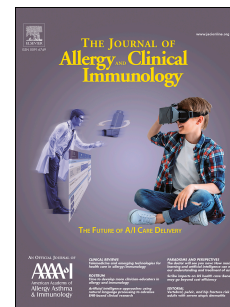


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Long-Term, Open-Label Extension Study of the Efficacy and Safety of Epicutaneous Immunotherapy for Peanut Allergy in Children: PEOPLE 3-Year Results

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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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Conflicts of Interest:

Todd D. Green, Romain Lambert, Aurélie Peillon, Timothée Bois, are employees of DBV Technologies. **Dianne E. Campbell** is a part-time employee of DBV Technologies and reported receiving grant support from National Health and Medical Research Council of Australia and personal fees from Allergenis, Westmead Fertility Centre and Financial Markets Foundation for Children. **Hugh A Sampson** is a part-time employee of DBV Technologies, reports receiving consultancy fees from N-Fold Therapeutics, grant funding from the National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID), and royalties from Elsevier. **Sara Anvari** reported receiving grants from DBV Technologies during the conduct of the study and grants from the US NIAID and Aimmune Therapeutics outside of the submitted work. **Amal Assa'ad** reported receiving research grants from Aimmune, DBV Technologies, Astellas, Sanofi, and Regeneron. **Philippe Bégin** reported receiving grants through his institution from DBV Technologies during the conduct of the study and personal fees from Novartis, Aralez, and

Pfizer and grants from Merck, Sanofi, and the Canadian Allergy, Asthma, and Immunology Foundation outside the submitted work. **Kirsten Beyer** reported receiving grants from DBV Technologies during the conduct of the study; outside the submitted work she reports grants and personal fees from Aimmune Therapeutics and ALK as well as personal fees from Allergopharma, Bencard, DBV and Mabylon AG. **Drew Bird** reports 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 non-financial support from Aimmune Therapeutics, personal fees from Food Allergy Research and Education, personal fees and non-financial 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, outside the submitted work. 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 healthcare advisory board for Food Allergy Canada, was an expert panel and coordinating committee member of the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored Guidelines for Peanut Allergy Prevention, and is co-lead of the CSACI oral immunotherapy guidelines. **Sharon Chinthrajah** received grants from NIAID, CoFAR, Aimmune, DBV Technologies, Astellas, AnaptysBio, Novartis, and Regeneron; personal fees from Novartis, Genentech, Allergenis, Before Brands, and Alladapt. **Hey Chong** reports receiving consultancy fees from Horizon. **Carla M. Davis** reports research contract funding from DBV Technologies, Regeneron Pharmaceuticals, and Aimmune Therapeutics, and is a consultant for Moonlight Therapeutics. **David M. Fleischer** has received research support to his institution from DBV Technologies and Aimmune Therapeutics; reports clinical medical advisory board membership with DBV Technologies; has served as a consultant for DBV Technologies, AllerGenis, Aquestive Therapeutics, Aravax, Genentech, Nasus, and Intrommune Therapeutics; has received honorarium for lectures from DBV Technologies and receives royalties from UpToDate. **Matthew Greenhawt** is supported by grant #5K08HS024599-02 from the Agency for Healthcare Research and Quality; is 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; is 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; is a member of the scientific advisory council for the National Peanut Board; has 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; is an associate editor for the Annals of Allergy, Asthma & Immunology; and is a member of the Joint Taskforce on Allergy Practice Parameters. **Jonathan O'B Hourihane** receives research funding and consultancy fees from Aimmune Corporation, and research funding from Johnson&

Johnson. **Stacie Jones** is a member of the Research Advisory Board for FARE and Scientific Advisory Board for Aimmune Therapeutics, and reports receiving consultation fees for FDA 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. Kim** reports clinical medical advisory board membership with DBV Technologies; consultancy with Aimmune Therapeutics, DBV Technologies, AllerGenis, Allakos, Ukko, and Vibrant America; and receives grant support to his institution from the National Institute of Allergy and Infectious Diseases (NIH/NIAID), National Center for Complementary and Integrative Health (NIH/NCCIH), FARE and the Wallace Research Foundation. **Lars Lange** reports receiving consulting and lecturer fees from DBV Technologies. **Bruce Lanser** reports grants and personal fees from Aimmune Therapeutics, grants from DBV Technologies, grants from Regeneron, personal fees from Allergenics, personal fees from Hycor, personal fees from GSK, personal fees from Genentech, outside the submitted work; and is a member of the NIH/NIAID-sponsored CoFAR. **Stephanie Leonard** reports receiving grants from DBV Technologies and Aimmune Therapeutics; grants and personal fees as a member of the medical advisory board of Food Allergy Research and Education; and consulting fees for work with LabCorp outside the submitted work. **Vera Mahler** became 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** received research grants from DBV Technologies, Astellas Pharma, NIH NIAID ITN, Nutricia Danone; she is 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 therapy; she authors topics for Up To Date and is the deputy editor for the Annals of Allergy, Asthma and Immunology. **Daniel Petroni** received 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** received 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** reports receiving research funding from DBV technologies and Aimmune therapeutics and honorarium from Medscape, and participating in IDMC for Regeneron and clinical advisory boards for FARE. **Lynda C. Schneider** is a researcher or consultant for DBV Technologies, Regeneron Pharmaceuticals, Pfizer, Abbvie, and Aimmune; she received funding for an investigator-initiated study from Genentech. **Wayne Shreffler** reported receiving personal fees and research funding from DBV Technologies during the conduct of the study and grants from Sanofi, the NIH, and Food Allergy Research and Education and personal fees from Aimmune Therapeutics scientific advisory board. **Gordon Sussman** is an advisory board member for Novartis, Aralez, CSL Behring, and Sanofi; he reports 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 has participated in clinical trials (PI) for Novartis, GSK, Genentech, DBV technologies, Aimmune, CSL Behring, Astrazeneca, Stallergenes, Merck, Pfizer, Dyax, Biocryst, Greencross, Kendrion, Leo Pharma, Regeneron, Sanofi, Blueprint, ALK, Amgen, and Cliantha. Robert Wood reported receiving grants from the

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The following authors have nothing to disclose: **Aideen Byrne** and **Andreas Maronna**. No other disclosures were reported.

Declaration of Funding:

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Abstract:

Background: We previously reported the safety and efficacy of epicutaneous immunotherapy (EPIT™) for peanut allergy (250 µg, daily epicutaneous peanut protein; DBV712 250µg) in a 12-month randomized controlled study (PEPITES) of peanut-allergic children aged 4-11 years.

Objective: To assess interim safety and efficacy of an additional 2 years of EPIT from the ongoing (5-year treatment) open-label extension PEOPLE study.

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

Results: 198 (93%) of 213 eligible subjects who had received DBV712 250µg in PEPITES entered PEOPLE, of whom 141 (71%) had assessable DBPCFC at Month 36. At Month 36, 51.8% (73/141) of subjects reached an eliciting dose (ED) of ≥ 1000 mg, compared with 40.4% (57/141) at Month 12. 75.9% (107/141) demonstrated increased ED compared to baseline. 13.5% (19/141) tolerated the full DBPCFC of 5444 mg. Median cumulative reactive dose increased from 144 to 944 mg. 18 subjects underwent an optional SU assessment; 14/18 (77.8%) maintained an ED 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 low (1%).

Conclusion: 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.

Key Messages:

- Epicutaneous immunotherapy (EPIT) demonstrated durable, long-term clinical benefit with an additional two years of treatment in peanut-allergic children (4-11 years)
- High compliance and low discontinuation rates due to adverse events 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

229 **Capsule Summary:**

230 This report represents the largest long-term study of peanut immunotherapy, out to 3 years,
231 demonstrating long-term tolerability, low treatment-related discontinuations, and durable
232 improvements in peanut desensitization thresholds with epicutaneous immunotherapy.

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Key Words:

Peanut allergy
Food Allergy
Immunotherapy
Desensitization
Eliciting Dose
Epicutaneous Immunotherapy (EPIT)
Sustained Unresponsiveness

Abbreviations:

AE=adverse event
CI=confidence interval
CRD=cumulative reactive dose
DBPCFC=double-blind placebo-controlled food challenge
ED=eliciting dose
EPIT=epicutaneous immunotherapy
HRQL=health-related quality of life
ICH GCP =International Council for Harmonisation Good Clinical Practice
IgE=immunoglobulin E
IgG4=immunoglobulin G4
IQR=interquartile range
mBOCF=modified baseline observation carried forward
mLOCF=modified last observation carried forward
medDRA=Medical Dictionary for Regulatory Activities
MMRM=mixed-effect model repeated measure
OIT=oral immunotherapy
OLFUS-VIPES=Open-Label Follow-Up Study of VIPES
PEOPLE=PEPITES Open-Label Extension
PEPITES=Peanut EPIT Efficacy and Safety
PP=per protocol
PT=preferred term
Q1=first quartile
Q2=second quartile
SAE=serious adverse event
SD=standard deviation
SPT=skin prick test
SU=sustained unresponsiveness
TEAE=treatment-emergent adverse event
Tregs=regulatory T cells
VIPES=Viaskin Peanut's Efficacy and Safety

Introduction

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, peanut allergy results in more emergency room visits for anaphylaxis compared with other food allergies,^{2,3} with 1 in 4 children with peanut allergy requiring an emergency room 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 peanut-allergic patients, their families, and allergists.⁴⁻⁶ Moreover, it is estimated that 50% of peanut-allergic children will react to 30-100 mg of peanut protein and most to less than 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%-14% in peanut-allergic individuals, 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 one of 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 study that included children aged 6 to 11 years and an open-label phase (OLFUS-VIPES) of up to 36 total months of treatment, the efficacy and safety of an epicutaneous peanut patch, Viaskin Peanut 250µg peanut protein (DBV712 250 µg), was assessed in PEPITES (NCT02636699), a phase 3, randomized, double-blind, placebo-controlled study of children with peanut allergy aged 4 to 11 years.²⁰ In PEPITES, DBV712 250 µg was well

tolerated, and a statistically significant difference ($P<0.001$) 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 open-label extension PEOPLE 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, whilst 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 (ICH GCP) 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 (**Figure 1**). The study protocol is available in Supplement 1 in the Online Repository. 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 (DBPCFC) were conducted as previously described during the PEPITES study²⁰ following the PRACTALL criteria after 1 and 3 years of active treatment (Month 12 and Month 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 (**Table E1**, online repository). Subjective symptoms (e.g., abdominal pain or oropharyngeal itching) were assessed and recorded, but alone 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 consistent with the 2016 US Food and Drug Administration Allergenic 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 aged 4 to 11 years 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 two Month-12 DBPCFC visits, were offered enrollment in PEOPLE (**Figure 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 μ g 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 Guidelines²⁴), 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 autoinjectors available. The PEOPLE study population is comprised of 2 groups according to the treatment allocation in PEPITES (**Figure 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 (Supplement, Protocol V7).

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 endpoints included ED at each

time point; CRD of peanut protein; the percentage of subjects unresponsive to the highest dose of peanut protein (i.e., 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 immunoglobulin E (IgE) and immunoglobulin G4 (IgG4) and peanut skin prick test (SPT) 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 ICH GCP definition. Skin reactions were openly graded by the site investigator from 0 to 4, according to European Academy of Allergy and Clinical Immunology (EAACI) and the Global Allergy and Asthma European Network (GA²LEN), where Grade 0 is no skin reaction and Grade 4 is erythema and vesicles (**Table E2**, online repository).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 organs 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 μ g 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 μ g subjects who received at least 1 dose of study drug during PEOPLE. The completer set was defined as all DBV712 250 μ g

subjects from the safety set having evaluable DBPCFC results at both Month 12 and Month 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 Month 12 and Month 36 and compliance of $\geq 80\%$.

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 (i.e., 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 Month-36 ED by Wilcoxon's test.

Categorical variables were summarized using number of observations and percentages, and continuous variables were summarized using descriptive statistics. For the main endpoint, the 95% confidence interval (CI) between paired binomial proportions was calculated using the Newcombe's method based on Wilson score intervals with continuity correction. Supportive analyses of the main endpoint were performed using Modified Baseline Observation Carried Forward (mBOCF) 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 Month-36 DBPCFC was not reached, the mBOCF 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 (93.0%) subjects opted to enter PEOPLE (safety set) (Figure

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 141/198 (71.2%) subjects who entered PEOPLE 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 7 (of 148 completers) 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 Month-36 DBPCFC.

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; i.e., 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 11/50 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 1**. The 50 subjects who were not included in the completer set were, in general, similar to the overall population (**Table 1**), but had higher median baseline peanut-sIgE, and one dose increment lower median Month-12 ED, with large overlap in IQR with that of the completer set (**Table 1**). This was not true of the 11 subjects who commenced but did not complete the Month-36 DBPCFC, where no differences were observed compared with the completer set, including in baseline or Month-12 median ED (**Table E3**, online repository).

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

Changes in eliciting dose

At Month 36, 51.8% (73/141) of subjects in the PP set reached an ED of ≥ 1000 mg, compared with 40.4% (57/141) at Month 12 (11.3% difference; 95% CI: 2.8-19.6) (**Figure 2; Table E4**, online repository). Following 3 years of treatment, 75.9% (107/141) of subjects demonstrated an increase in ED compared to baseline. Of the subjects who had a baseline ED of ≤ 100 mg, 67.4% (62/92) 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 Month 12 and Month 36 from 4.3% (6/141) to 18.4% (26/141). In addition, at Month 36, 13.5% (19/141) of subjects were able to tolerate the full DBPCFC of 5444 mg (i.e., passed the DBPCFC without meeting the prespecified, modified PRACTALL stopping criteria). Within the completers set, using mLOCF for imputation, 43.9% (87/198) of subjects reached an ED of ≥ 1000 mg at Month 36 compared with 35.9% (71/198) at Month 12, and under all imputations, response was generally in favor of 36 months compared with 12 months of treatment (**Figure E1**, online repository).

When the results were analyzed according to the primary outcome criteria used in PEPITES, which considers lower and higher baseline ED strata, 55.3% (78/141) of subjects 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 (**Figure 3**).

When analyzed by mixed-effect model repeated measure (MMRM) over the 3-year treatment period, there was a 5.0-fold (95% CI: 4.0-6.3) 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: 10.7-47.3). In those with a baseline ED > 10 mg (n=123), the geometric mean ED increased 4.0-fold by Month 36 (95% CI: 3.2-5.0).

Overall, the response observed between the DBPCFC at Month 12 and at Month 36 was maintained and/or improved in the majority of subjects (**Table 2**). By Wilcoxon's test (using paired data), there was a significant difference in ED between Month 12 and Month 36 in both PP and completer sets ($P=0.006$ and 0.032 , respectively). At Month 36, 49.3% (73/148) of subjects in the completer set reached an ED of ≥ 1000 mg, compared with 41.2 % (61/148) at Month 12 (8.1.% difference; 95% CI: -0.05-16.5). At Month 36, 43.9% (87/198) of subjects in the safety set reached an ED of ≥ 1000 mg, compared with 35.9% (71/198) at Month 12 using mLOCF imputation (8.1.% difference; 95% CI: -2.0-14.1). Of the 11 (7.8%) subjects 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 IgE (**Table E5**, online repository); 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 Month 12 to Month 36, but a similar IgG4 trajectory relative to the remainder of the cohort (**Figure 4**).

Changes in cumulative reactive dose and immune markers

Mean and median CRD rose over the 3-year treatment period (**Figure 5**). At Month 36, 24.1% (34/141) of subjects reached a CRD of 3444 mg compared to 15.6% (22/141) at Month 12. This trend was similarly observed when analyzed by MMRM using log-transformed data (**Figure E2**, online repository). Peanut IgG4 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 IgE levels increased initially at the start of the study and then returned to baseline, remaining around or below baseline through Month 36 (**Figure 4**). The median (IQR) absolute change in SPT mean wheal diameter from baseline to Month 36 was 3.5 mm (-5.5, -1); with median values of 11 mm (9-14) at baseline, 7.5 mm (6-10) at Month 12, and 7.5 mm (6.5-10) at Month 36.

Sustained unresponsiveness (SU)

Seventy-three subjects who reached an ED ≥ 1000 mg at Month 36 were eligible to undertake an SU assessment, which was entirely 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 μ g for 2 months (whilst maintaining a peanut-free diet) and underwent a further DBPCFC at Month 38 whilst still off treatment. Of these subjects, 77.8% (14/18) 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 **Figure E3** (online repository). Baseline, 12-, and 36-Month characteristics were similar between those subjects who opted in or out of this assessment, including Month-12 median ED, and IgE/IgG4, except for median Month-36 ED, which was one increment higher in those who opted in (**Table E6**, online repository).

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 (**Table E7**, online repository). The most commonly reported *treatment-related* TEAEs were application site reactions, observed in 77.8% (154/198) of subjects, including erythema (63.1%), pruritus (45.5%), and site swelling (20.2%) (**Table 3**). During PEOPLE, no treatment-related SAEs were reported.

Fewer TEAEs were reported over the third year of treatment (162 [88.0%] subjects; 927 events) compared to the first and second years (191 [96.5%] subjects; 1835 events and 196 [99.0%] subjects; 1628 events, respectively) (**Table E7**, online repository). Overall, fewer subjects experienced local skin reactions over time, particularly from Month 18 onwards, and

during the third year of treatment, local skin reactions were observed in 29.9% (55/184) of subjects. The majority of local skin reactions (as assessed by investigators) were Grade 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, **Table E8**, online repository). There were no episodes of epinephrine use related to treatment reported throughout the PEOPLE study (years 2 and 3 among the 198 subjects) (**Table 3**). 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 among 23 subjects, excluding reactions at food challenge. Details of these episodes are available in **Table E8** (online repository).

Between the start of PEOPLE (Month 12) and Month 36, 4 (2.0%) subjects 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 one-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 current results demonstrate desensitization over 36 months of treatment and support the long-term tolerability and clinical benefit of DBV712 250 µg in peanut-allergic children. Overall, more than 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 3-4 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 12-18 months. Most large oral immunotherapy (OIT) studies have reported results limited to 12 or 18 months treatment duration.²⁷⁻²⁹ The longest peanut immunotherapy study published to date followed 39 subjects receiving OIT out to 5 years and demonstrated SU in 12 subjects after 1 month of peanut avoidance.³⁰ The POISED study, which included 120 subjects followed to a maximum of 156 weeks under varying OIT regimens, reported that discontinuation of treatment or lower doses of daily oral peanut exposure increased the likelihood of regaining clinical reactivity to peanut.³¹ The CoFAR6 consortium followed 56 of 74 subjects out to a total of up to 130 weeks of treatment with EPIT, with an interim report suggesting longer treatment with 250- μ g peanut protein could lead to improved outcomes beyond 1 year.³²

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 peanut-allergic children 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 peanut-allergic children 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 μ g for 12 months based upon 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 Month 12 to Month 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 IgG4, 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% (19/141) of subjects 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- μ g peanut protein.

Exploratory analyses in a small sub-cohort of subjects, who were eligible (ED $\geq$ 1000 mg) and willing to stop therapy for a 2-month period and be reassessed with a further DBPCFC, suggest that DBV712 250 μ g 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% (14/19),^{19,37} we observed that 77.8% (14/18) of subjects 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 3rd quartile exceeding 100 kU_A/L, 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 18/73 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 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 (Tregs), primarily in regional peripheral lymph nodes, capable of

656 suppressing the allergic response³⁹⁻⁴³ with no significant, early allergen-driven effector cell
657 desensitization. This suggests both a different mechanism of action of EPIT compared with
658 immunotherapy delivered by alternative routes, and a mechanism by which SU following
659 cessation of immunotherapy might occur. Although a direct effect on effector cell
660 desensitization may also contribute to this response, a role for Treg induction is supported by
661 the presence of hypermethylation of the *Gata 3* promoter region and hypomethylation of *Fox p*
662 *3* promoter region on Tregs in murine EPIT models.⁴⁴ It is, therefore, plausible that the
663 therapeutic trajectory of EPIT treatment, as suggested by animal models and seen in a high
664 proportion of subjects who underwent SU evaluation in the VIPES-OLFUS and PEOPLE studies,
665 may lead to more sustained duration of desensitization, with effects continuing after therapy
666 has ceased.

667 There are currently no data to support strong differentiating features at baseline that
668 could be used to predict an individual peanut-allergic child's response to therapy. In a recent
669 post-hoc analysis of PEPITES, those with lower median baseline peanut s-IgE may exhibit a more
670 robust treatment response (manuscript submitted May 2020), although the trial was not
671 designed to detect such differences, so conclusions must be interpreted with caution. In
672 addition, given the overall very high baseline IgEs of the entire cohort, even lower peanut-
673 specific IgE levels are still relatively high compared with the general peanut-allergic population,
674 and the baseline ED required for entry ensured a sensitive and sensitized cohort vulnerable to
675 accidental ingestion reactions. Further work and exploration in this area continue. As the
676 subjects were predominantly Caucasian, it was not possible to determine whether there are
677 any differences in response related to race or ethnicity at this stage. We identified a subgroup
678 of subjects who did not respond to treatment over the 3-year period and did not identify any
679 differences in baseline characteristics or biomarkers measured during the study that were able
680 to distinguish these subjects from those who responded to treatment. It will be important to
681 continue to search for possible, as yet unidentified factors and novel biomarkers that may assist
682 in identifying these patients prior to or early in treatment. We did identify a small proportion
683 (7.8%) of subjects who, having reached an ED of 1000 mg or greater after 12 months of
684 therapy, see a decrease at 36 months' time. No baseline characteristics distinguish these

subjects, nor did they have apparent differences in the induction of peanut IgG4 at 12, 24, or 36 months, which would have identified them as at-risk for this trajectory. However, they did have a tendency to lesser decreases in their peanut-sIgE at 24 and 36 months compared to the remainder of the cohort. 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 endpoints.

The safety profile of DBV712 250 µg in PEOPLE was consistent with that observed in the clinical program to date in over 1000 subjects¹⁸⁻²⁰ and in alignment with preclinical data showing little or no systemic peanut protein absorption.⁴⁵ 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 SAEs 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 which 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 1, the baseline characteristics of the analysis set were very similar between the completer set (n=148), PP set (n=141), safety set

(n=198), and the original PEPITES cohort; however, there was a large drop-out 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 (i.e., not willing to interrupt therapy), as well as reluctance/fear to undergo another DBPCFC. Indeed, while the dropout rate from Month 12 to Month 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-sIgG4 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,⁴⁶ 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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905 [treatment-peanut-allergy-children](https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treatment-peanut-allergy-children)

922 **Tables**

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Table 1. 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 Per-Protocol Population (n =141)	PEOPLE Non- Completer 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-specific IgE, median, kUA/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-specific IgG4, 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 eliciting dose, 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 eliciting dose, 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)
300mg	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(ies) other than peanut	198 (83.2)	169 (85.4)	125 (84.5)	119 (84.4)	44 (88.0)
Month 12					
Month 12 Peanut protein eliciting dose, 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)

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Table 2. Proportion of Treatment Responders in the Per Protocol Data Set (n=141) at Month 12 and Month 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%)

Percentages are based on the number of subjects with non-missing values for each group.
Responders: subjects reaching an ED ≥ 1000 mg.

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Table 3. Summary of Treatment-Emergent Adverse Events (TEAEs) Considered Related to Treatment During the PEOPLE Study (Month 12 to Month 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

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932 n=number of subjects with at least 1 AE; m=number of AEs.

933 *Any AEs related to double-blind, placebo-controlled, food challenges were excluded.

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Figure Legends

Figure 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.

Figure 2. Proportion of Subjects from Per Protocol Data Set at Each Eliciting Dose (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 per protocol population. For study entry, subjects were required to have an ED at baseline of ≤ 300 mg of peanut protein.

Figure 3. Proportion of Subjects Meeting Prespecified Primary Outcome at Month 12 and Month 36 in PEOPLE Per Protocol Set According to Primary Outcome Criteria in PEOPLE, PEPITES, and OLFUS-VIPES.

The proportion of subjects in the PEOPLE per protocol data set ($n=141$) at Month 12 and at Month 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).

Figure 4. Relative Change from Baseline in Peanut IgG4 and IgE Over the 3-year Treatment Period in the Per Protocol Data Set ($n=141$) and by Responder Group.

In the per protocol data set, median (IQR) levels of peanut-specific IgG4 were 0.64 mg/L (0.27; 1.33) at baseline and 5.005 mg/L (1.98; 8.83) at Month 36 (A); median (IQR) levels of peanut-specific IgE were 69.9 kU_A/L (15.1; 173) at baseline and 38.4 kU_A/L (7.21; 186) at Month 36 (B). Changes from baseline in IgG4 (C) and IgE (D) were assessed according to responder status at Month 12 and Month 36: subjects who were non-responders at both Month 12 and Month 36

(orange), non-responders at Month 12 who were responders at Month 36 (light blue), responders at Month 12 who were non-responders at Month 36 (yellow), and responders at both Month 12 and Month 36 (black).

Figure 5. Cumulative Reactive Doses of Peanut Protein at Baseline, Month 12, and Month 36 in the Per Protocol Data Set (n=141).

Mean and median cumulative reactive doses (mg peanut protein) in the per protocol data set (n=141) were measured during the DBPCFCs at baseline (Month 0), Month 12, and Month 36.

Figure 1. Study Design

PEPITES

356 peanut-allergic subjects (4-11 years)
US, Canada, Australia,
Germany, Ireland

▲
M0

DBV712 250 µg
(n=238)

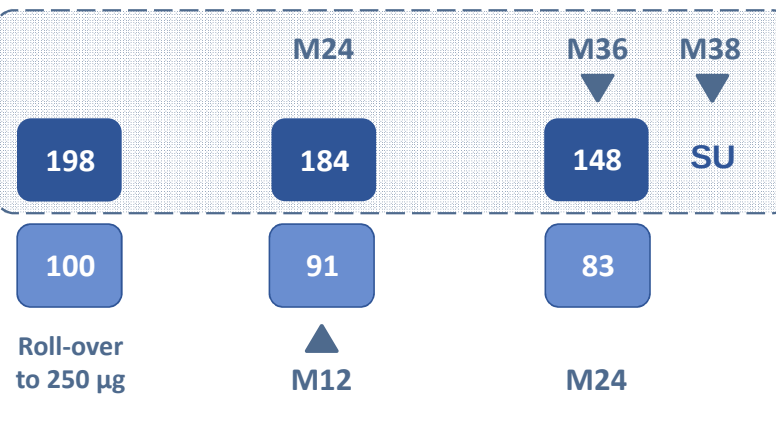
213

▲
M12

Placebo
(n=118)

107

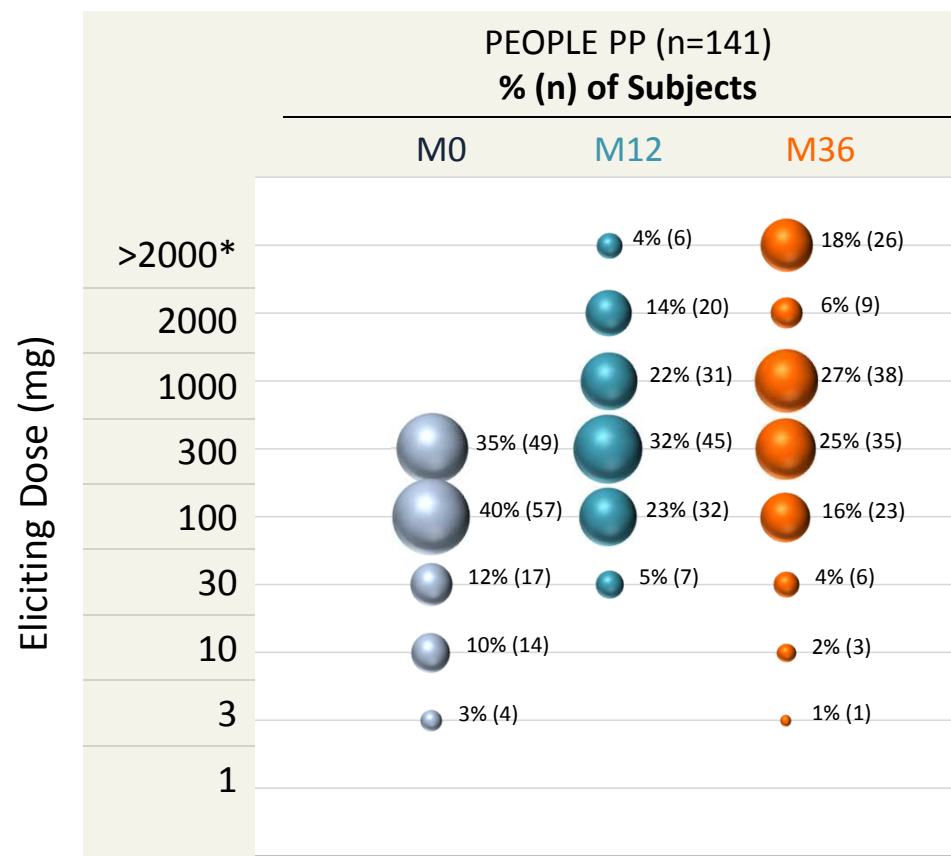
PEOPLE



▲ Double-blind, placebo-controlled food challenge completed.

△ Double-blind, placebo-controlled food challenge planned.

M=month; SU=sustained unresponsiveness.

Figure 2. Proportion of Subjects from Per Protocol Data Set at Each Eliciting Dose (Baseline, Month 12, and Month 36)

*ED >2000 mg included subjects: passing the 2000 mg dose at Month 12 without stopping criteria, passing the 2000 mg dose at Month 36 without stopping criteria, or starting the second dose of 2000 mg at Month 36.

Figure 3. Proportion of Subjects Meeting Prespecified Primary Outcome at Month 12 and Month 36 in PEOPLE Per Protocol Set According to Primary Outcome Criteria in PEOPLE, PEPITES, and OLFUS-VIPES

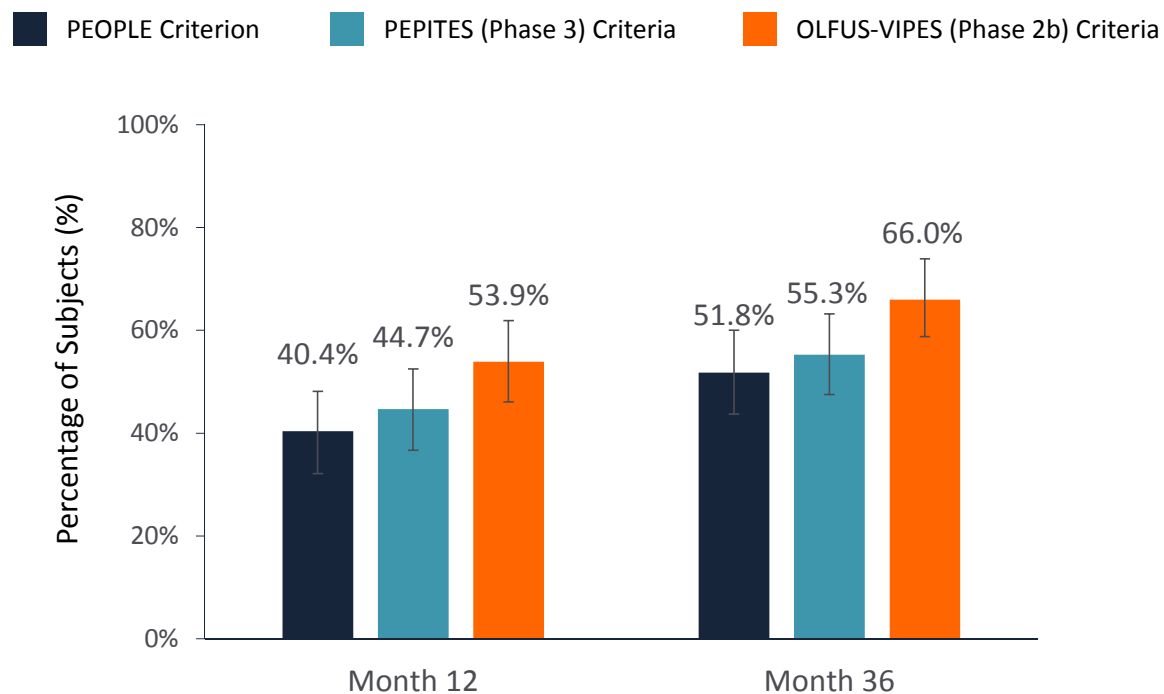


Figure 4A-D. Relative Change from Baseline in Peanut IgG4 (A,C) and IgE (B,D) Over the 3-year Treatment Period in the Per Protocol Data Set (n=141) and by Responder Group

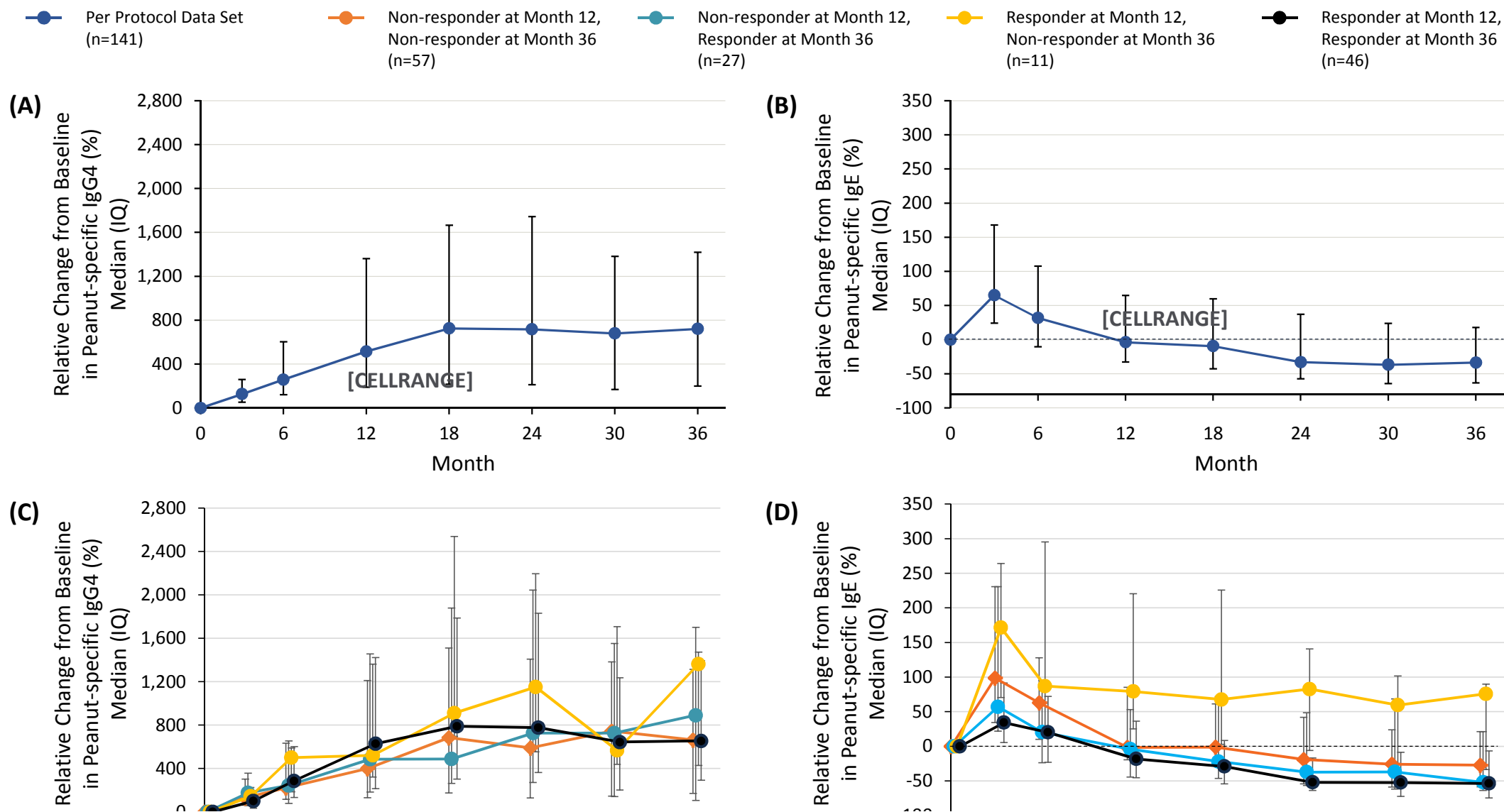


Figure 5. Cumulative Reactive Doses of Peanut Protein at Baseline, Month 12, and Month 36 in the Per Protocol Data Set (n=141)

