Long-term, open-label extension study of the efficacy and safety of epicutaneous immunotherapy for peanut allergy in children: PEOPLE 3-year results

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Background: The PEPITES (Peanut EPIT Efficacy and Safety) trial, a 12-month randomized controlled study of children with peanut allergy and 4 to 11 years old, previously reported the safety and efficacy of epicutaneous immunotherapy (EPIT) for peanut allergy (250 μg, daily epicutaneous peanut protein; DBV712 250 μg).

Objective: We sought to assess interim safety and efficacy of an additional 2 years of EPIT from the ongoing (5-year treatment) PEOPLE (PEPITES Open-Label Extension) study.

Methods: Subjects who completed PEPITES were offered enrollment in PEOPLE. Following an additional 2 years of daily DBV712 250 μg, subjects who had received DBV712 250 μg in PEPITES underwent month-36 double-blind, placebo-controlled food challenge with an optional month-38 sustained unresponsiveness assessment.

Results: Of 213 eligible subjects who had received DBV712 250 μg in PEPITES, 198 (93%) entered PEOPLE, of whom 141 (71%) had assessable double-blind, placebo-controlled food challenge at month 36. At month 36, 51.8% of subjects (73 of 141) reached an eliciting dose of ≥1000 mg, compared with 40.4% (57 of 141) at month 12; 75.9% (107 of 141) demonstrated increased eliciting dose compared with baseline;

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and 13.5% (19 of 141) tolerated the full double-blind, placebo-controlled food challenge of 5444 mg. Median cumulative reactive dose increased from 144 to 944 mg. Eighteen subjects underwent an optional sustained unresponsiveness assessment; 14 of those (77.8%) maintained an eliciting dose of ≥1000 mg at month 38. Local patch-site skin reactions were common but decreased over time. There was no treatment-related epinephrine use in years 2 or 3. Compliance was high (96.9%), and withdrawals due to treatment-related adverse events were low (1%).

Conclusions: These results demonstrate that daily EPIT treatment for peanut allergy beyond 1 year leads to continued response from a well-tolerated, simple-to-use regimen. (J Allergy Clin Immunol 2020;146:863-74.)

Key words: *Peanut allergy, food allergy, immunotherapy, desensitization, eliciting dose, epicutaneous immunotherapy, EPIT, sustained unresponsiveness*

Abbreviations used

AE:	Adverse event
CRD:	Cumulative reactive dose
DBPCFC:	Double-blind placebo-controlled food challenge
ED:	Eliciting dose
EPIT:	Epicutaneous immunotherapy
HRQL:	Health-related quality of life
IQR:	Interquartile range
mLOCF:	Modified last observation carried forward
PP:	Per protocol
sIgE:	Specific IgE
SU:	Sustained unresponsiveness
TEAE:	Treatment-emergent adverse event

Peanut allergy affects up to 2.2% of children in the United States, equating to approximately 1.6 million children.[1] Among children with a food allergy, those with peanut allergy report the highest rates of anaphylaxis and severe reactions.[1] Moreover, compared with other food allergies, peanut allergy results in more emergency department visits for anaphylaxis,[2,3] with 1 in

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Andrew Bird reported receiving grants from DBV Technologies related to this submission and personal fees from DBV Technologies outside of the submitted work; the following potential conflicts of interest are outside of the submitted work: grants, personal fees, and nonfinancial support from Aimmune Therapeutics, personal fees from Food Allergy Research and Education, personal fees and nonfinancial support from American College of Allergy, Asthma and Immunology, grants from Nestle Health Sciences, personal fees from Nutricia North America, personal fees from Pharm-Olam International LTD, personal fees and other from Pfizer Pharmaceuticals, personal fees from Prota Therapeutics, personal fees from Allergy Therapeutics, Ltd, grants from NIH-NIAID, grants from Novartis, personal fees from AllerGenis, personal fees from Abbott Nutrition International. Terri Brown-Whitehorn reported receiving grants and personal fees from DBV Technologies. Edmond S. Chan has received research support from DBV Technologies, has been a member of advisory boards for Pfizer, Pediapharm, Leo Pharma, Kaleo, DBV, is a member of the health care advisory board for Food Allergy Canada, was an expert panel and coordinating committee member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention, and is co-lead of the Canadian Society of Allergy and Clinical Immunity oral immunotherapy guidelines. Sharon Chinthrajah received grants from NIAID, Consortium of Food Allergy Research, Aimmune, DBV Technologies, Astellas, AnaptysBio, Novartis, and Regeneron and personal fees from Novartis, Genentech, Allergenis, Before Brands, and Alladapt. Hey Jin Chong reported receiving consultancy fees from Horizon. Carla M. Davis reported research contract funding from DBV Technologies, Regeneron Pharmaceuticals, and Aimmune Therapeutics, and she is a consultant for Moonlight Therapeutics. David M. 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Matthew Greenhawt reported grant support (5K08HS024599-02) from the Agency for Healthcare Research and Quality; serving as an expert panel and coordinating committee member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; has served as a consultant for the Canadian Transportation Agency, Thermo Fisher, Intrommune, and Aimmune Therapeutics; serving as a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, Sanofi/Genzyme, Genentech, GlaxoSmithKline, Nutricia, Kaléo Pharmaceutical, Nestlé, Aquestive Therapeutics, Allergy Therapeutics, AllerGenis, Aravax, Prota Therapeutics, and Monsanto; serving as a member of the scientific advisory council for the National Peanut Board; received honorarium for lectures from Thermo Fisher, Aimmune Therapeutics, DBV Technologies, BEFORE Brands, multiple state allergy societies, the American College of Allergy, Asthma and Immunology, the European Academy of Allergy and Clinical Immunology; serving as an associate editor for the *Annals of Allergy, Asthma & Immunology*; and serving as a member of the Joint Taskforce on Allergy Practice Parameters. Jonathan O'B. Hourihane reported receiving research funding and consultancy fees from Aimmune Corporation, and research funding from Johnson & Johnson. Stacie M. Jones reported serving as a member of the Research Advisory Board for Food Allergy Research and Education (FARE) and Scientific Advisory Board for Aimmune Therapeutics and receiving consultation fees for US Food and Drug Advisory Committee for Aimmune Therapeutics; grant funding from NIAID Consortium for Food Allergy Research and Immune Tolerance Network; and clinical trials funding from Aimmune Therapeutics, DBV Technologies, Genentech, Regeneron, Sanofi, and Astellas, Inc. Edwin H. 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Vera Mahler became an employee of the Paul-Ehrlich-Institut (Federal Institute for Vaccines and Biomedicines), Langen, Germany, after participation as investigator in the trial; measures are in place for unbiased marketing authorization procedures. Anna Nowak-Wegrzyn reported receiving research grants from DBV Technologies, Astellas Pharma, NIH/NIAID Immune Tolerance Network, and Nutricia Danone; serving as a member of the Data Monitoring Committee for the clinical trials of dupilumab for peanut allergy and has served on the advisory board for Genentech regarding omalizumab for food allergy as mono or combined

4 children with peanut allergy requiring an emergency department visit each year for management of allergic reactions.[1]

Avoidance of peanut is inherently difficult because of its widespread consumption, and more active treatment options are needed and desired by patients with peanut allergy, their families, and allergists.[4-6] Moreover, it is estimated that 50% of children with peanut allergy will react to 30 to 100 mg of peanut protein and most to <1 peanut (approximately 300 mg of peanut protein).[7,8] Therefore, despite strict avoidance and readiness to manage allergic reactions, these reactions continue to occur with an estimated annual incidence of 12% to 14% in individuals with peanut allergy, affecting ~40% of patients within 3 years of their diagnosis.[9,10]

Health-related quality of life (HRQL) is significantly impaired in children with peanut allergy and their families, in part because of the stress and anxiety stemming from fear of allergic reactions due to accidental exposures.[11-14] Patients and caregivers have expressed a desire for treatment options that would provide a degree of desensitization to peanut that would reduce the risk of reactions following accidental exposure and improve quality of life, with minimal risk from the treatment itself.[4]

Epicutaneous immunotherapy (EPIT) is among several immunotherapies currently under investigation in clinical trial programs for the potential treatment of peanut allergy. EPIT for peanut allergy aims to utilize the unique immune properties of the skin to induce desensitization using an epicutaneous patch.[15-17] Following several phase 2 clinical trials,[18,19] including the VIPES (Viaskin Peanut's Efficacy and Safety) study that included children 6 to 11 years old and an open-label phase (Open-Label Follow-up Study of VIPES [OLFUS-VIPES]) of up to 36 months of treatment, the efficacy and safety of an epicutaneous peanut patch, Viaskin Peanut 250 μg peanut protein (DBV712 250 μg), was assessed in PEPITES (Peanut EPIT Efficacy and Safety [NCT02636699]), a phase 3, randomized, double-blind, placebo-controlled study of children with peanut allergy 4 to 11 years old.[20] In PEPITES, DBV712 250 μg 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%) treatment groups was observed. Subjects who successfully completed the 12-month PEPITES study were offered the opportunity to enroll in the PEOPLE (PEPITES Open-Label Extension) study (NCT03013517), the largest long-term study of EPIT for peanut allergy, which was initially designed to assess a total of 3 years of treatment with DBV712 250 μg and has now been extended to a total duration of therapy across PEPITES and PEOPLE of 5 years, with years 4 and 5 currently in progress.

The objective of the current report is to present data on subjects from the PEOPLE study, initially randomized to receive DBV712 250 μg, who have now completed 3 years of active treatment, while years 4 and 5 of the open-label extension study continue.

METHODS

Study design

PEOPLE is an open-label follow-on of the PEPITES study to evaluate the long-term efficacy and safety of DBV712 250 μg following up to 5 years of active treatment. The study is being conducted in accordance with the International Council for Harmonisation Good Clinical Practice Guidelines,[21] the Declaration of Helsinki, and all applicable regulatory requirements. Subjects entering PEOPLE received 24 months of open-label treatment if they were in the active treatment arm of PEPITES and will receive 36 months of open-label treatment if they were in the placebo arm of PEPITES. Subjects in both treatment arms will then have the option of a further 24 months of treatment, to a potential total active treatment time over PEPITES and PEOPLE of 5 years (Fig 1). The study protocol is available in this article's Online Repository (available at www.jacionline.org). Subjects and their families received no compensation for study participation, aside from reimbursement for travel and parking expenses to attend study visits, where required by regional governance bodies.

Standardized, double-blind, placebo-controlled food challenges (DBPCFCs) were conducted as previously described during the PEPITES study[20] following the PRACTALL (Practical Allergy) criteria after 1 and 3 years of active treatment (month-12 and -36 DBPCFCs, respectively).[22] The eliciting dose (ED) was defined as the dose ingested immediately prior to emergence of objective signs or symptoms meeting prespecified stopping criteria requiring treatment (see Table E1 in this article's Online Repository at www.jacionline.org). Subjective symptoms (eg, abdominal pain or oropharyngeal itching) were assessed and recorded, but alone they were insufficient to stop the challenge. Reaching an ED in this context means the dose during the DBPCFC that elicited the prespecified objective symptoms. The cumulative reactive dose (CRD) was defined as the sum of all doses (including partial doses) up to and including the ED, which led to the emergence of the prespecified symptoms. The ED and CRD were the DBPCFC parameters assessed consistently at every point of PEPITES and PEOPLE, and these parameters are consistent with the 2016 US Food and Drug Administration Allergenic

therapy; authored topics for UpToDate; and serving as the deputy editor for the *Annals of Allergy, Asthma and Immunology*. Daniel Petroni reported receiving grants from DBV Technologies during the conduct of the study and grants from Aimmune, HAL Allergy, and Astellas outside the submitted work. Susan L. Prescott reported receiving research grants from DBV Technologies related to this submission; outside the submitted work she received speaker fees from Danone Nutricia and Swisse and consultancy fees from Bayer and Sanofi. Jacqueline A. Pongracic reported receiving research funding from DBV Technologies and Aimmune Therapeutics and honorarium from Medscape, and participating on the independent data monitoring committee for Regeneron and clinical advisory boards for FARE. Lynda C. Schneider reported serving as a researcher or consultant for DBV Technologies, Regeneron Pharmaceuticals, Pfizer, AbbVie, and Aimmune and receiving funding for an investigator-initiated study from Genentech. Wayne G. Shreffler reported receiving personal fees and research funding from DBV Technologies during the conduct of the study and grants from Sanofi, the NIH, and FARE and personal fees from Aimmune Therapeutics for serving on the scientific advisory board. Gordon Sussman reported serving as an advisory board member for Novartis, Aralez, CSL Behring, and Sanofi; receiving grant or honorarium from Novartis, Aralez, Pediapharm, GSK, Genentech, DBV Technologies, Aimmune, CSL Behring, AstraZeneca, Stallergenes, Merck, Pfizer, Dyax, Biocryst, Greencross, Kendrion, Shire, Leopharma, Regeneron, and mdBriefCase; and participating in clinical trials (principal investigator) for Novartis, GSK, Genentech, DBV Technologies, Aimmune, CSL Behring, AstraZeneca, Stallergenes, Merck, Pfizer, Dyax, Biocryst, Greencross, Kendrion, Leo Pharma, Regeneron, Sanofi, Blueprint, ALK-Abelló, Amgen, and Cliantha. Robert Wood reported receiving grants from the NIH, DBV Technologies, Aimmune Therapeutics, Astellas, HAL Allergy, Sanofi, and Regeneron. William H. Yang reported receiving speaker fees from CSL Behring, Takeda (Shire), Novartis, Merck, and AstraZeneca; being a member of the advisory board for CSL Behring, Takeda (Shire), Novartis, Sanofi, Merck, and AstraZeneca; receiving research grants from CSL Behring, Takeda (Shire), Pharming, BioCryst, Novartis, Regeneron, Glenmark, AnaptysBio, Dermira, Genentec, Galderma, Pfizer, and Roche. The rest of the authors declare that they have no relevant conflicts of interest.

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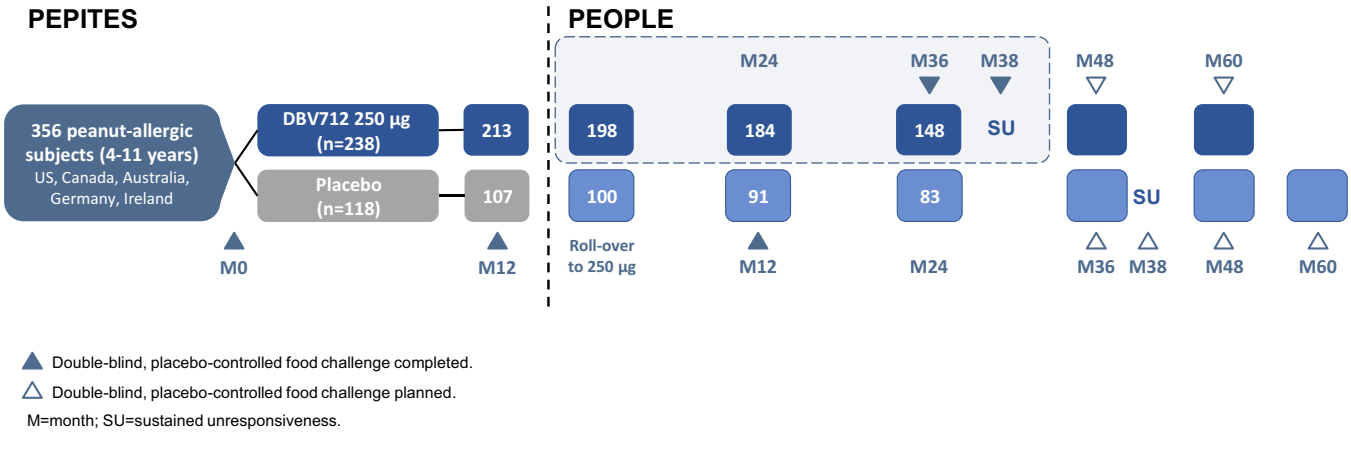

FIG 1. Study design. Eligible subjects in PEPITES were enrolled in the long-term follow-on study, PEOPLE, for up to 5 years of treatment with DBV712 250 µg. Subjects receiving placebo during PEPITES received treatment with DBV712 250 µg in PEOPLE. The highlighted area represents the scope of the current report. *M*, Month.

Products Advisory Committee briefing statement on determining response in food immunotherapy clinical trials.[23] Subjects were challenged to a maximum cumulative dose of 3444 mg of peanut protein at month 12 in PEPITES and 5444 mg at month 36 of active treatment in PEOPLE. When the total final dose was reached without eliciting symptoms meeting the prespecified stopping criteria, as described above, the subject was considered to have tolerated that dose. Subjects achieving an ED of ≥1000 mg during the month-36 DBPCFC were eligible to undergo an optional sustained unresponsiveness (SU) assessment, with an additional DBPCFC conducted after a 2-month treatment discontinuation (during which time strict peanut avoidance was continued).

Subjects and eligibility

Subjects 4 to 11 years old were initially enrolled in PEPITES according to the eligibility criteria as previously described,[20] including being required to react (based on a scoring system requiring sufficient level of objective signs) on DBPCFC to an ED of ≤300 mg peanut protein at baseline. All subjects who completed PEPITES, including the final of the 2 month-12 DBPCFC visits, were offered enrollment in PEOPLE (Fig 1). Visit 1, the start of the open-label treatment period, was conducted on the same day as or within 1 week of the final visit in PEPITES.

The current report is restricted to the outcomes of those subjects who were initially randomized to receive DBV712 250 µg in PEPITES and who have received a further 2 years of DBV712 250 µg therapy in PEOPLE. It does not include those subjects initially randomized to placebo.

Inclusion criteria

All subjects who successfully completed the month-12 DBPCFC in PEPITES were considered eligible to enter the PEOPLE study. Subjects with a past history of anaphylaxis were not excluded; however, those having a history of severe anaphylaxis (hypotension requiring vasopressor support, hypoxia requiring mechanical ventilation, or neurological compromise) to peanut or with an unstable chronic condition, including poorly controlled asthma (per Global Initiative for Asthma Guidelines[24]), were excluded from entry into the PEPITES study due to ethical and safety concerns regarding the performance of multiple DBPCFCs (including potentially after placebo treatment) in these subjects.

Interventions

In PEOPLE, all subjects received an unblinded daily dose of 250 µg peanut protein per patch immediately following enrollment, were required to maintain a peanut-free diet, and continued to have epinephrine auto-injectors available. The PEOPLE study population comprised 2 groups according to the treatment allocation in PEPITES (Fig 1): the DBV712 250 µg group included subjects who received active treatment in both PEPITES and PEOPLE. The placebo + DBV712 250 µg group includes subjects who received the placebo in PEPITES followed by DBV712 250 µg in PEOPLE; this latter group has not yet completed their month-36 DBPCFC and, therefore, are not reported in this publication. Unblinding of PEPITES allocation occurred on October 16, 2017 (see Protocol version 7.0 in this article's Online Repository at www.jacionline.org).

Outcomes

Key outcomes of interest for assessing treatment response in this analysis included the percentage of DBV712 250 µg subjects reaching an ED of ≥1000 mg after 3 years of active treatment, and the difference between this and the percentage of subjects reaching an ED of ≥1000 mg after 1 year of active treatment. Further prespecified end points included ED at each time point; CRD of peanut protein; the percentage of subjects unresponsive to the highest dose of peanut protein (ie, showing no objective symptoms leading to stopping the DBPCFC with a cumulative dose of 5444 mg peanut protein at 3 years); and the percentage of treatment responders defined per the PEPITES primary outcome (subjects with baseline ED of ≤10 mg reaching ≥300 mg or baseline ED between >10 mg and ≤300 mg reaching ED of ≥1000 mg). SU was assessed after the 2-month off-treatment period by the percentage of subjects reaching an ED of ≥1000 mg at the month-38 compared with the month-36 DBPCFC within this subset. Peanut-specific IgE and IgG_4 and peanut skin prick test average wheal diameters were explored longitudinally during the active treatment period. Compliance was defined as the total number of patches applied in the treatment period divided by the number of days in that period.

Adverse event (AE) outcomes included treatment-emergent adverse events (TEAEs) and serious TEAEs. AEs were assessed by investigators, with serious AEs defined according to the International Council for Harmonisation Good Clinical Practice definition. Skin reactions were openly graded by the site investigator from 0 to 4, according to European Academy of Allergy and Clinical Immunology and the Global Allergy and Asthma European Network, where grade 0 is no skin reaction and grade 4 is erythema and vesicles (see Table E2 in this article's Online Repository at www.jacionline.org).[25] Site investigators assessed the causality/relationship between the study drug and AE, including anaphylaxis, according to the causality criteria (related, probable, possible, unlikely, or not related). Anaphylactic reactions were defined as the occurrence of acute hypotension (>20% drop in blood pressure) or associated cardiovascular symptoms or 2 or more concomitant acute allergic symptoms from at least 2 different organ systems.[26] AEs related to a DBPCFC were excluded from the safety analyses.

Statistics

All analyses reported here were conducted exclusively in the DBV712 250 μg group after they completed 3 years of active treatment. The safety set, completer set, and per protocol (PP) set were defined *a priori*. The safety set included all DBV712 250 μg subjects who received at least 1 dose of study drug during PEOPLE. The completer set was defined as all DBV712 250 μg subjects from the safety set having evaluable DBPCFC results at both months 12 and 36. The PP set was defined as those subjects who completed all treatment according to the study protocol without major deviations that could affect the assessment of the treatment effect, which included an evaluable DBPCFC performed as required by the protocol at months 12 and 36 and compliance of ≥80%.

Additional *post hoc* analyses included ED and CRD change from baseline (PEPITES entry) to month 36 according to the following: the overall percentage of treatment responders, as defined per the OLFUS-VIPES primary outcome (subjects reaching an ED of ≥1000 mg and/or ≥10-fold increase from baseline ED);[19,20] the percentage of subjects tolerating (ie, passing the DBPCFC without meeting the prespecified, modified PRACTALL stopping criteria) a cumulative dose of ≥3444 mg peanut protein during a DBPCFC; and the difference between paired month-12 and -36 EDs by Wilcoxon test.

Categorical variables were summarized using number of observations and percentages, and continuous variables were summarized using descriptive statistics. For the main end point, the 95% CI between paired binomial proportions was calculated using the Newcombe method based on Wilson score intervals with continuity correction. Supportive analyses of the main end point were performed using modified baseline observation carried forward and modified last observation carried forward (mLOCF) imputations for subjects who had at least started the peanut challenge at the month-36 DBPCFC and for the whole safety set, where month-36 ED was missing. If an ED at the month-12 and/or -36 DBPCFC was not reached, the modified baseline observation carried forward ED was considered as the higher value of the last dose given at the DBPCFC in question and the ED value at baseline. The mLOCF ED was considered as the higher value of the last dose given at the DBPCFC in question and the ED value at the previous DBPCFC.

RESULTS

Subject characteristics

Of the 213 subjects who were randomized in the active treatment arm of PEPITES and completed the 12-month trial, 198 subjects (93.0%) opted to enter PEOPLE (safety set) (Fig 1). A total of 50 subjects did not continue the study through to month 36 or had incomplete assessments at month 36 and were not part of the "completer set" (n = 148).

A total of 141 subjects (71.2%) who entered PEOPLE (n = 198) were considered the PP set, having completed all treatment according to the study protocol including assessable DBPCFC outcomes. Efficacy data were analyzed from these 141 subjects. Of the 148 completers, 7 were excluded from the PP analysis set: 1 subject was excluded for compliance of 62.6%, while 6 had DBPCFC-related protocol deviations, rendering the determination of the DBPCFC result unreliable during either the month-12 or -36 DBPCFCs.

The 50 subjects who did not complete the study to month 36 included 39 subjects who discontinued the study before month 36 and 11 who started the month-36 DBPCFC but did not complete it. Of the 39 subjects who discontinued before month 36, 30 withdrew consent, 4 withdrew due to AEs, and 5 were lost to follow-up, with 27 of these 39 discontinuing between months 30 and 36. Six of 39 subjects (3% of the 198 subjects enrolling in PEOPLE; ie, safety set) withdrew consent because they were tired of applying the patch. A total of 22 subjects (44% of subjects who discontinued the study) withdrew either prior to or during the month-36 assessments because of fear of DBPCFC and/or distaste of food challenge material. Of the remaining 11 of 50 subjects who started the month-36 DBPCFC, 7 subjects withdrew their consent because of fear of DBPCFC and/or distaste of challenge material during assessment, 3 refused to complete the DBPCFC, and 1 DBPCFC was terminated before stopping criteria was reached.

The baseline characteristics of the PEOPLE study populations (including PP, completer, and safety set) and that of the whole PEPITES cohort were comparable across groups and are presented in Table I. The 50 subjects who were not included in the completer set were, in general, similar to the overall population (Table I), but had higher median baseline peanut-specific IgE (sIgE), and 1 dose increment lower median month-12 ED, with large overlap in interquartile range (IQR) with that of the completer set (Table I). This was not true of the 11 subjects who commenced but did not complete the month-36 DBPCFC, where no differences were observed when compared with the completer set, including in baseline or month-12 median ED (see Table E3 in this article's Online Repository at www.jacionline.org).

Overall mean compliance rate in the whole safety set was 98.1 ± 4.1% observed over 3 years of treatment and 96.9 ± 5.45% during the 2 years of treatment in PEOPLE (n =198).

Changes in ED

At month 36, 51.8% of subjects (73 of 141) in the PP set reached an ED of ≥1000 mg, compared with 40.4% (57 of 141) at month 12 (11.3% difference; 95% CI, 2.8 to 19.6) (Fig 2; see Table E4 in this article's Online Repository at www.jacionline.org). Following 3 years of treatment, 75.9% of subjects (107 of 141) demonstrated an increase in ED compared with baseline. Of the subjects who had a baseline ED of ≤100 mg, 67.4% (62 of 92) reached an ED of at least 300 mg. The proportion of subjects who tolerated the 3444-mg dose (the highest possible cumulative dose at month 12) increased between months 12 and 36 from 4.3% (6 of 141) to 18.4% (26 of 141). In addition, at month 36, 13.5% of subjects (19 of 141) were able to tolerate the full DBPCFC of 5444 mg (ie, passed the DBPCFC without meeting the prespecified, modified PRACTALL stopping criteria). Within the completer set, using mLOCF for imputation, 43.9% of subjects (87 of 198) reached an ED of ≥1000 mg at month 36 compared with 35.9% (71 of 198) at month 12, and under all imputations, response was generally in favor of 36 months compared with 12 months of treatment (see Fig E1 in this article's Online Repository at www.jacionline.org).

When the results were analyzed according to the primary outcome criteria used in PEPITES, which considers lower and higher baseline ED strata, 55.3% of subjects (78 of 141) were considered treatment responders based on reaching an ED of ≥300 mg (for subjects with a baseline ED ≤10 mg) or ≥1000 mg (for subjects with a baseline ED >10 mg and ≤300 mg) at month 36 (Fig 3).

When analyzed by mixed-effect model repeated measure over the 3-year treatment period, there was a 5.0-fold (95% CI, 4.0 to 6.3) increase in geometric mean ED in the PP population (n = 141). In subjects with a baseline ED of ≤10 mg (n = 18), there was a 22.5-fold increase in geometric mean ED (95% CI, 10.7 to 47.3). In those with a baseline ED >10 mg (n = 123), the geometric mean ED increased 4.0-fold by month 36 (95% CI, 3.2 to 5.0).

TABLE I. Demographics and subject characteristics by data set

Subject characteristics	PEPITES safety population (n = 238)	PEOPLE safety population (n = 198)	PEOPLE completer population (n = 148)	PEOPLE PP population (n = 141)	PEOPLE noncompleter population (n = 50)
Baseline (PEPITES enrollment)					
Age, median (Q1, Q3), y	7 (6, 9)	7 (5, 9)	7 (5.5, 9)	7 (5, 9)	8 (5, 9)
Sex, no. (%)					
Male	149 (62.6)	124 (62.6)	89 (60.1)	88 (62.4)	35 (70.0)
Female	89 (37.4)	74 (37.4)	59 (39.9)	53 (37.6)	15 (30.0)
Race/ethnic origin, no. (%)					
White	194 (81.5)	159 (80.3)	117 (79.1)	110 (78)	42 (84.0)
Black or African American	1 (0.4)	1 (0.5)	1 (0.7)	1 (0.7)	0
Asian	19 (8)	15 (7.6)	12 (8.1)	12 (8.5)	3 (6.0)
Hispanic	2 (0.8)	2 (1)	1 (0.7)	1 (0.7)	1 (2.0)
Other	22 (9.2)	21 (10.6)	17 (11.5)	17 (12.1)	4 (8.0)
Peanut-sIgE, median (kU_A/L)	77.95	77.15	70.75	69.9	114.5
Q1, Q3 (range)	20, 192 (0.78-1008.38)	19.83, 184 (0.78-978)	16.15, 175 (0.78-978)	15.1, 173 (0.78-978)	47.70; 258.00
Peanut-$sIgG_4$, median (mg/L)	0.69	0.68	0.63	0.64	0.76
Q1, Q3 (range)	0.28, 1.39 (0.07-10.2)	0.28, 1.33 (0.07-10.2)	0.27, 1.32 (0.07-10.2)	0.27, 1.33 (0.07-10.2)	0.32; 1.51
Peanut protein ED, median (mg)	100	100	100	100	100
Q1, Q3 (range)	30, 300 (1-300)	30, 300 (1-300)	30, 300 (1-300)	100, 300 (3-300)	10,300 (1-300)
Peanut protein ED, no. (%)					
1 mg	3 (1.3)	2 (1)	1 (0.7)	0	1 (2.0)
3 mg	10 (4.2)	9 (4.5)	5 (3.4)	4 (2.8)	4 (8.0)
10 mg	28 (11.8)	25 (12.6)	16 (10.8)	14 (9.9)	9 (18.0)
30 mg	24 (10.1)	21 (10.6)	18 (12.2)	17 (12.1)	3 (6.0)
100 mg	97 (40.8)	78 (39.4)	58 (39.2)	57 (40.4)	20 (40.0)
300 mg	76 (31.9)	63 (31.8)	50 (33.8)	49 (34.8)	13 (26.0)
Ongoing medical history at PEPITES baseline, no. (%)					
Asthma	111 (46.6)	95 (48)	68 (45.9)	62 (44)	27 (54.0)
Eczema/atopic dermatitis	101 (42.4)	81 (40.9)	60 (40.5)	56 (39.7)	21 (42.0)
Allergic rhinitis	131 (55)	113 (57.1)	77 (52)	73 (51.8)	36 (72.0)
Allergy other than peanut	198 (83.2)	169 (85.4)	125 (84.5)	119 (84.4)	44 (88.0)
Month 12					
Month 12 peanut protein ED, median (mg)	300	300	300	300	100
Q1, Q3 (range)	100, 1000 (1-2000)	100, 1000 (10-2000)	100, 1000 (30-2000)	100, 1000 (30-2000)	100, 300 (10-2000)

Q, Quartile.

Overall, the response observed between the DBPCFC at months 12 and at 36 was maintained and/or improved in the majority of subjects (Table II). By Wilcoxon test (using paired data), there was a significant difference in ED between months 12 and 36 in both PP and completer sets ($P = .006$ and .032, respectively). At month 36, 49.3% of subjects (73 of 148) in the completer set reached an ED of ≥1000 mg, compared with 41.2% (61 of 148) at month 12 (8.1% difference; 95% CI, −0.05 to 16.5). At month 36, 43.9% of subjects (87 of 198) in the safety set reached an ED of ≥1000 mg, compared with 35.9% (71 of 198) at month 12 using mLOCF imputation (8.1% difference; 95% CI, −2.0 to 14.1).

Of the 11 subjects (7.8%) who reached an ED of ≥1000 mg at month 12 but not at month 36, there were no clear baseline characteristics that could be associated with this trajectory, including age, baseline ED, or peanut-sIgE (see Table E5 in this article's Online Repository at www.jacionline.org); in addition, compliance was >90% in 9 subjects and between 80% and 90% in the remaining 2 subjects over the course of 3 years of treatment. These 11 subjects had less relative decrease in their peanut-sIgE from months 12 to 36, but a similar IgG4 trajectory relative to the remainder of the cohort (Fig 4).

Changes in CRD and immune markers

Mean and median CRD rose over the 3-year treatment period (Fig 5). At month 36, 24.1% of subjects (34 of 141) reached a CRD of 3444 mg compared with 15.6% (22 of 141) at month 12. This trend was similarly observed when analyzed by mixed-effect model repeated measure using log-transformed data (see Fig E2 in this article's Online Repository at www.jacionline.org). Peanut-$sIgG_4$ levels progressively increased throughout the first 18 months of treatment and remained at peak levels for the remainder of the treatment to month 36, whereas peanut-sIgE levels increased initially at the start of the study and then returned to baseline, remaining around or below baseline through month 36 (Fig 4). The median absolute change in skin prick test mean wheal diameter from baseline to month 36 was 3.5 mm (IQR, −5.5, −1); with median values of 11 mm (IQR, 9-14) at

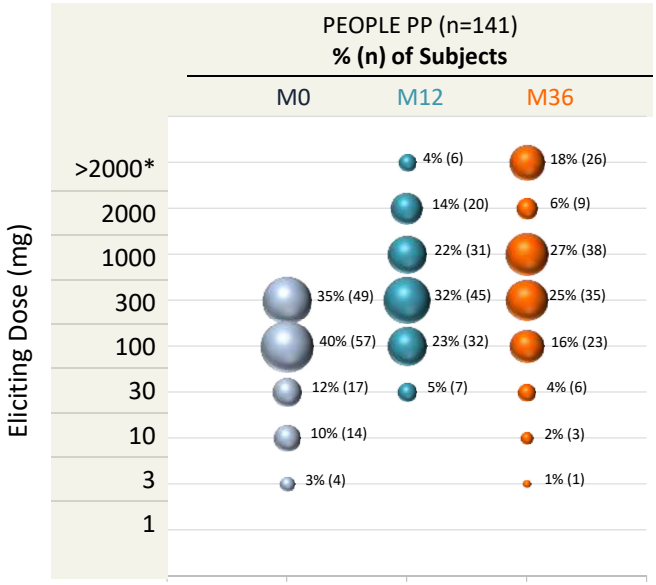

FIG 2. Proportion of subjects from PP data set at each ED (baseline, month 12, and month 36). The percentage of subjects at each ED was determined at baseline (M0), month 12 (M12), and month 36 (M36) in the PP population. For study entry, subjects were required to have an ED at baseline of ≤300 mg of peanut protein.

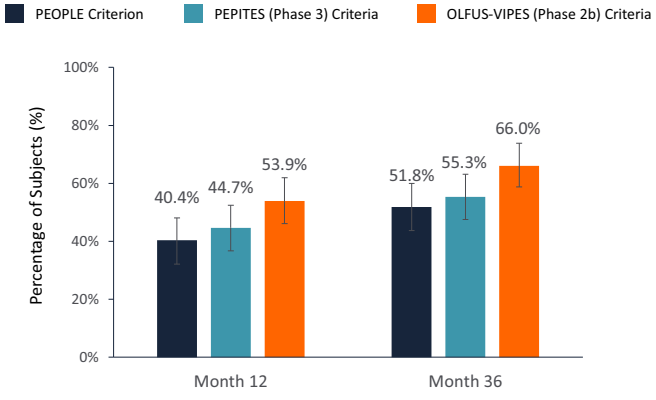

FIG 3. Proportion of subjects meeting prespecified primary outcome at months 12 and 36 in PEOPLE PP set according to primary outcome criteria in PEOPLE, PEPITES, and OLFUS-VIPES. The proportion of subjects in the PEOPLE PP data set (n = 141) at months 12 and at 36 meeting the prespecified primary outcome criteria of PEOPLE, PEPITES, and OLFUS-VIPES (PEOPLE: ED ≥1000 mg; PEPITES: ED ≥300 mg if baseline ED ≤10 mg or ≥1000 mg if baseline ED >10 mg and ≤300 mg; OLFUS-VIPES: ED ≥1000 mg or ≥10-fold baseline).

baseline, 7.5 mm (IQR, 6-10) at month 12, and 7.5 mm (IQR, 6.5-10) at month 36.

Sustained unresponsiveness

Seventy-three subjects who reached an ED ≥1000 mg at month 36 were eligible to undertake an SU assessment, which was optional. Those who did not elect to undertake this assessment continued daily treatment as part of the PEOPLE extension study. Those who elected to undertake the assessment recommenced daily therapy at the end of the SU assessment. Eighteen subjects elected to stop DBV712 250 μg for 2 months (while maintaining a peanut-free diet) and underwent a further DBPCFC at month 38 while still off treatment. Of these subjects, 77.8% (14 of 18) maintained an ED of ≥1000 mg. Of the 4 subjects who did not maintain an ED of ≥1000 mg at month 38, 3 subjects reached an ED of 300 mg and 1 subject reached an ED of 100 mg. Three of these 4 subjects maintained a higher ED at month 38, following the cessation of therapy, compared with their baseline ED. The individual ED trajectories over the 38-month period for these 18 subjects are shown in Fig E3 (see this article's Online Repository at www.jacionline.org). Baseline, 12-month, and 36-month characteristics were similar between those subjects who opted in or out of this assessment, including month-12 median ED, and IgE/IgG$_4$, except for median month-36 ED, which was 1 increment higher in those who opted in (see Table E6 in this article's Online Repository at www.jacionline.org).

TABLE II. Proportion of treatment responders in the PP data set (n = 141) at months 12 and 36

	Responder at month 36	
	Yes	No
Responder at month 12		
Yes	46 (32.6)	11 (7.8)
No	27 (19.1)	57 (40.4)

Responders are subjects reaching an ED ≥1000 mg.
Values are no. (%). Percentages are based on the number of subjects with nonmissing values for each group.

Adverse events

In the safety set (n = 198), the median study duration in PEOPLE was 754.5 days (range, 35-953), with a median treatment exposure duration of 735 days (range, 39-863). From the start of the PEOPLE study to month 36, the incidence of all TEAEs (irrespective of treatment relatedness) was 100%, with the majority of TEAEs being reported as mild or moderate (see Table E7 in this article's Online Repository at www.jacionline.org). The most commonly reported treatment-related TEAEs were application site reactions, observed in 77.8% of subjects (154 of 198), including erythema (63.1%), pruritus (45.5%), and site swelling (20.2%) (Table III). During PEOPLE, no treatment-related serious adverse events were reported.

Fewer TEAEs were reported over the third year of treatment (162 subjects [88.0%]; 927 events) compared with over the first and second years (191 subjects [96.5%]; 1835 events and 196 subjects [99.0%]; 1628 events, respectively) (Table E7). Overall, fewer subjects experienced local skin reactions over time, particularly from month 18 onward, and during the third year of treatment, local skin reactions were observed in 29.9% of subjects (55 of 184). The majority of local skin reactions (as assessed by investigators) were grades 1 (43.9%) or 2 (40.9%) with no grade 4 events.

A single anaphylactic reaction was reported over the 2-year PEOPLE treatment period as possibly related to DBV712 250 μg (assessed as mild, which resolved without any treatment) (see Table E8 in this article's Online Repository at www.jacionline.org). There were no episodes of epinephrine use related to treatment reported throughout the PEOPLE study (years 2 and 3 among the 198 subjects) (Table III). There were an additional 29 anaphylactic reactions, reported and assessed by the investigators to be unrelated to DBV712 250 μg over the 2-year period

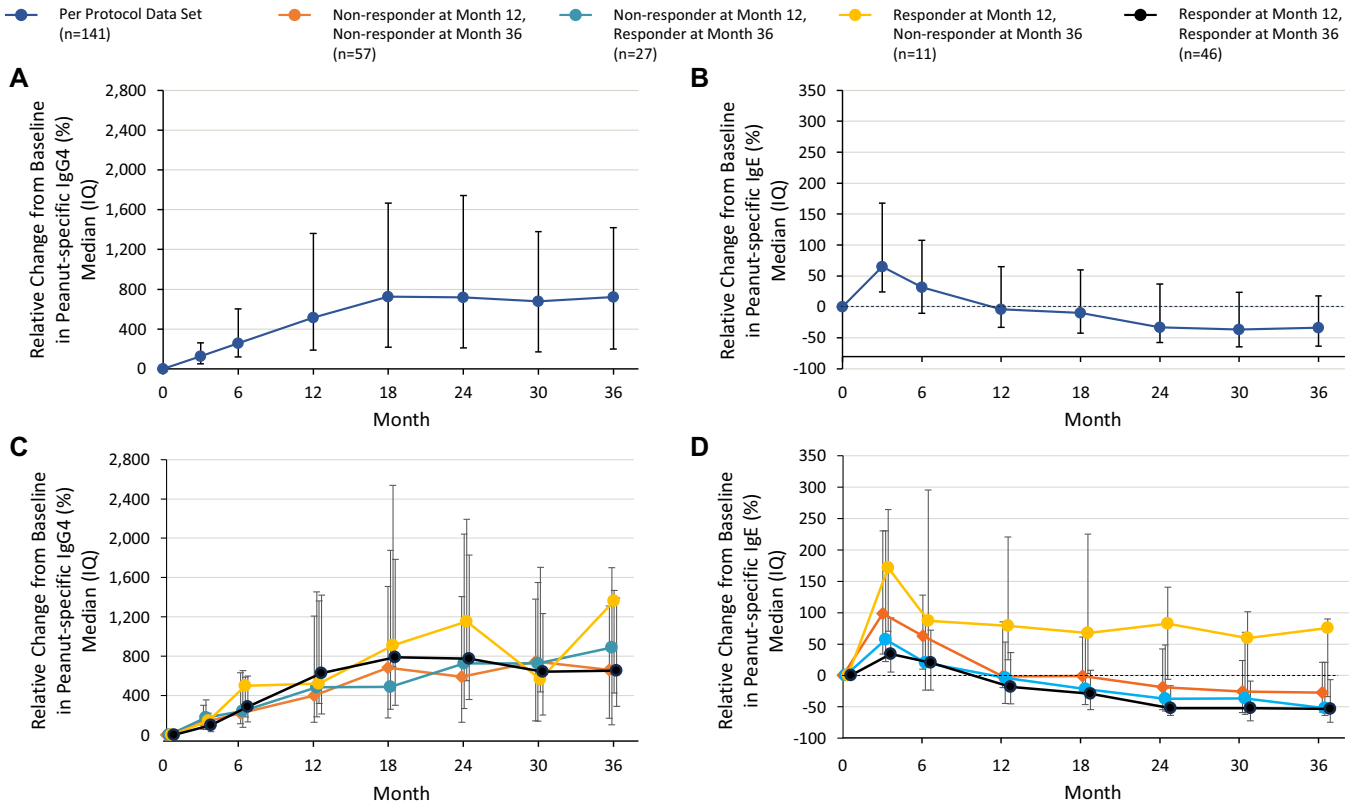

FIG 4. Relative change from baseline in peanut-sIgG$_4$ and -sIgE over the 3-year treatment period in the PP data set (n = 141) and by responder group. In the PP data set, median levels of peanut-sIgG$_4$ were 0.64 mg/L (IQR, 0.27, 1.33) at baseline and 5.005 mg/L (IQR, 1.98, 8.83) at month 36 **(A)**, and median levels of peanut-sIgE were 69.9 kU$_A$/L (IQR, 15.1, 173) at baseline and 38.4 kU$_A$/L (IQR, 7.21, 186) at month 36 **(B)**. Changes from baseline in IgG$_4$ **(C)** and IgE **(D)** were assessed according to responder status at months 12 and 36: subjects who were nonresponders at both months 12 and 36 *(orange)*, nonresponders at month 12 who were responders at month 36 *(light blue)*, responders at month 12 who were nonresponders at month 36 *(yellow)*, and responders at both months 12 and 36 *(black)*.

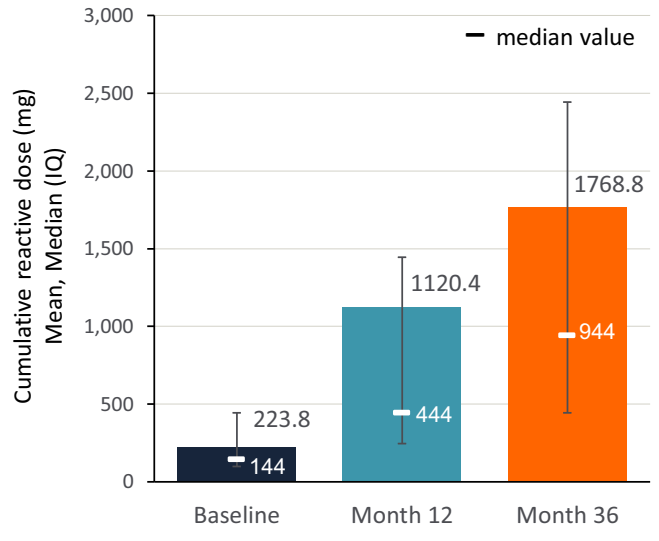

FIG 5. CRDs of peanut protein at baseline, month 12, and month 36 in the PP data set (n = 141). Mean and median CRDs (mg peanut protein) in the PP data set (n = 141) were measured during the DBPCFCs at baseline (month 0), month 12, and month 36.

among 23 subjects, excluding reactions at food challenge. Details of these episodes are available in Table E8.

Between the start of PEOPLE (month 12) and month 36, 4 subjects (2.0%) discontinued due to TEAEs: 1 subject due to moderate application site pruritus, mild application site rash, and swelling; 1 due to moderate application site pruritus; 1 due to benign lymphoid tissue hyperplasia of the oropharynx, with reactive follicular hyperplasia on biopsy (deemed unrelated to treatment by the investigator); and 1 due to anxiety.

DISCUSSION

The PEOPLE trial represents the largest long-term trial evaluating peanut allergy immunotherapy to date. An extended duration of study participation was possible with the simple 1-dose regimen that was associated with high compliance and low treatment-related discontinuation rates. The potency of the skin as a route for desensitization is illustrated by the very low total dose skin exposure required over the 3-year treatment period: only ~273 mg of peanut protein, approximately a single peanut kernel. In this analysis of the ongoing open-label study, which is assessing DBV712 250 μg treatment out to 5 years, the

TABLE III. Summary of TEAEs considered related to treatment during the PEOPLE study (months 12 to 36 of active treatment) in the safety population (n = 198)

	DBV712 250 μg (n = 198)	
	n	m
Any TEAE considered related to treatment	158 (79.8)	805
By preferred term (occurring in ≥2% of subjects)		
Administration site erythema	125 (63.1)	282
Administration site pruritus	90 (45.5)	178
Administration site swelling	40 (20.2)	90
Administration site papules	29 (14.6)	43
Administration site urticaria	24 (12.1)	41
Administration site eczema	12 (6.1)	14
Administration site erosion	12 (6.1)	13
Administration site dermatitis	7 (3.5)	7
Administration site discoloration	4 (2.0)	4
Administration site rash	4 (2.0)	5
Urticaria	8 (4.0)	8
Eczema	4 (2.0)	9
TEAE considered related to treatment		
Serious	0	0
Severe	9 (4.5)	31
Moderate	43 (21.7)	163
Mild	149 (75.3)	611
TEAEs related to treatment leading to epinephrine intake	0	0
TEAEs related to treatment leading to temporary discontinuation	20 (10.1)	67
TEAEs related to treatment leading to permanent discontinuation	2 (1.0)	4

n, Number of subjects with at least 1 AE; *m*, number of AEs.
Values in n column are no. (%) and in m column are no. Any AEs related to double-blind, placebo-controlled food challenges were excluded.

current results demonstrate desensitization over 36 months of treatment and support the long-term tolerability and clinical benefit of DBV712 250 μg in children with peanut allergy. Overall, more than one-half of subjects, all of whom started in PEPITES with a baseline ED of ≤300 mg, achieved an ED of ≥1000 mg, which is equivalent to approximately 3 to 4 peanut kernels, and overall, three-quarters of subjects improved their ED from baseline to month 36. ED increases in the most sensitive subjects were especially robust; while the group as a whole experienced a 5-fold increase in geometric mean ED over 36 months, the group who entered with an ED of ≤10 mg saw a 22-fold increase over the treatment period, and there was a large change in the CRD from a median of 144 mg to 944 mg over the 3 years.

There are few prior reports of treatment outcomes for peanut immunotherapy beyond 12 to 18 months. Most large oral immunotherapy studies have reported results limited to 12- or 18-month treatment duration.[27-29] The longest peanut immunotherapy study published to date followed 39 subjects receiving oral immunotherapy out to 5 years and demonstrated SU in 12 subjects after 1 month of peanut avoidance.[30] The POISED (Peanut Oral Immunotherapy Study: Safety, Efficacy, and Discovery) study,[31] which included 120 subjects followed to a maximum of 156 weeks under varying oral immunotherapy regimens, reported that discontinuation of treatment or lower doses of daily oral peanut exposure increased the likelihood of regaining clinical reactivity to peanut. The CoFAR6 (Epicutaneous Immunotherapy [EPIT] for Peanut Allergy: A Randomized, Double-Blind, Placebo-Controlled, Phase II Study in Children and Adult) trial consortium[32] followed 56 of 74 subjects out to a total of 130 weeks of treatment with EPIT, with an interim report suggesting longer treatment with 250 μg peanut protein could lead to improved outcomes beyond 1 year.

Peanut allergy has a significant economic impact and an adverse effect on HRQL for both patients and caregivers, with fear of reactions due to accidental exposure a key driver of impairment in HRQL.[33] As such, caregivers of children with peanut allergy express a desire for therapy that will offer a level of protection against unintentional peanut exposure.[4] Therapies such as EPIT, that are well tolerated and can reduce the risk of reactions to accidental ingestion, can potentially lead to improvements in HRQL, as we have recently demonstrated.[34] Given that most children with peanut allergy react to a single peanut kernel (~300 mg of peanut protein) or less,[35] we believe the improvements observed with EPIT, and specifically the improvement in ED over 36 months of therapy as presented here, are meaningful and may reduce the risk of reaction from accidental exposure as predicted by quantitative risk assessment approach that models potential risk reduction. For example, a 73% to 78% reduction in risk of reaction per eating occasion for packaged foods was predicted for children treated with DBV712 250 μg for 12 months based on the PEPITES study results, with up to 93% risk reduction to cross-contamination through restaurant meals.[6,36]

It is encouraging that in the present study, the total median cumulative reactive and tolerated doses of peanut increased substantially from months 12 to 36, suggesting there is an enhancement of effect over the second and third years of therapy. This is supported by the changes observed in peanut-sIgG$_4$, which progressively increased throughout the first 18 months of treatment and remained at peak levels for the remainder of the treatment to month 36. In addition, a higher proportion of subjects were tolerant to 3444 mg at month 36 than at month 12, and 13.5% of subjects (19 of 141) completed the full DBPCFC at month 36 (cumulative dose of 5444 mg) without meeting stopping criteria. This further supports the notion that continued increases in threshold, not just a maintenance of effect beyond 12 months of therapy, is observed in a proportion of subjects undergoing EPIT with 250 μg peanut protein.

Exploratory analyses in a small subcohort of subjects, who were eligible (ED ≥1000 mg) and willing to stop therapy for a 2-month period and be reassessed with a further DBPCFC, suggest that DBV712 250 μg may offer a sustained effect even after a period without treatment and with peanut avoidance. Consistent with the high rates of SU previously reported in the open-label extension of the phase 2b study in a similar age range (6-11 years) at 73.7% (14 of 19),[19,37] we observed that 77.8% of subjects (14 of 18) in PEOPLE were able to maintain protection for a 2-month period while off therapy and without peanut consumption. Consistent with previous observations, those subjects who attained SU tended to have a lower baseline peanut-sIgE, although the IQR was large, with the third quartile exceeding 100 kU$_A$/L (kU$_A$ = kilo unit of allergen-specific IgE), limiting the value of this parameter for predicting any given individual's response.[38] This capacity of EPIT to drive SU in these subjects may relate to the proposed mechanism of action of EPIT. It is likely that unwillingness to undergo further DBPCFC was the major reason why only 18 of 73 eligible subjects underwent the SU assessment

in this study, with the characteristics of the subjects who opted-in similar to those who opted-out. Likewise, approximately one-half of all withdrawals from the study were accounted for due to dislike or distaste for the food challenge, and very few were related to the actual treatment itself.

Based on preclinical studies, EPIT-delivered allergen is captured in the superficial layers of the skin by Langerhans cells, as well as dermal dendritic cells, which induce a specific population of regulatory T cells, primarily in regional peripheral lymph nodes, capable of suppressing the allergic response[39-43] with no significant, early allergen-driven effector cell desensitization. This suggests both a different mechanism of action of EPIT compared with immunotherapy delivered by alternative routes and a mechanism by which SU following cessation of immunotherapy might occur. Although a direct effect on effector cell desensitization may also contribute to this response, a role for regulatory T cell induction is supported by the presence of hypermethylation of the *Gata-3* promoter region and hypomethylation of *FoxP3* promoter region on regulatory T cells in murine EPIT models.[44] It is, therefore, plausible that the therapeutic trajectory of EPIT treatment, as suggested by animal models and seen in a high proportion of subjects who underwent SU evaluation in the OLFUS-VIPES and PEOPLE studies, may lead to more sustained duration of desensitization, with effects continuing after therapy has ceased.

There are currently no data to support strong differentiating features at baseline that could be used to predict the response to therapy of an individual child with peanut allergy. In a recent *post hoc* analysis of PEPITES, those with lower median baseline peanut-sIgE may exhibit a more robust treatment response,[45] although the trial was not designed to detect such differences, so conclusions must be interpreted with caution. In addition, given the overall very high baseline IgEs of the entire cohort, even lower peanut-sIgE levels are still relatively high compared with these level for the general population with peanut allergy, and the baseline ED required for entry ensured a sensitive and sensitized cohort vulnerable to accidental ingestion reactions. Further work and exploration in this area continue. As the subjects were predominantly Caucasian, it was not possible to determine whether there are any differences in response related to race or ethnicity at this stage. We identified a subgroup of subjects who did not respond to treatment over the 3-year period and did not identify any differences in baseline characteristics or biomarkers measured during the study that were able to distinguish these subjects from those who responded to treatment. It will be important to continue to search for possible, as yet unidentified factors and novel biomarkers that may assist in identifying these patients prior to or early in treatment. We did identify a small proportion (7.8%) of subjects who, having reached an ED of 1000 mg or greater after 12 months of therapy, saw a decrease at 36 months' time. No baseline characteristics distinguish these subjects, nor did they have apparent differences in the induction of peanut-sIgG$_4$ at 12, 24, or 36 months, which would have identified them as being at risk for this trajectory. However, compared with the remainder of the cohort, they did have a tendency to lesser decreases in their peanut-sIgE at 24 and 36 months. Given the small numbers (n = 11) in this subgroup, this observation should be interpreted with caution. Treatment continues for an additional 2 years in PEOPLE, and it is plausible that subjects who have shown resistance to EPIT or fluctuations during the first 3 years may improve at the 4- and 5-year end points.

The safety profile of DBV712 250 μg in PEOPLE was consistent with that observed in the clinical program to date in over 1000 subjects[18-20] and in alignment with preclinical data showing little or no systemic peanut protein absorption.[46] Overall, there were fewer safety events of interest associated with DBV712 250 μg relative to published data,[20] such as no epinephrine use deemed related to treatment, highlighting a favorable benefit-to-risk profile. Local application-site reactions decreased in frequency and severity over the 3-year period. The most common AEs were mild-to-moderate skin reactions localized to the administration site, and no treatment-related serious adverse events were reported. One subject experienced a case of mild anaphylaxis that was determined by the investigator to be possibly related to DBV712 250 μg and resolved without medical intervention. Treatment compliance remained very high throughout the study at a mean of 98% over 3 years. Study withdrawals were very infrequently related to treatment, but most often due to the ongoing requirement to undertake peanut food challenges, an issue that will continue to be problematic for clinical trials of treatment for food allergy until a reliable surrogate for assessing outcome emerges. Overall, this suggests that as EPIT is continued, the therapeutic window and benefit-to-risk ratio becomes more pronounced with both accruing benefits and lower rates of adverse events.

Weaknesses of the current study include the open-label nature of the extension study; due to ethical and logistical concerns, the placebo phase of the trial was limited to 12 months. As assessment of ongoing treatment response and safety were the primary goals of this 3-year analysis, we elected to analyze efficacy by including those subjects with reliable DBPCFC data. Only 7 subjects were excluded on this basis, and as per Table I, the baseline characteristics of the analysis set were very similar among the completer set (n = 148), PP set (n = 141), safety set (n = 198), and the original PEPITES cohort; however, there was a large dropout rate due to reluctance to undergo repeated peanut challenges in the form of DBPCFCs. On this basis, we believe the analyses presented are representative and generalizable. Conclusions regarding the potential for EPIT to induce SU are limited by the fact that only a small subset of eligible subjects elected to participate in the SU assessment. This may have been due to perceived benefit associated with continuing treatment with the patch (ie, not willing to interrupt therapy), as well as reluctance/fear to undergo another DBPCFC. Indeed, while the dropout rate from months 12 to 36 of this open-label study was approximately 25%, over one-half of those who discontinued did so in the final 6 months of the study, with concerns about the DBPCFC (fear of reaction at challenge and/or distaste of challenge material) identified as the leading reason. Study discontinuation due to TEAEs was low at 2%. The median baseline peanut-sIgE was greater in the 50 subjects who discontinued and were not included in the completer set; however, they had a similar increase in peanut-sIgG$_4$ and decrease in peanut-sIgE as those in the completer set over the first 2 years of treatment. It is possible that the 50 subjects who did not successfully complete the study may have influenced the outcome of the remaining PP population.

Immunotherapy for peanut allergy has progressed significantly over this century, with an orally administered product recently approved by the US Food and Drug Administration[47] and other forms of peanut immunotherapy under investigation. It is likely

that EPIT has different mechanistic and clinical outcomes because it provides low dosing of allergen via the skin over several years. Data presented here suggest that EPIT may represent a persistent and durable treatment option, on a background of being well tolerated. Moreover, EPIT has minimal impact or restrictions on daily activities and lifestyle and is easy to use, resulting in high compliance rates. While longer-term data with EPIT will continue to accumulate with the current study continuing to 5 years, the present results demonstrate that daily EPIT for peanut allergy beyond 1 year leads to continued response to treatment, with ED improvements that may translate into increased protection from reactions due to accidental peanut ingestion.

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Key messages

- **EPIT demonstrated durable, long-term clinical benefit with an additional 2 years of treatment in children with peanut allergy (4-11 years old).**
- **High compliance and low discontinuation rates due to AEs enabled extended study participation.**
- **Results from this largest, long-term peanut allergy immunotherapy trial to date further support the overall favorable benefit-to-risk profile of EPIT.**

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