tends to be life-long, and accidental ingestion remains problematic with an annual incidence ranging from approximately 3% to at least 12%.[17,21] Given the potentially serious consequences of accidental consumption and the unpredictability of anaphylactic reactions, an easy-to-use, well-tolerated approach with a favorable benefit:risk profile could afford those with peanut allergy, as well as caregivers and health care providers, a valuable therapeutic option for managing this serious condition.

Acknowledgments

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DBV Technologies was involved in the design and general oversight of the study but not in the collection and management

of the data; analysis and interpretation of the data included contributions from DBV Technologies—employed and —contracted statisticians; and nonauthor contributors from DBV Technologies were involved in the preparation, review, approval, and decision to submit the manuscript for publication. DBV Technologies did not have the right or ability to veto the authors' final decision to submit the manuscript for publication. All data were collected electronically, managed, analyzed, and locked by the contract research organization (Parexel International) before being released to the authors. An independent data and safety monitoring board oversaw the study conduct and reviewed blinded and unblinded AE data (Appendix E1). In addition, checks of data integrity were performed by DBV Technologies, which included site visits and site audits, as well as contract research organization oversight.

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TABLE E1. Staging system of severity of anaphylaxis

Stage	Defined by
1. Mild: Skin and subcutaneous tissues, gastrointestinal (GI) and/or mild respiratory	Flushing, urticaria, periorbital, or facial angioedema; mild abdominal pain and/or emesis; mild dyspnea, wheeze, or upper respiratory symptoms
2. Moderate: Mild symptoms plus features suggesting moderate respiratory, cardiovascular, or GI symptoms	Marked dysphagia, hoarseness, and/or stridor; shortness of breath, wheezing, and retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea, and/or mild dizziness
3. Severe: Hypoxia, hypertension (more 20% drop in blood pressure) or neurological compromise	Cyanosis of $SpO_2 \leq 92\%$ at any stage, confusion, cardiovascular collapse, loss of consciousness, incontinence, bradycardia, and cardiac arrest

Adapted from Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-7.

TABLE E2. Most frequent TEAEs by SOC and Preferred Term (occurring in ≥5% of subjects in any treatment group; double-blind safety population), regardless of treatment relatedness

Summary of adverse events	Viaskin Peanut 250 μg (n = 294) n (%) m*	Placebo (n = 99) n (%) m*
Most frequent TEAEs (≥5% of patients in either treatment group)		
Upper respiratory tract infection	55 (18.7) 87	24 (24.2) 32
Viral upper respiratory tract infection	52 (17.7) 77	16(16.2) 25
Pyrexia	52 (17.7) 63	14 (14.1) 16
Headache	42 (14.3) 77	6 (6.1) 23
Application site eczema	31 (10.5) 34	5 (5.1) 6
Asthma	31 (10.5) 59	5 (5.1) 6
Urticaria	29 (9.9) 44	7 (7.1) 9
Anaphylactic reaction	24 (8.2) 24	3 (3.0) 3
Vomiting	23 (7.8) 26	5 (5.1) 5
Rhinitis allergic	22 (7.5) 35	2 (2.0) 2
Cough	19 (6.5) 26	12 (12.1) 13
Eczema	19 (6.5) 21	7 (7.1) 16
Viral infection	19 (6.5) 28	7 (7.1) 11
Oropharyngeal pain	18 (6.1) 21	3 (3.0) 4
Pharyngitis streptococcal	17 (5.8) 25	5 (5.1) 7
Influenza	16 (5.4) 18	5 (5.1) 5
Gastroenteritis	16 (5.4) 17	2 (2.0) 2
Ear infection	14 (4.8) 14	6 (6.1) 7
Gastroenteritis viral	14 (4.8) 14	6 (6.1) 7
Hypersensitivity	14 (4.8) 18	6 (6.1) 6
Nasal congestion	12 (4.1) 18	6 (6.1) 12
Seasonal allergy	12 (4.1) 21	5 (5.1)

Percentages are based on the number of subjects in the safety population for each treatment group. Adverse events were classified into SOC and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. Subjects were counted once per Preferred Term.

SOC, System Organ Class; *TEAE*, treatment-emergent adverse event.

*m indicates the number of events.

TABLE E3. Summary of local events among subjects with evaluable diary data by event

Event	Viaskin Peanut (n = 293)* n (%) 95% Wilson CI	Placebo (n = 99) n (%) 95% Wilson CI
Itching	292 (99.7) 98.1; 99.9	61 (61.6) 51.8; 70.6
Grade 1	27 (9.2) 6.4; 13.1	34 (34.3) 25.7; 44.1
Grade 2	147 (50.2) 44.5; 55.9	21 (21.2) 14.3; 30.3
Grade 3	118 (40.3) 34.8; 46.0	6 (6.1) 2.8; 12.6
Redness	293 (100) 98.7; 100.0	82 (82.8) 74.2; 89.0
Grade 1	21 (7.2) 4.7; 10.7	45 (45.5) 36.0; 55.3
Grade 2	141 (48.1) 42.5; 53.8	32 (32.3) 23.9; 42.1
Grade 3	131 (44.7) 39.1; 50.4	5 (5.1) 2.2; 11.3
Swelling	292 (99.7) 98.1; 99.9	48 (48.5) 38.9; 58.2
Grade 1	27 (9.2) 6.4; 13.1	35 (35.4) 26.6; 45.2
Grade 2	146 (49.8) 44.1; 55.5	9 (9.1) 4.9; 16.4
Grade 3	119 (40.6) 35.2; 46.3	4 (4.0) 1.6; 9.9

CI, Confidence interval.
*n = number of subjects with evaluable diary data (subjects with at least 1 page of diary entered).

TABLE E4. Summary of all episodes of anaphylaxis, regardless of relatedness to treatment

Age (y)	Time of onset after last patch application (h)	Suspected trigger	Relatedness* (as assessed by the clinical site investigator)	Severity assessment by investigator	Epinephrine given? (Y/N)	Medications given	Disposition regarding patch	Short narrative
5	1-2	Viaskin Peanut	Related	Moderate	Y	Epinephrine, diphenhydramine	Resumed 2 days after episode	7 days after start of Viaskin Peanut—coughing, sniffing, sneezing, wheezing, and hives. No new foods no other obvious trigger. Multiple known food and aeroallergen allergies.
10	1-2	Viaskin Peanut	Possibly related	Mild	N	Cetirizine, diphenhydramine, salbutamol	Resumed next day	25 days after starting Viaskin Peanut—onset of sore throat, compression sensation, mild pruritus, and widespread urticaria. Last eaten 3-4 hours prior. No obvious other trigger.
9	1	Viaskin Peanut	Related	Mild	N	Diphenhydramine, mometasone furoate (nasal)	Resumed 9 days later episode	28 days after start of Viaskin Peanut—onset of difficulty breathing, rhinitis, and hives on neck and back. No other obvious trigger. Known multiple aeroallergen sensitivities.
11	15	Snack bar	Unrelated	Mild	Y	Epinephrine, diphenhydramine	Resumed next day	75 days after start of Viaskin Peanut—onset of throat tightness, chest pain, dizziness, cough, nasal congestion, and shortness of breath 10 minutes after eating a snack bar. Known multiple food allergies.
10	12	Lupine	Unrelated	Moderate	N	Cetirizine	No interruption	89 days after start of Viaskin Peanut—onset of tingly mouth, stomachache, lightheadedness, and throat itchiness after eating lupine containing pancakes. Known multiple food allergies including lupine.
10	Patch not on at time of reaction	Chocolate ice-cream	Unrelated	Moderate	Y	Epinephrine, diphenhydramine	No interruption	183 days after start of placebo—onset of abdominal pain, urticaria on neck and torso, and ear erythema 5 minutes after ingesting chocolate ice cream from buffet. Known multiple food allergies.

6	1-2	Viaskin Peanut	Related	Mild	N	Nil	Resumed next day	23 days after start of Viaskin Peanut—onset of throat irritation, cough, and lethargy whilst driving in a car to dinner.
8	20	Unknown	Unrelated	Moderate	Y	Epinephrine, prednisolone, diphenhydramine	No interruption	40 days after start of Viaskin Peanut—onset of rash on face, facial swelling, one episode of vomiting, and somnolence with no obvious trigger. Had eaten at a friend's house at a birthday party that afternoon. Known multiple food allergies.
6	1	Viaskin Peanut	Probably related	Moderate	Y	Epinephrine, diphenhydramine, famotidine, methylprednisolone, cetirizine	Permanently discontinued	31 days after start of Viaskin Peanut—onset of generalized hives, rhinorrhea, a splotchy rash on the face, and persistent cough shortly after application of patch an ingestion of Nutella on bread.
6	20	Snack bar	Unlikely related	Moderate	Y	Epinephrine, diphenhydramine, dexamethasone, ondansetron	No interruption	58 days after start of Viaskin Peanut—onset of nausea vomiting, throat pain, stomach pain, and pain with breathing 30 minutes after ingesting a snack bar.
8	1	Viaskin Peanut	Probably related	Moderate	Y	Epinephrine, diphenhydramine, albuterol, prednisolone	Resumed 5 days after episode	23 days after start of Viaskin Peanut—onset of hives, cough, chest tightness, and scratchy/itchy throat approximately 35 minutes after patch was applied and 3 hours after last meal.
6	1	Unknown	Unlikely related	Moderate	N	Diphenhydramine, albuterol prednisolone	Resumed next day	17 days after start of Viaskin Peanut—onset of pruritus, hives, cough, and wheeze approximately 30 minutes after patch applied and whilst deep cleaning of the house was occurring. Known multiple food and aeroallergen allergies.
6	18	Milkshake	Unrelated	Moderate	Y	Epinephrine, diphenhydramine, and prednisolone	Resumed next day	158 days after start of Viaskin Peanut—onset of nausea, and one episode of vomiting, and delayed coughing 10 minutes after consuming a milkshake. Known multiple food allergies.

(continued)

TABLE E4. *(Continued)*

Age (y)	Time of onset after last patch application (h)	Suspected trigger	Relatedness* (as assessed by the clinical site investigator)	Severity assessment by investigator	Epinephrine given? (Y/N)	Medications given	Disposition regarding patch	Short narrative
6	10	? Jellybean	Unrelated	Mild	N	Nil	Resumed next day	87 days after start of Viaskin Peanut—onset of abdominal pain, palpitations, urticaria on arm and trunk 30 minutes after eating jellybeans at a friend's house. Known multiple food allergies, rhinitis and drug allergy.
7	<1	Viaskin Peanut	Probably related	Moderate	Y	Epinephrine, cetirizine, diphenhydramine	Resumed 6 weeks later	9 days after start of Viaskin Peanut—onset of nausea, shortness of breath, and hives on torso and legs 90 minutes after patch application and 110 minutes after dinner. Known multiple food allergies.
7	1	Viaskin Peanut	Related	Moderate	Y	Epinephrine, diphenhydramine, prednisolone, ranitidine	Resumed 6 days later	15 days after start of Viaskin Peanut—onset of torso hives, throat tightening, wheezing, and coughing. Last meal was 3 hours prior.
10	21	? Meatballs	Unrelated	Moderate	Y	Epinephrine, diphenhydramine,	Resumed next day	129 days after start of Viaskin Peanut—onset of cough, abdominal pain, nausea, and hives 15 minutes after eating a frozen meatball meal and fruit. Known multiple food allergies.
5	Patch not on at time of event	Peanut in smoothie	Unrelated	Moderate	Y	Epinephrine, diphenhydramine, ranitidine, ondansetron, dexamethasone	No interruption	8 days after start of Viaskin Peanut—onset of hives, itchy mouth 5 minutes after accidental ingestion of a peanut containing smoothie.
5	25	Almond	Unrelated	Moderate	Y	Epinephrine, diphenhydramine, dexamethasone, ranitidine	Resumed 3 days later	132 days after start of Viaskin Peanut—onset of hives, and vomiting minutes after ingesting a pastry containing almond. Known multiple food allergies including almond.

10	2-3	Viaskin Peanut	Probably related	Moderate	Y	Epinephrine diphenhydramine dexamethasone, prednisone	Permanently discontinued	9 days after start of Viaskin Peanut—onset of hives, wheezing, angioedema, itchy throat, and ear erythema approximately $2^1/_2$ hours after patch application. Last meal was 40 minutes before last patch application.
9	11-12	Candy bar	Unrelated	Severe	Y	Epinephrine, diphenhydramine	Resumed next day	122 days after start of Viaskin Peanut—onset of throat itching, tightness abdominal pain and pruritus leading to facial swelling, coughing, and gagging, with onset immediately after ingestion of a chocolate candy bar with hazelnuts.
4	12+ hours	Snack bar	Unlikely related	Moderate	Y	Epinephrine, diphenhydramine, albuterol	Resumed 2 days later	138 days after start of placebo—onset of coughing, wheezing, and itchy mouth immediately after eating a chocolate chip snack bar. Known multiple food allergies.
6	Patch not on at time of event	Birthday cake	Unrelated	Moderate	N	Diphenhydramine	No interruption	11 days after start of Viaskin Peanut—onset of hives, abdominal pain, nausea, nasal congestion, and sneezing 5 minutes after eating birthday cake and lasagna at a birthday celebration.
4	6	Peanut in candy	Unrelated	Moderate	Y	Epinephrine, diphenhydramine, albuterol, methylprednisolone, famotidine	Resumed next day	18 days after start of placebo—onset of wheezing, erythema, and hoarse voice after ingestion of peanut containing chocolate candy. Known multiple food allergies.
11	1	Viaskin Peanut	Related	Moderate	N	Diphenhydramine	Resumed next day	38 days after start of Viaskin Peanut—onset of widespread erythema, hives, rhinitis, and itchy throat 1 hour after shower and patch application.

(continued)

TABLE E4. *(Continued)*

Age (y)	Time of onset after last patch application (h)	Suspected trigger	Relatedness* (as assessed by the clinical site investigator)	Severity assessment by investigator	Epinephrine given? (Y/N)	Medications given	Disposition regarding patch	Short narrative
7	5	Viaskin Peanut	Related	Moderate	N	Diphenhydramine, albuterol	Resumed next day	9 days after start of Viaskin Peanut—onset of cough, wheeze, rhinitis, and hives on back approximately 5 hours after last patch application. No history of new foods eaten that day. Known multiple food allergies.
4	8	Viaskin Peanut	Probably related	Moderate	Y	Epinephrine, diphenhydramine	Resumed next day	22 days after start of Viaskin Peanut—onset of cough, sore throat, pruritus, and nausea whilst playing basketball outside, approximately 8 hours after last patch application. Known multiple food and aeroallergen allergies.

*Relatedness assessment made by the clinical site investigator, at the time of episode, as per protocol.

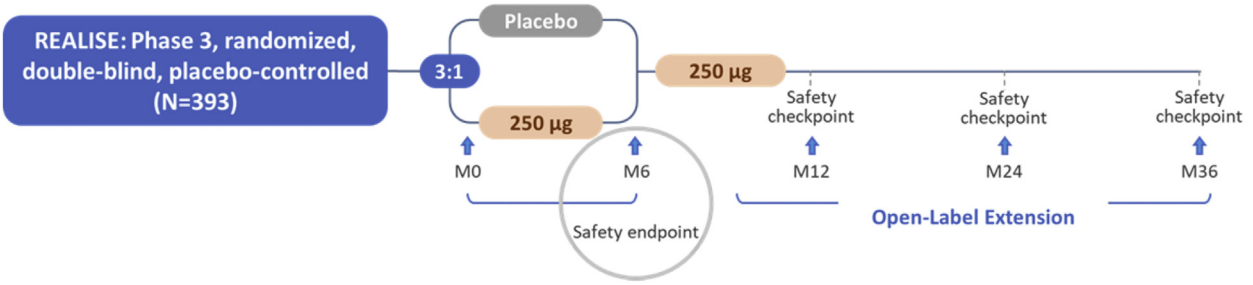

FIGURE E1. REALISE study design. *M*, Month; *REALISE*, REAL LIfe Use and Safety of EPIT.

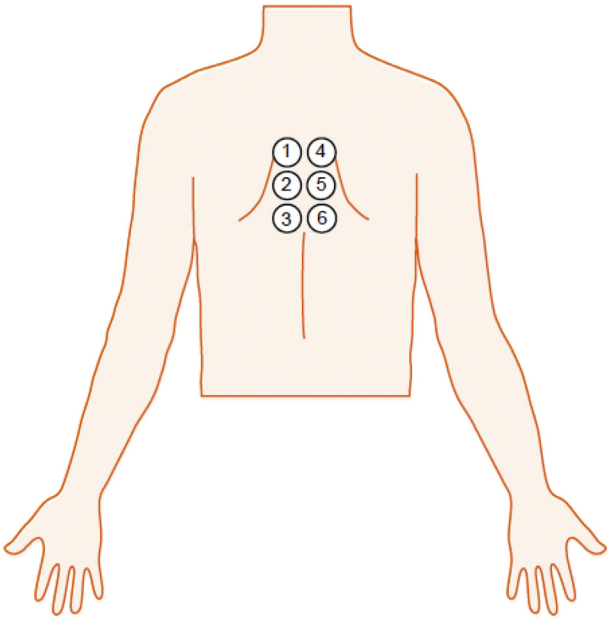

FIGURE E2. Interscapular patch placement. The location of patch application was the interscapular area of the back of the participants. There were 6 zones for applying the patch, 3 on each side of the spine. The first patch was applied on zone 1, the second on zone 2 (after removal of the first patch), and so forth, until all 6 zones had been used. After zone 6, dosing restarted with zone 1 and continued sequentially, as described.

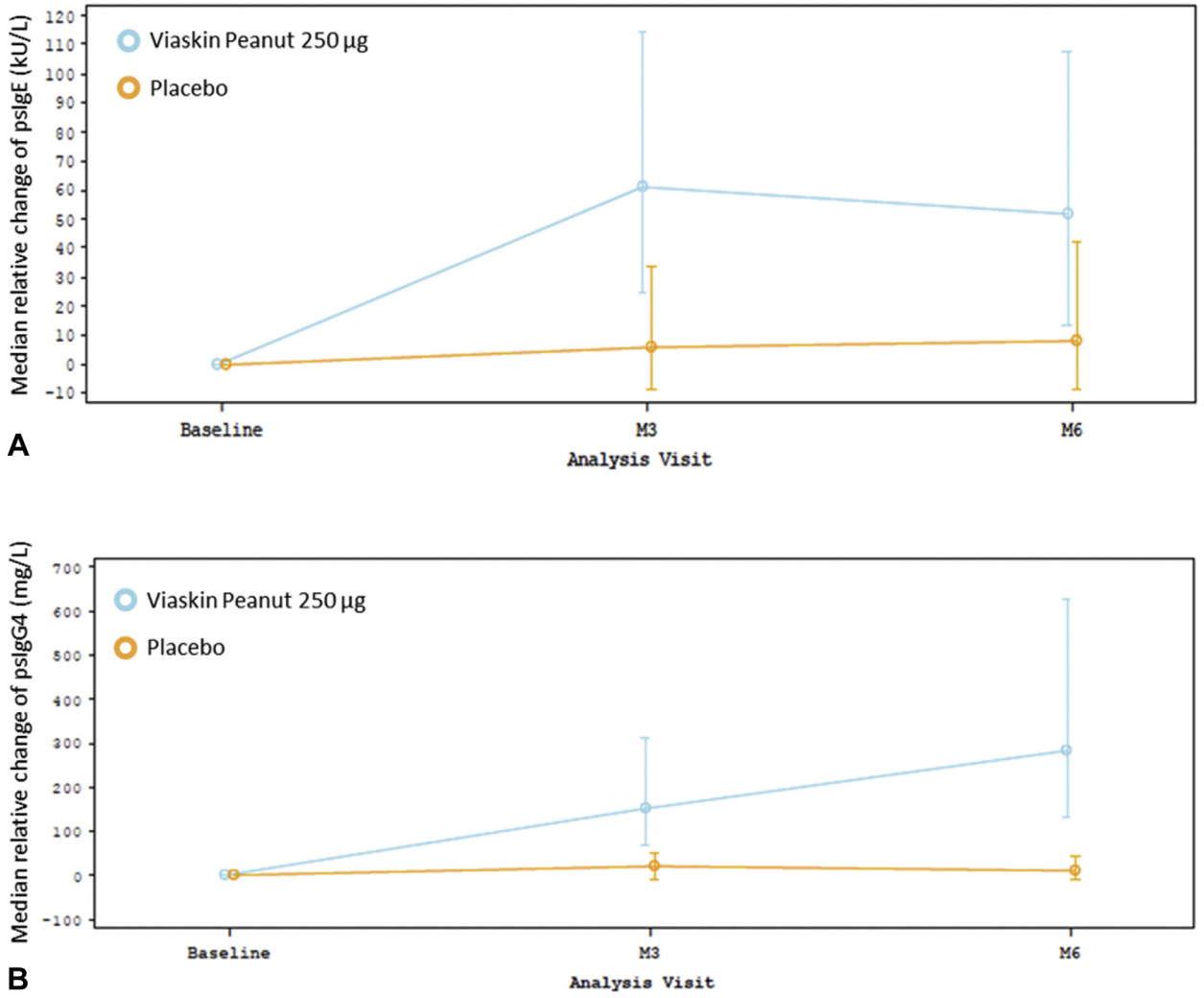

FIGURE E3. Median (and interquartile range) of relative change from baseline in (**A**) peanut-specific IgE and (**B**) peanut-specific IgG4 by the treatment group (double-blind period safety population). *M*, Month; *pslgE*, peanut-specific immunoglobulin E; *pslgG4*, peanut-specific immunoglobulin G4.