

ORIGINAL ARTICLE

Phase 3 Trial of Epicutaneous Immunotherapy in Toddlers with Peanut Allergy

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ABSTRACT

BACKGROUND

No approved treatment for peanut allergy exists for children younger than 4 years of age, and the efficacy and safety of epicutaneous immunotherapy with a peanut patch in toddlers with peanut allergy are unknown.

METHODS

We conducted this phase 3, multicenter, double-blind, randomized, placebo-controlled trial involving children 1 to 3 years of age with peanut allergy confirmed by a double-blind, placebo-controlled food challenge. Patients who had an eliciting dose (the dose necessary to elicit an allergic reaction) of 300 mg or less of peanut protein were assigned in a 2:1 ratio to receive epicutaneous immunotherapy delivered by means of a peanut patch (intervention group) or to receive placebo administered daily for 12 months. The primary end point was a treatment response as measured by the eliciting dose of peanut protein at 12 months. Safety was assessed according to the occurrence of adverse events during the use of the peanut patch or placebo.

RESULTS

Of the 362 patients who underwent randomization, 84.8% completed the trial. The primary efficacy end point result was observed in 67.0% of children in the intervention group as compared with 33.5% of those in the placebo group (risk difference, 33.4 percentage points; 95% confidence interval, 22.4 to 44.5; $P<0.001$). Adverse events that occurred during the use of the intervention or placebo, irrespective of relatedness, were observed in 100% of the patients in the intervention group and 99.2% in the placebo group. Serious adverse events occurred in 8.6% of the patients in the intervention group and 2.5% of those in the placebo group; anaphylaxis occurred in 7.8% and 3.4%, respectively. Serious treatment-related adverse events occurred in 0.4% of patients in the intervention group and none in the placebo group. Treatment-related anaphylaxis occurred in 1.6% in the intervention group and none in the placebo group.

CONCLUSIONS

In this trial involving children 1 to 3 years of age with peanut allergy, epicutaneous immunotherapy for 12 months was superior to placebo in desensitizing children to peanuts and increasing the peanut dose that triggered allergic symptoms. (Funded by DBV Technologies; EPITOPE ClinicalTrials.gov number, NCT03211247.)

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PEANUT ALLERGY AFFECTS APPROXIMATELY 2% of children in the United States, Canada, and other westernized countries, and the prevalence has risen rapidly over the past 20 years.¹⁻⁴ Peanut allergy is a common cause of pediatric anaphylaxis,⁵⁻⁸ has substantial economic costs,^{9,10} and persists into adulthood for the majority of those affected.^{11,12} Peanut is a common culinary ingredient, which complicates strict avoidance; severe reactions can occur from unintended exposure to small quantities.¹³⁻¹⁵ Living with peanut allergy is often associated with adverse psychosocial effects in children and their caregivers.¹⁶⁻¹⁸ Families have indicated that treatments protecting their children against reactions from unintentional peanut exposures would improve the children's socialization and the quality of life of the children and their families.¹⁹

Although treatment strategies are emerging, approved therapies for children under 4 years of age do not exist. Desensitization, defined as an increase in the reaction-dose threshold to a food allergen (which would thereby reduce the reaction risk from unintended ingestion), is a primary treatment goal.^{20,21} Early peanut consumption during infancy can substantially reduce a child's risk of peanut allergy.²² Thus, at these ages, the developing immune system may be particularly amenable to desensitization,²³⁻²⁶ which provides an important rationale for prioritizing treatments that target younger children. Peanut oral immunotherapy is available in noncommercialized forms for children younger than 4 years of age and can induce desensitization,^{23,24} but the therapy is associated with potentially arduous administration schedules and a risk of treatment-associated systemic adverse events such as anaphylaxis and gastrointestinal events,²⁷⁻²⁹ which creates a need for approaches with alternative routes of administration and different safety profiles.

Epicutaneous immunotherapy with patch-based nonoral immunotherapy has shown consistent evidence of efficacy, safety, and high treatment adherence in children 4 to 11 years of age with peanut allergy.³⁰⁻³² Epicutaneous immunotherapy accomplishes these results with substantially lower allergen doses (microgram vs. milligram) than those used in other therapeutic alternatives. On the basis of these findings, we

conducted the phase 3 Epicutaneous Immunotherapy in Toddlers with Peanut Allergy (EPITOPE) trial to assess the efficacy and safety of epicutaneous immunotherapy with a peanut patch containing 250 μ g of peanut protein (Viaskin Peanut, DBV Technologies) in children 1 to 3 years of age with peanut allergy.

METHODS

TRIAL DESIGN

We performed this phase 3, double-blind, randomized, placebo-controlled trial at 51 sites in eight countries across the United States, Canada, Australia, and Europe (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The safety and appropriate dose for use in children 1 to 3 years of age were established in a previous substudy that involved 51 children with peanut allergy who had undergone randomization to receive 12 months of placebo or peanut-protein-containing patches at a dose of 100 μ g or 250 μ g, with the 250- μ g dose having been approved by an independent data and safety monitoring board.³³

The sponsor, DBV Technologies, designed the trial with investigator input. Data were gathered by principal investigators (who are also coauthors) at each site and were analyzed by members of the writing committee. The roles of the authors are listed in the Supplementary Appendix. The authors participated in the writing and editing of the manuscript and made the decision to submit the manuscript for publication. All the authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol (available with the statistical analysis plan at NEJM.org).

The trial was conducted under an investigational new drug application submitted to the Food and Drug Administration and with clinical trial approvals from review boards in Australia, Canada, and European site countries. The protocol stipulated that investigators could not independently publish results without consultation with the sponsor.

The protocol and informed consent document were approved by institutional review boards at the trial sites. Written informed consent was obtained from legally authorized representatives of the patients.

PATIENTS

Key inclusion criteria were physician-diagnosed peanut allergy, a peanut-specific IgE level greater than 0.7 kUA per liter and a skin-prick test with a largest wheal diameter of at least 6 mm, and an eliciting dose of peanut protein of 300 mg or less as measured in a double-blind, placebo-controlled food challenge. Complete inclusion and exclusion criteria are shown in Table S1 in the Supplementary Appendix. Screening and a peanut double-blind, placebo-controlled food challenge at month 12 were conducted according to the guidelines of the Practical Allergy (PRACTALL) consensus report with the use of a standardized, blinded food matrix.³⁴ At the screening peanut challenge, peanut-protein doses of 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, and 300 mg (with 300 mg as the maximum dose) were administered every 30 minutes; the challenge was stopped when signs and symptoms met prespecified stopping criteria (Table S2). The dose that triggered symptoms that met stopping rules was considered the eliciting dose. For the month 12 food challenge, 1000-mg and 2000-mg doses were added (maximum cumulative dose, 3444 mg). Randomization was stratified according to site. Treatment adherence was defined as the total number of patches applied in the treatment period divided by the number of days in that period.

INTERVENTIONS

Viaskin Peanut 250 μ g (peanut patch) is an epicutaneous system consisting of unmodified lyophilized peanut protein within an occlusive chamber (details of patch components and application are shown in Fig. S2). Patients underwent randomization, in a 2:1 ratio, to receive the peanut patch or placebo patch (identical in size, shape, and appearance) applied daily to the interscapular area for 12 months. The first patch was applied for 3 hours under medical supervision. The duration of daily application was adjusted at home over 4 weeks according to a prespecified schedule. No restrictions were placed on any activities, including bathing or swimming, while patients were wearing the patch.

OUTCOMES

The primary measure of treatment effect was the percentage of patients in the intervention group as compared with those in the placebo group

who met the responder end point after 12 months of treatment. A patient was defined as meeting our response criterion if the baseline eliciting dose was more than 10 mg of peanut protein and the post-treatment eliciting dose was at least 1000 mg of peanut protein (the equivalent of approximately 3 to 4 peanuts) or if the baseline eliciting dose was 10 mg or less of peanut protein and the post-treatment eliciting dose was at least 300 mg of peanut protein (the equivalent of approximately 1 peanut).

The two key secondary end points that were included in a hierarchical plan to adjust for multiple testing were the change from baseline to month 12 in the cumulative reactive dose and eliciting dose in the intervention group as compared with the placebo group. Other prespecified secondary end points were response defined by an eliciting dose of at least 1000 mg of peanut protein at month 12, regardless of the screening eliciting dose; response defined by a cumulative reactive dose of at least 3444 mg of peanut protein at month 12; and the change in severity of symptoms elicited during the challenge from baseline to month 12.

Adverse events that occurred during treatment were evaluated for all patients who had received at least one dose of the assigned intervention or placebo. Adverse events that occurred during treatment were graded as mild, moderate, or severe and serious according to the Common Terminology Criteria for Adverse Events, version 4.03,³⁵ and were classified according to the *Medical Dictionary for Regulatory Activities*, version 20.1. Local application-site reactions were graded on a prespecified scale ranging from 0 to 4, with higher numbers indicating more serious reactions, as described in Section 6.2.6 of the protocol. Adverse events of special interest were defined as local (patch-site reactions, potentially leading to skin barrier disruption, or grade 4 reactions) or systemic (any acute systemic allergic reaction not associated with a food challenge, regardless of causal relationship to the peanut patch or placebo). Anaphylactic reactions were defined according to the criteria of the National Institute of Allergy and Infectious Diseases³⁶ or by investigator report of anaphylaxis or anaphylactic reaction, or both, regardless of severity and causal relationship to the peanut patch.

STATISTICAL ANALYSIS

We estimated that 350 patients (with 233 assigned to receive the intervention and 117 to receive placebo) would give the trial 90% power to detect an absolute difference in the lower boundary of the 95% confidence interval (calculated with the use of the Newcombe hybrid score method) of at least 15 percentage points. A 40% response with the intervention and 10% response with placebo (absolute risk difference, 30 percentage points) were assumed for comparison of the primary end points of response in the two groups after 12 months.

The primary analysis included all the patients according to their group assignment (full analysis set) and was assessed with the use of a two-sided Farrington–Manning 95% confidence interval for the difference in response between the groups. For the primary analysis, missing data for the food challenge at month 12 were imputed according to the type of intercurrent event (defined as an event that occurred after the application of treatment or placebo and either precluded observation of the variable or affected the interpretation of it) (Table S3). If statistical significance was observed for the primary outcome, a hierarchical procedure was applied to testing two secondary end points (cumulative reactive dose of peanut protein and eliciting dose of peanut protein at month 12) to control the familywise error rate at 0.05. Other efficacy and subgroup analyses that were not subject to multiple testing corrections were calculated as point estimates with 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiplicity and cannot be used in place of hypothesis testing. Prespecified sensitivity analyses were performed as described in the protocol document. All the analyses were prespecified except for the proportions of patients with a response according to the specific eliciting dose at baseline (Fig. S3), which was descriptive and post hoc.

RESULTS**PATIENTS, TREATMENT EXPOSURE, AND ADHERENCE**

The trial was conducted between July 31, 2017, and April 27, 2022, at 51 sites in eight countries across the United States, Canada, Australia, and Europe. A total of 362 patients underwent ran-

domization and were included in the primary efficacy and safety analyses. Of the total, 68.8% were male, the median age was 2.5 years (interquartile range, 1.7 to 3.2), and 63.3% were White. A total of 244 patients were assigned to receive the intervention and 118 patients to receive placebo (Fig. 1) and were assessed according to their group assignment. There were 67 patients in the subgroup with an eliciting-dose level of 10 mg or less and 295 patients in the subgroup with an eliciting-dose level of more than 10 mg. At baseline, the demographic characteristics of the patients in the two groups were balanced (Table 1).

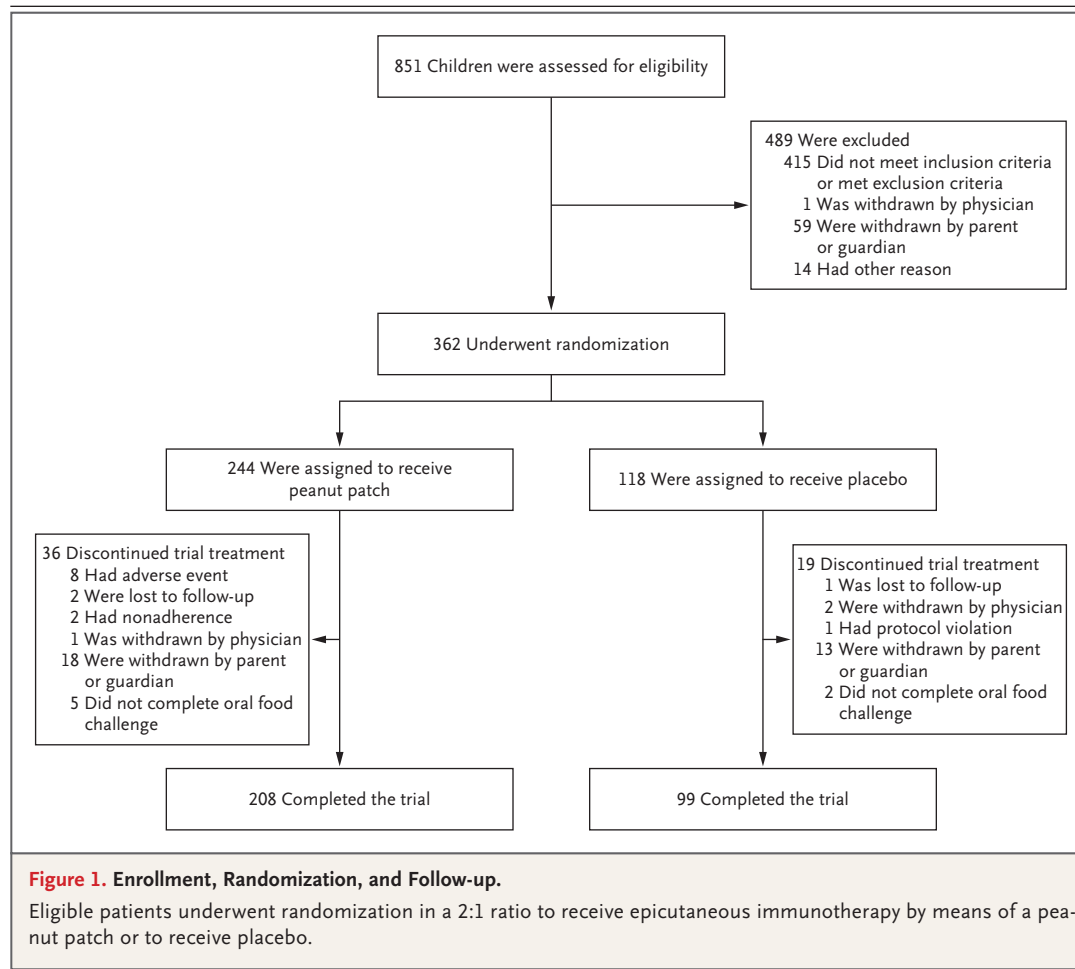
The median overall exposure to the patches was 376 days (interquartile range, 368 to 419). After the initial prespecified period of increasing duration of wear, the median average daily duration was 22.2 hours (interquartile range, 19.4 to 23.4) in the intervention group and 23.7 hours (interquartile range, 22.9 to 24.0) in the placebo group. Treatment adherence was high and similar in the two groups, with a mean ($\pm$ SD) adherence of $97.0\pm 6.9\%$; 84.8% of patients (208 in the intervention group and 99 in the placebo group) completed the assigned intervention or placebo use.

PRIMARY END POINT

At month 12, a significantly larger percentage of patients in the intervention group than in the placebo group met the responder end point (67.0% vs. 33.5%), for a difference of 33.4 percentage points (95% confidence interval [CI], 22.4 to 44.5; $P<0.001$) (Fig. 2A). In a post hoc analysis, a treatment effect was suggested across all eliciting doses at baseline that were greater than 1 mg (Fig. S3). Results from all the prespecified primary end point sensitivity analyses were also consistent with the primary analysis (Fig. 2B), including those involving patients with treatment and assessment peanut challenges outside the month 12Sp window (primarily attributable to study-site access limitations related to coronavirus 2019). The results of all prespecified subgroup analyses of the primary end point are shown in Figure S4.

SECONDARY AND EXPLORATORY END POINTS

Two key secondary end points were assessed hierarchically. First, patients in the intervention



group had a median change in cumulative reactive dose from baseline to month 12 of 1300 mg (interquartile range, 140 to 3000) as compared with a median change of 0 mg (interquartile range, 0 to 1000) for patients who received placebo. As calculated with the use of an analysis of covariance (ANCOVA) model, the geometric least-squares mean ratio (the mean change in cumulative reactive dose in the intervention group as compared with the placebo group) was 3.13 ($P < 0.001$).

Second, patients in the intervention group had a median change in eliciting dose from baseline to month 12 of 900 mg (interquartile range, 90 to 1700) as compared with a change of 0 mg (interquartile range, 0 to 700) among patients who received placebo. As calculated with the use of an ANCOVA model, the geometric least-squares mean ratio was 2.96 ($P < 0.001$).

In addition, 64.2% of patients who received the peanut patch had an eliciting dose of at least 1000 mg regardless of their baseline eliciting-dose subgroup, as compared with 29.6% of the patients in the placebo group (difference, 34.7 percentage points; 95% CI, 23.6 to 45.7). A cumulative reactive dose of at least 3444 mg at month 12 was observed in 37.0% of the patients in the intervention group, as compared with 10.0% of patients in the placebo group (difference, 27.0 percentage points; 95% CI, 17.9 to 36.1). At the baseline peanut challenge, the proportions of mild, moderate, and severe objective signs and symptoms in the intervention and placebo groups were balanced. At month 12, the distribution of maximum symptom severity was shifted to less severe symptoms in the intervention group, coincident with an increased eliciting dose and more patients who met the re-

Table 1. Characteristics of the Patients at Baseline.*

Variable	Peanut Patch (N=244)	Placebo (N=118)
Median age (IQR) — yr	2.5 (1.8–3.2)	2.4 (1.7–3.1)
Sex — no. (%)		
Male	165 (67.6)	84 (71.2)
Female	79 (32.4)	34 (28.8)
Race or ethnic group — no. (%)†		
White	159 (65.2)	70 (59.3)
Asian	41 (16.8)	24 (20.3)
Black	1 (0.4)	1 (0.8)
Native Hawaiian or other Pacific Islander	2 (0.8)	0
Other	33 (13.5)	17 (14.4)
Missing	8 (3.3)	6 (5.1)
Peanut-specific IgE — kUA/liter		
Median (IQR)	13.4 (4.0–65.9)	14.8 (4.9–52.1)
Range	0.8–971.0	0.7–1031.0
Peanut-specific IgG4 — mg/liter		
Median (IQR)	0.4 (0.1–1.3)	0.4 (0.1–1.0)
Range	0.1–76.7	0.1–16.3
Eliciting dose of peanut protein — mg		
Median (IQR)	100 (30–300)	100 (30–300)
Range	1–300	1–300
At baseline — no. (%)		
1 mg	7 (2.9)	1 (0.8)
3 mg	17 (7.0)	3 (2.5)
10 mg	27 (11.1)	12 (10.2)
30 mg	27 (11.1)	17 (14.4)
100 mg	72 (29.5)	37 (31.4)
300 mg	94 (38.5)	48 (40.7)
Medical history — no. (%)		
Asthma	39 (16.0)	27 (22.9)
Eczema or atopic dermatitis	194 (79.5)	96 (81.4)
Allergic rhinitis	49 (20.1)	23 (19.5)
Food allergy other than peanut	161 (66.0)	81 (68.6)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range, and kUA allergen-specific unit.

† Race or ethnic group was reported by the patients' families or caregivers.

sponder end point in the active group than in the placebo group (Fig. 3 and Fig. S5).

The peanut-specific IgE level decreased from baseline to month 12 in the patients who received the intervention and increased in the pa-

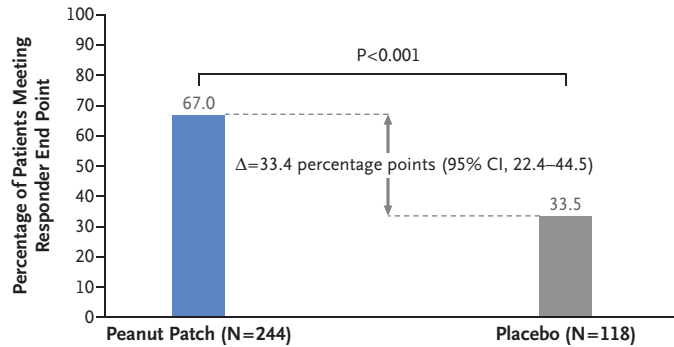
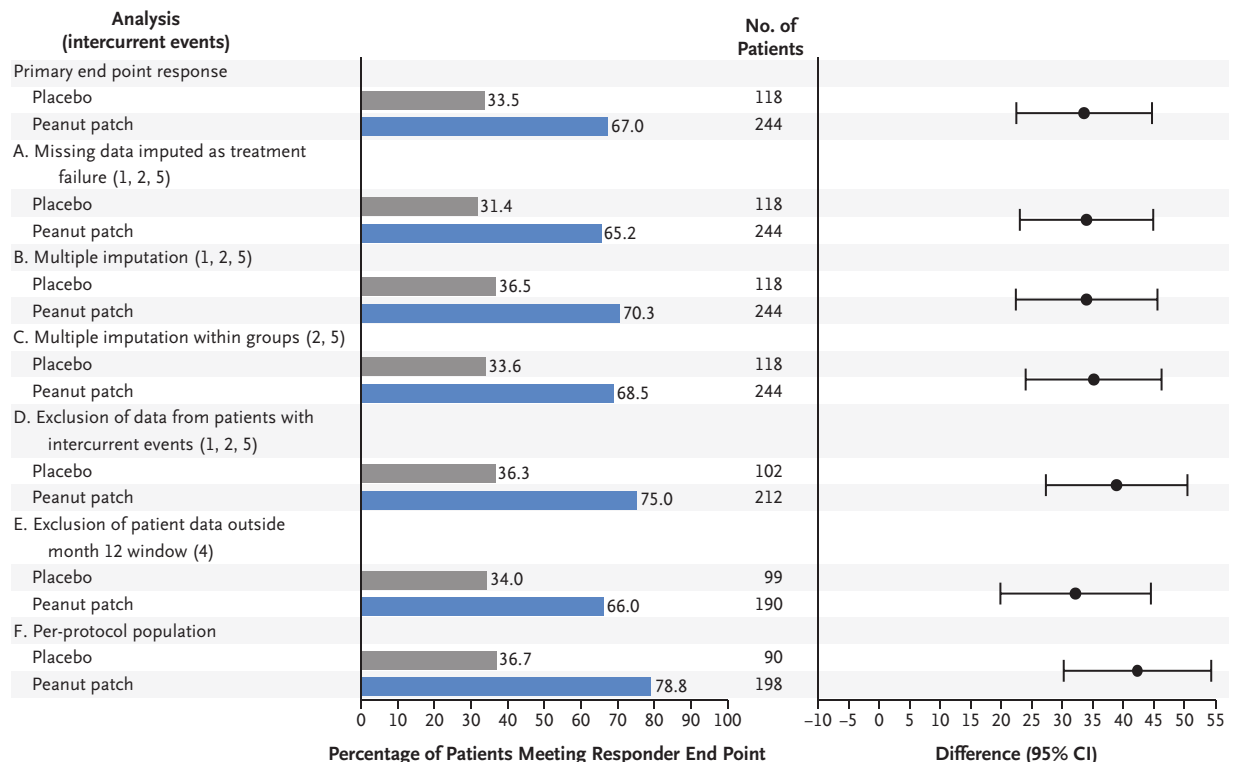
tients who received placebo. In contrast, the peanut-specific IgG4 level increased from baseline to month 12 in the patients who received the intervention, with little change in peanut-specific IgG4 levels in the patients who received placebo (Fig. S6).

SAFETY ASSESSMENTS

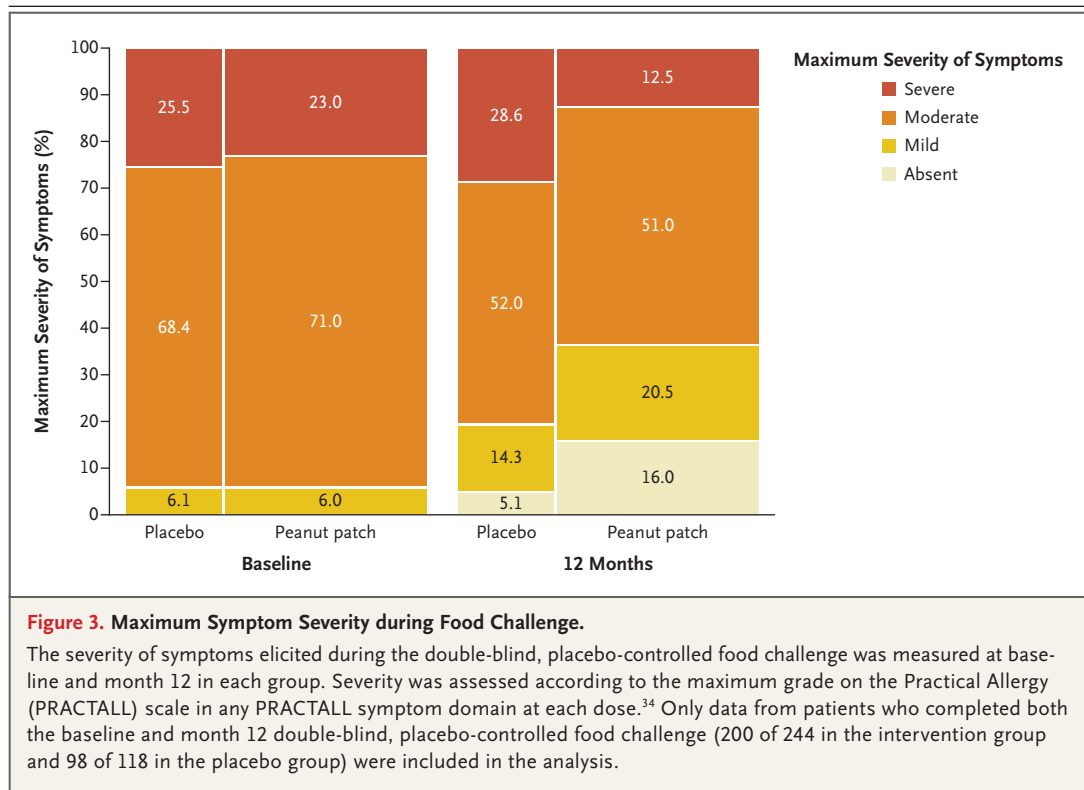
Adverse events that occurred during the treatment period were observed in 100% of the patients in the intervention group and 99.2% of those in the placebo group (Table 2 and Table S4). The most common adverse events were application-site reactions, including erythema (intervention group, 98.0%; placebo group, 90.7%), pruritus (94.7% and 61.0%, respectively), and site swelling (72.5% and 39.0%, respectively). As determined by the investigators, skin reactions were more frequent at the beginning of the receipt of intervention or placebo (months 0–3) but subsequently decreased in frequency and were mostly grade 1 (erythema, or erythema and infiltration) or 2 (erythema and few papules); one patient in the intervention group (0.4%) had a local grade 4 adverse event of special interest (erythema and vesicles) at the month 3 visit. Local adverse events that occurred during the treatment period and lasted more than 90 days occurred in 81.6% of the patients in the intervention group and in 55.1% of patients in the placebo group. Topical corticosteroid agents for the treatment of local application-site reactions were used at least once during the treatment period in 95.9% of patients in the intervention group and 63.6% of those in the placebo group (Table 2 and Table S5).

Serious adverse events (excluding those that occurred during food challenges) were reported in 21 patients in the intervention group (8.6%) and in 3 in the placebo group (2.5%) (Table S6). One patient in the intervention group (0.4%) had a serious adverse event (periorbital edema) that investigators deemed to have been related to treatment.

Anaphylaxis was reported in 7.8% of patients in the intervention group and 3.4% of those in the placebo group. Site investigators considered 26 anaphylactic reactions (occurring outside food challenges) that occurred in 20 patients (17 in the intervention group [7%] and 3 in the placebo group [2.5%]) to have been systemic adverse events of special interest, irrespective of

A Primary Analysis**B Sensitivity Analyses****Figure 2. Primary and Sensitivity Analyses of the Primary End Point.**

The primary measure of treatment effect was an assessment of the percentages of patients who met the responder end point after 12 months of epicutaneous immunotherapy treatment or placebo (Panel A). A patient was defined as meeting the criterion for a response if the patient's baseline eliciting dose was more than 10 mg of peanut protein and the month 12 eliciting dose was at least 1000 mg or the initial eliciting dose was 10 mg or less of peanut protein and the month 12 eliciting dose was at least 300 mg. Prespecified sensitivity analyses of the primary efficacy analysis (Panel B) were defined as follows: missing data imputed as treatment failure for intercurrent events 1, 2, and 5 (Analysis A); a multiple imputation method was used for intercurrent events 1, 2, and 5 (Analysis B) and for intercurrent events 2 and 5 (Analysis C); data excluded for patients with intercurrent event 1, 2, or 5 (Analysis D); data excluded for patients whose double-blind, placebo-controlled food challenge fell outside the month 12 window (Analysis E); and analysis of data from the per-protocol population (Analysis F). Intercurrent events (events that occurred after the application of treatment or placebo and either precluded observation of the variable or affected the interpretation of it) were the following: 1, trial discontinuation before month 12; 2, the patient refused the food challenge entirely at month 12; 3, the patient started the food challenge at month 12 but did not complete it; 4, the patient completed the food challenge outside the month 12 window owing to closed center or postponed visit; and 5, the patient completed the trial but did not complete the month 12 food challenge owing to closed center or postponed visit.



the assessed causal relationship. Summaries of these anaphylactic reactions, some of which included allergic reactions to nonpeanut food allergens, are shown in Table S7A. Four anaphylactic reactions (1.6%), all of which occurred in patients in the intervention group, were deemed by investigators to have been related to treatment; three of the reactions were treated with a single dose of epinephrine and one with no epinephrine, and all were of mild or moderate severity. In two patients (both 3 years of age), reactions occurred on the first day of patch application; one of the two patients received epinephrine and discontinued trial participation. Both had 100-mg eliciting doses and peanut-specific IgE levels that were above the trial population median (Table S7B). No anaphylactic reactions occurred during sleep.

Accidental peanut consumption occurred in 24 patients in the intervention group (9.8%) and 15 patients in the placebo group (12.7%). Occurrences of allergic reactions and anaphylaxis due to accidental peanut consumption (according to investigator reports) in the intervention group (13 allergic reactions [5.3%] and 3 anaphylaxis

events [1.2%]) were less frequent than in the placebo group (12 [10.2%] and 3 [2.5%], respectively).

A total of 14 adverse events that occurred during the trial led to permanent trial discontinuation by eight patients in the intervention group (3.3%); no patients in the placebo group discontinued trial participation due to adverse events. In seven patients, the adverse events that led to discontinuation were deemed to be possibly related or related to the intervention, including local application-site reactions (in four patients), eczema (in one), anaphylaxis (in one), and abnormal behavior or application-site reaction or eczema (in one).

DISCUSSION

In this phase 3 trial, treatment with a peanut patch was superior to placebo in desensitizing children 1 to 3 years of age with peanut allergy, with consistent efficacy findings across numerous subgroup and sensitivity analyses. Anaphylaxis occurred in 19 children in the intervention group and 4 in the placebo group and was

Table 2. Adverse Events.*

Event	Peanut Patch (N=244)	Placebo (N=118)
	<i>number (percent)</i>	
Occurred during trial		
Any	244 (100)	117 (99.2)
Associated with assigned intervention or placebo	244 (100)	112 (94.9)
Serious		
Any	21 (8.6)	3 (2.5)
Associated with assigned intervention or placebo	1 (0.4)	0
Severe		
Any	63 (25.8)	12 (10.2)
Associated with assigned intervention or placebo	57 (23.4)	11 (9.3)
Moderate		
Any	225 (92.2)	91 (77.1)
Associated with assigned intervention or placebo	208 (85.2)	59 (50.0)
Mild		
Any	242 (99.2)	117 (99.2)
Associated with assigned intervention or placebo	238 (97.5)	110 (93.2)
Any local adverse event of special interest†	48 (19.7)	12 (10.2)
Any systemic adverse event of special interest†	22 (9.0)	5 (4.2)
System organ class‡		
Administration-site condition	243 (99.6)	111 (94.1)
General disorder	93 (38.1)	52 (44.1)
Skin and subcutaneous disorder	163 (66.8)	82 (69.5)
Immune system disorder	86 (35.2)	25 (21.2)
Anaphylactic reaction		
Any	19 (7.8)	4 (3.4)
Associated with assigned intervention or placebo	4 (1.6)	0
Nonanaphylactic hypersensitivity reaction		
Any	24 (9.8)	11 (9.3)
Associated with assigned intervention or placebo	3 (1.2)	0
Eye disorder	26 (10.7)	14 (11.9)
Infections and infestation	203 (83.2)	94 (79.7)
Gastrointestinal disorder	101 (41.4)	47 (39.8)
Respiratory, thoracic, and mediastinal disorder	123 (50.4)	58 (49.2)
Injury, poisoning, and procedural complication	63 (25.8)	33 (28.0)
Led to temporary discontinuation of assigned intervention or placebo	63 (25.8)	16 (13.6)
Led to permanent discontinuation of assigned intervention or placebo	8 (3.3)	0
Led to epinephrine intake	25 (10.2)	8 (6.8)
Led to systemic or inhaled corticosteroid use	69 (28.3)	35 (29.7)
Led to topical corticosteroid use	234 (95.9)	75 (63.6)

* Adverse events that occurred with intervention or placebo were graded as mild, moderate, severe, or serious according to the Common Terminology Criteria for Adverse Events, version 4.03.

† Local adverse events of special interest were defined as reactions at patch sites potentially leading to skin barrier disruption, and systemic adverse events of special interest were defined as anaphylaxis or systemic hypersensitivity reactions leading to receipt of epinephrine regardless of the causal relationship to intervention or placebo.

‡ System organ classes are listed by the preferred term according to the *Medical Dictionary for Regulatory Activities*, version 20.1. Only adverse events that were reported in at least 5% of the patients in either group are listed.

judged by investigators to have been related to treatment in 4 patients in the intervention group, of whom 1 discontinued treatment and 3 resumed treatment without further anaphylactic episodes. The cause of anaphylaxis in the 4 patients in the placebo group was not deemed to have been related to the receipt of placebo.

This trial showed peanut desensitization with the use of nonoral immunotherapy. A previously published phase 3 trial that involved children between the ages of 4 and 11 years showed that epicutaneous immunotherapy with the peanut patch was associated with a low occurrence of anaphylaxis.³⁰⁻³² Consistent with previous studies involving the use of the peanut patch, adverse events that occurred during the EPITOPE trial were reported in most patients but were primarily mild-to-moderate local skin reactions that decreased in frequency through the duration of the trial. Although severe local application-site skin reactions occurred in more patients in the intervention group than in the placebo group, these reactions infrequently led to trial discontinuation, and they improved over time.

Few studies have been published on the use of peanut-allergy treatments in toddlers and young children. Among these studies are one that was blinded and placebo-controlled and another that was blinded.^{23,24} A recently published multicenter, double-blind, placebo-controlled, peanut-flour oral immunotherapy trial that involved children between the ages of 1 and 4 years showed a significant treatment effect, with treatment-related epinephrine use of 22% and eosinophilic esophagitis in 3% of participants.²³ Similar to reports in older children, adverse events in that oral immunotherapy trial were primarily oral, gastrointestinal, lower respiratory, and systemic in nature.³⁷⁻³⁹

Although the EPITOPE trial had a high number of patients in the placebo group who met the responder end point, this trial was conducted in a population of children who were at an age at which natural resolution is expected to be at its highest, and the findings are consistent with recent Australian population-level data showing that 29% of children outgrow peanut allergy by 6 years of age.¹² In addition, the patients in the placebo group who met the responder end point included those who had outgrown their allergy as well as those who had increased their response threshold but remained allergic to higher

peanut doses, as suggested by the 10% of patients in the placebo group who reached a cumulative reactive dose of at least 3444 mg at the month 12 challenge.

Our trial has several limitations. First, patients with a history of severe peanut anaphylaxis (e.g., intubation and ventilation or inotropic support) were excluded, a safety measure similar to that incorporated in other food-allergy treatment trials that involved food challenges. This exclusion could limit generalizability, although a real-world study of peanut-patch use in children between the ages of 4 and 11 years, which included patients with severe anaphylaxis, noted no major safety concerns.³² Second, consistent with other food-allergy treatment studies, a lack of racial diversity among patients may limit generalizability. Although more male patients than female patients underwent randomization in our trial, this distribution is consistent with that in other trials and reflects atopy rates in childhood.¹⁰ A summary of the representativeness of the patient sample is shown in Table S8. Third, the appropriate duration of peanut-patch use for maximal treatment response is unknown, and sustained effects after treatment cessation were not assessed. Data from the open-label extension in the pivotal trial involving children between the ages of 4 and 11 years showed desensitization effects are enhanced with longer treatment.³¹ A 24-month, open-label extension of the EPITOPE trial to determine continued treatment response is ongoing (ClinicalTrials.gov number, NCT03859700) and has enrolled 88% of all eligible EPITOPE trial participants.

In this phase 3 trial involving children between the ages of 1 and 3 years with peanut allergy, 12 months of daily epicutaneous immunotherapy with a patch containing 250 μ g of peanut protein (approximately 1/1000 of one peanut) resulted in a higher frequency of desensitization than the use of placebo, a level that was sufficient to lessen the likelihood of allergic reactions upon accidental exposure.

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APPENDIX

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