

An evaluation of factors influencing response to epicutaneous immunotherapy for peanut allergy in the PEPITES trial

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ABSTRACT

Background: Epicutaneous immunotherapy (EPIT) for peanut allergy is a potential novel immunotherapy that utilizes the unique cutaneous immunologic properties to induce desensitization. A randomized, double-blind, placebo-controlled Phase 3 trial (PEPITES) in peanut-allergic children 4–11 years demonstrated an epicutaneous patch (DBV712) with 250 µg peanut protein was statistically superior to placebo in inducing desensitization following 12 months of daily treatment.

Objective: To investigate what baseline and in-study factors influenced response to DBV712 250 µg, with a focus on patch adhesion, by posthoc analysis of PEPITES data.

Methods: A posthoc multivariate model built with log-transformed Month 12 eliciting dose (ED) as the dependent variable was used to assess the influence of baseline characteristics and patch adhesion. Baseline characteristics and treatment response were also evaluated by stratifying subjects into decile subgroups by patch detachment rates over the 12-month study.

Results: Multivariate analysis identified higher baseline ED and lower baseline peanut-specific IgE as the variables most predictive of higher Month 12 ED, followed by mean daily patch application duration, baseline SCORing Atopic Dermatitis (SCORAD) score, and age. By decile stratification, no association between patch detachment and treatment response was identified for 80% of DBV712-treated subjects. All DBV712-treated subjects, including those with the highest patch detachment rates, demonstrated treatment benefit measured by fold-changes in geometric mean ED.

Conclusion: We identified subject baseline characteristics of higher baseline ED and lower baseline peanut-specific IgE as most predictive of higher Month 12 ED. For the majority of treated subjects, patch detachment did not impact treatment response. A minority of subjects, highly sensitive to peanut at baseline, had lower prespecified responder rates and higher patch detachment rates, yet still benefited from treatment based upon fold-changes in ED.

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BACKGROUND

Epicutaneous immunotherapy (EPIT) is currently under investigation as a novel approach for the treatment of peanut allergy. By utilizing the unique immune properties of the skin, EPIT aims to induce desensitization using microgram amounts of allergen through an epicutaneous patch system applied daily.^{1,2}

DBV712 consists of an ultra-low dose (250 µg, ~1/1000 of a single peanut kernel) of peanut protein extract on an epicutaneous system (or patch) which has defining properties different from the traditional transdermal (TD) patch. During manufacturing, the peanut proteins are evenly deposited onto the backing of an occlusive film through an electrospray process. The primary

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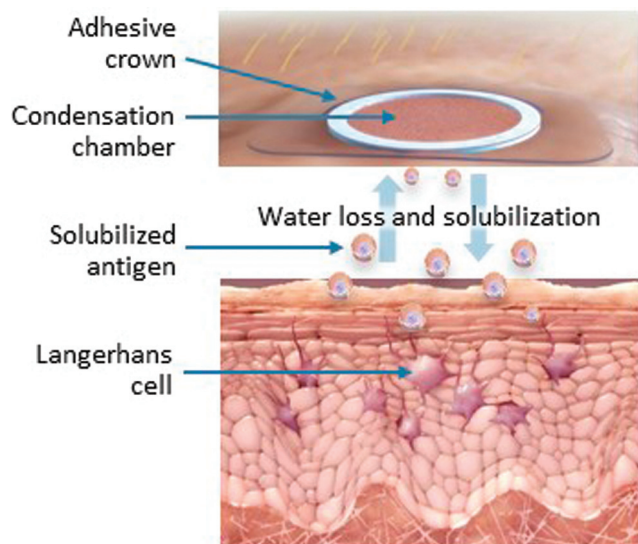


Figure 1. Overview of DBV712 Patch. The DBV712 patch consists of several layers, including an occlusive film onto which the peanut proteins are evenly deposited using an electrospray process. An adhesive foam crown, which forms an occlusive seal around the allergen-containing condensation chamber, allows the film to sit above, not in contact with, the skin. Natural transepidermal water loss and perspiration lead to solubilization of the peanut proteins, and the occlusive chamber leads to increased allergen permeability of the outer layer of the epidermis. This allows small amounts of soluble peanut protein to penetrate the epidermis and to be taken up by antigen-presenting cells (APCs), such as Langerhans cells, which then initiate a unique immunologic response cascade.

attachment element of the DBV712 patch is provided by a highly adhesive foam crown, which forms an occlusive seal around the allergen-containing chamber allowing the film to sit above, not in contact with, the skin (Fig. 1). A polyurethane (PU) covering film acts as a secondary adhesive element to keep the adhesive crown in place, and also reduces the profile of the crown, thereby reducing the risk of incidental detachment by clothing or contact with other materials. The adhesive properties of the DBV712 patch are designed to be sufficiently strong to provide an acceptable level of attachment, but also to minimize pain while preventing damage upon removal from the sensitive, atopic skin of allergic patients. Natural transepidermal water loss and perspiration lead to solubilization of the peanut proteins, and the occlusive chamber leads to increased allergen permeability of the outer layer of the epidermis. This allows small amounts of soluble peanut allergens to penetrate the epidermis and to be taken up by antigen-presenting cells (APCs), which then initiate a unique immunologic response cascade.¹⁻³ Epidermal delivery results in desensitization to the allergen with minimal, if any, direct systemic exposure.

The DBV712 development program included a pivotal Phase 3 randomized, double-blind, placebo-controlled trial, PEPITES, which was designed to assess peanut desensitization in peanut-allergic children aged 4–11 years.⁴ The responder rates (based on predefined primary end point criteria) were 35.3% and 13.6% for DBV712 250 µg (n = 238) and placebo (n = 118), respectively, with a treatment difference of 21.7% and a p-value of <0.001. The 95% confidence interval of the difference was 12.4% to 29.8%, which did not meet the prespecified lower bound margin of 15%, the clinical significance of which is uncertain. However, both the placebo and DBV712 250 µg groups entered the Phase 3 trial with similar baseline geometric mean ED values, 70.4 mg and 78.1 mg, respectively. At the end of Month 12, the active group had an increase in geometric mean ED of nearly fourfold (282.0 mg, approximately one peanut kernel) while the placebo group remained relatively unchanged (79.3 mg) in the intent-to-treat population.

In PEPITES, DBV712 250 µg was applied once daily with no protocol-mandated restrictions related to observation periods following application or activities such as exercise or hot bath/shower, or disruptions during viral infections with fever/other illnesses, or asthma exacerbations. Although DBV712 250 µg has a simple, easy-to-use treatment regimen that was associated with high compliance (98.5% in PEPITES),⁴ this report details further assessment of daily use and factors that may influence treatment response.

OBJECTIVE

The objective of this report was to investigate the influence and relationship of baseline and in-study factors on DBV712 250 µg treatment response with a particular focus on patch adhesion by posthoc analysis of PEPITES data.

METHODS

Study Design and Participants

The study design and clinical assessments of the Phase 3 PEPITES clinical trial have been previously published in detail.⁴ In brief and as above, 356 peanut-allergic subjects aged 4–11 years were randomized 2:1 to receive daily DBV712 250 µg or placebo for 12 months, in a randomized, double-blind, placebo-controlled trial. The prespecified primary study endpoint was based on achieving a Month 12 ED of either ≥300 mg or ≥1000 mg depending on a baseline ED of ≤10 mg or >10 mg, respectively, at the DBPCFC. The proportion of subjects meeting this endpoint is referred to as the “responder rate”.

Key inclusion criteria included a peanut-specific IgE (sIgE) level greater than 0.7 kU_A/L, a peanut skin-prick test (SPT) with a largest wheal diameter of 6 millimeter

or greater (children aged 4–5 years) or 8 millimeter or greater (children aged ≥ 6 years) and an ED (the single highest dose at which a patient exhibited objective signs or symptoms of an immediate hypersensitivity reaction) of 300 mg (approximately one peanut) or less of peanut protein based on a DBPCFC.

As above, the PEPITES protocol did not require any limitations related to patch use around illness, physical activity, etc. Patch removal due to discomfort or itch prior to the recommended application period was at the discretion of the investigator and the parents/subject. Likewise, any treatment related to symptoms at the application site was at the discretion of the investigator. Families were provided with 1% hydrocortisone cream to use as required following patch removal, and oral antihistamine use was permitted. All concomitant medication use was recorded. The study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice (ICH GCP) Guidelines, the Declaration of Helsinki, and all applicable regulatory requirements.

Subject Diary

A subject diary was completed daily during the 12-month study period. Subjects' parents/caregivers were asked to record the date and time of patch application and removal, and to specify if the application duration was as recommended in the protocol, i.e., 6 hours per day the first week, 12 hours per day the second week, and then 24 ± 4 hours per day thereafter. When applicable, the reason for premature patch removal was to be reported as either "personal convenience", "patch fell off", "discomfort", or "other". If the patch detached within 2 hours of application, the parents/caregivers were instructed to replace it. For data analysis, missing data (i.e., the patch was detached without knowing the specific time of detachment) were imputed as having zero hours of attachment to provide a more conservative estimate of daily application hours. Subjects who had at least 28 days of application reported in the 12-month diary ($n = 352/356$) were included in adhesion analyses.

Statistical Analysis

Baseline variables were studied in a posthoc univariate model: baseline ED, peanut-sIgE, age, age at peanut allergy diagnosis, time since peanut allergy diagnosis, SCORing Atopic Dermatitis (SCORAD) score, sex, medical history of atopic dermatitis, medical history of asthma, medical history of other allergy, filaggrin mutation, and race. In addition to these baseline characteristics, variables linked to adhesion of the patches were also studied: average daily application duration, percentage of detached patches, mean of itching (graded daily from 0 to 3 during the first 6 months of

the study), and percentage of patches applied with moderate or severe application site reaction. These variables relative to patch adhesion were collected during the conduct of the treatment and were not defined *a priori*.

A posthoc multivariate model was built with log-transformed Month 12 ED as the dependent variable. From the 22 key baseline and postbaseline variables tested in the univariate analysis (selected based on clinical relevance and suspected impact on M12 ED), variables with a p-value < 0.15 were to be entered in the model. Correlation between selected variables was tested. When several variables correlated (Pearson Correlation Coefficients $\geq 30\%$), the variables with the smallest p-value were selected. The following variables were entered in the multivariate model: average daily application duration, mean of itching, age, sex, baseline ED (log-transformed), baseline peanut-sIgE (log-transformed), and SCORAD (in category: = 0; > 0 and < 15 ; ≥ 15).

A forward selection was performed. Variables were kept in the model if the p-value in the multivariate model was ≤ 0.10 and the p-values of the variables already selected in the multivariate model remained ≤ 0.10 (i.e., the variable added was not a confounding variable). We confirmed model fit by normality of residuals.

Patch Adhesion and Treatment Response

To further evaluate the role of patch adhesion in treatment response to DBV712 250 μg , the PEPITES population (DBV712 250 μg or placebo) was divided into deciles based upon the percentage of patches that detached before the recommended duration (24 ± 4 hours per day) during the 12-month treatment period. Within both groups (DBV712 250 μg or placebo), the first decile represents those 10% of subjects with the fewest patch detachments over the 12 months, and the 10th decile represents the 10% of subjects with the highest percentage of patch detachment. To gain a better understanding of the potential influence of patch detachment, multiple variables (i.e., median daily duration [hours/day], antibody levels, increases in ED, responder rates and itching scores) were evaluated for each of the 10 deciles.

RESULTS

Study Population and Baseline Characteristics

The characteristics of the PEPITES study population have been previously published.⁴ This population included subjects with a relatively high degree of sensitivity to peanut, based upon screening criteria and threshold ED (≤ 300 mg) at entry DBPCFC for inclusion and included a high percentage of children with atopic dermatitis, asthma, and other allergies (Table 1).

Table 1 Demographics and baseline characteristics of subjects in PEPITES

Category	DBV712 250 µg (n = 238)	Placebo (n = 118)
Age, median (Q1, Q3), years	7 (6, 9)	7 (5, 9)
Sex, n (%)		
Male	149 (62.6)	69 (58.5)
Female	89 (37.4)	49 (41.5)
Race/ethnic origin, n (%)		
White	194 (81.5)	96 (81.4)
Black or African American	1 (0.4)	2 (1.7)
Asian	19 (8)	8 (6.8)
Hispanic	2 (0.8)	0
Other ¹	22 (9.2)	12 (10.2)
Peanut-specific IgE, median (kU _A /L)	77.9	101
Q1, Q3 (range)	20, 192 (0.78–1008.4)	29.1, 232 (1.03–1104)
Peanut-specific IgG4, median (mg/L)	0.69	0.74
Q1, Q3 (range)	0.28, 1.39 (0.07–10.2)	0.29, 1.5 (0.07–12.7)
Median eliciting dose (mg peanut protein)	100	100
Q1, Q3 (range)	30, 300 (1–300)	30, 300 (1–300)
Baseline eliciting dose, n (%)		
1 mg	3 (1.3)	3 (2.5)
3 mg	10 (4.2)	7 (5.9)
10 mg	28 (11.8)	10 (8.5)
30 mg	24 (10.1)	19 (16.1)
100 mg	97 (40.8)	40 (33.9)
300 mg	76 (31.9)	39 (33.1)
Medical history, n (%)		
Asthma	117 (49.2)	52 (44.1)
Eczema/atopic dermatitis	139 (58.4)	79 (66.9)
Allergic rhinitis	132 (55.5)	67 (56.8)
Allergy(ies) other than peanut	205 (86.1)	100 (84.7)

IgE = immunoglobulin E; Q = quartile.

Table 2 Multivariate analysis of variables correlated to Month 12 ED in PEPITES

Variable	Parameter Estimate	Standard Error	Pr > t	Standardized Estimate
Intercept	1.81928	0.27368	<0.0001	0
Log-transformed Baseline ED	0.29128	0.05494	<0.0001	0.30641
Log-transformed Baseline IgE	−0.08820	0.02101	<0.0001	−0.24425
Average daily application duration	0.03035	0.00982	0.0022	0.17869
SCORAD in category	0.10747	0.04761	0.0249	0.12814
Age	−0.03161	0.01538	0.0411	−0.11690

ED = eliciting dose; IgE = immunoglobulin E; SCORAD = SCORing Atopic Dermatitis.

Multivariate Analysis

In the multivariate analysis, 5 variables were predictive of a greater ED at Month 12 (Table 2). Higher baseline ED and lower baseline peanut-sIgE were the variables most highly predictive of having a greater absolute ED at Month 12 (1st and 2nd, respectively). The variable with the 3rd highest correlation was

longer average daily patch application duration, followed by higher SCORAD, and then younger age at study baseline. Patch detachment, by quartile and/or by total proportion of premature detachments, was significant in the univariate analysis, but since this variable correlated highly with the average daily application duration, it was not selected for the multivariate model.

Table 3 Baseline characteristics and efficacy outcomes according to deciles of percent of patches detached in subjects randomized to DBV712 250 µg (N = 236)

	N	% Patches Detached Range	Median Daily Duration (hours) (0 imputation) ¹	Median sIgE at Baseline (kU _A /L)	Median sIgE at Baseline (kU _A /L)	Median IgG4 Relative Change (%) ²	Geometric Mean ED				Mean Itching Score ⁴
							Baseline (mg)	M12 (mg)	Ratio M12 to Baseline (95% CI)	Responder Rate at M12 (%) ³	
1 st decile	23	[0.0%–1.1%]	22.5	21.4	18.4	310	137.2	401.7	2.9 (1.5–5.9)	47.8	0.85
2 nd decile	24	[1.2%–2.5%]	22.5	42.8	20.2	444	92.2	305.2	3.3 (1.5–7.3)	37.5	0.89
3 rd decile	24	[2.5%–4.6%]	22.2	71.1	40.3	775	118.0	388.5	3.3 (1.7–6.4)	37.5	1.05
4 th decile	23	[4.7%–6.5%]	22.2	71.6	48.3	351	101.1	393.1	3.9 (1.8–8.5)	43.5	0.84
5 th decile	24	[6.5%–8.6%]	21.7	97.3	58.0	723	102.4	240.6	2.3 (1.1–5.1)	33.3	1.16
6 th decile	24	[8.8%–11.4%]	21.0	89.1	78.2	396	66.9	258.4	3.9 (1.9–7.8)	33.3	1.24
7 th decile	23	[12.0%–15.7%]	20.8	110.0	57.2	735	59.0	308.2	5.2 (2.2–12.3)	43.5	1.21
8 th decile	24	[16.1%–25.3%]	19.1	104.8	51.7	810	50.2	365.1	7.3 (3.3–16.0)	37.5	1.25
9 th decile	24	[25.7%–35.3%]	17.9	90.4	62.4	539	45.6	168.2	3.7 (1.4–9.9)	25.0	1.24
10 th decile	23	[36.9%–88.7%]	12.3	127.0	103.0	293	73.4	193.5	2.6 (1.4–4.8)	17.4	1.09

N = number of subjects with at least 28 patches applied; M = month; ED = eliciting dose; CI = confidence interval.

¹Patches without calculated duration were imputed as 0 hours.

²Relative change in median IgG4 calculated by: $100 \times (M12 - \text{baseline}) / \text{baseline}$.

³Responder rate using missing = failure imputation.

⁴Mean itching score during first 6 months of 12-month diary; scores ranged from 0–3 (0 = none; 1 = mild; 2 = moderate; 3 = severe).

Table 4 Baseline characteristics and efficacy outcomes according to deciles of percent of patches detached in subjects randomized to placebo (N = 116)

	N	% Patches Detached Range	Median Daily Duration (hours) (0 imputation) ¹	Median sIgE at Baseline (kU _A /L)	Median sIgE at h 2 Baseline (kU _A /L)	Median IgG4 Relative Change (%) ²	Geometric Mean ED				Responder Rate at M12 (%) ³	Mean Itching Score ⁴
							Baseline (mg)	M12 (mg)	Ratio M12 to Baseline (95% CI)			
1 st decile	11	[0.0%–0.3%]	23.0	29.0	22.8	0	107.4	62.2	0.6 (0.1–2.4)	18.2	0.21	
2 nd decile	12	[0.5%–1.1%]	23.1	106.8	84.7	8	66.4	93.3	1.4 (0.3–5.8)	16.7	0.05	
3 rd decile	12	[1.3%–1.7%]	22.7	139.0	64.9	12	79.7	80.4	1.0 (0.2–4.1)	8.3	0.02	
4 th decile	11	[1.7%–2.2%]	22.7	38.8	27.8	18	63.9	87.9	1.4 (0.3–5.5)	18.2	0.11	
5 th decile	12	[2.3%–2.5%]	22.9	52.7	39.0	0	87.3	107.7	1.2 (0.4–3.8)	8.3	0.16	
6 th decile	12	[2.6%–3.9%]	22.4	69.0	38.9	6	66.9	78.4	1.2 (0.3–4.9)	16.7	0.14	
7 th decile	11	[4.0%–5.7%]	22.2	152.0	106.0	13	97.2	87.9	0.9 (0.3–2.9)	0.0	0.03	
8 th decile	12	[6.1%–8.5%]	22.0	125.8	88.3	3	88.9	104.1	1.2 (0.4–3.2)	8.3	0.14	
9 th decile	12	[8.7%–15.0%]	21.7	196.5	114.4	18	66.4	66.4	1.0 (0.3–3.3)	16.7	0.13	
10 th decile	11	[17.2%–66.8%]	18.2	145.2	49.1	25	41.7	79.6	1.9 (0.4–9.0)	27.3	0.32	

N = number of subjects with at least 28 patches applied; M = month; ED = eliciting dose; CI = confidence interval.

¹Patches without calculated duration were imputed as 0 hours.

²Relative change in median IgG4 calculated by: $100 \times (M12\text{-baseline})/\text{baseline}$.

³Responder rate using missing = failure imputation.

⁴Mean itching score during first 6 months of 12-month diary; scores ranged from 0–3 (0 = none; 1 = mild; 2 = moderate; 3 = severe).

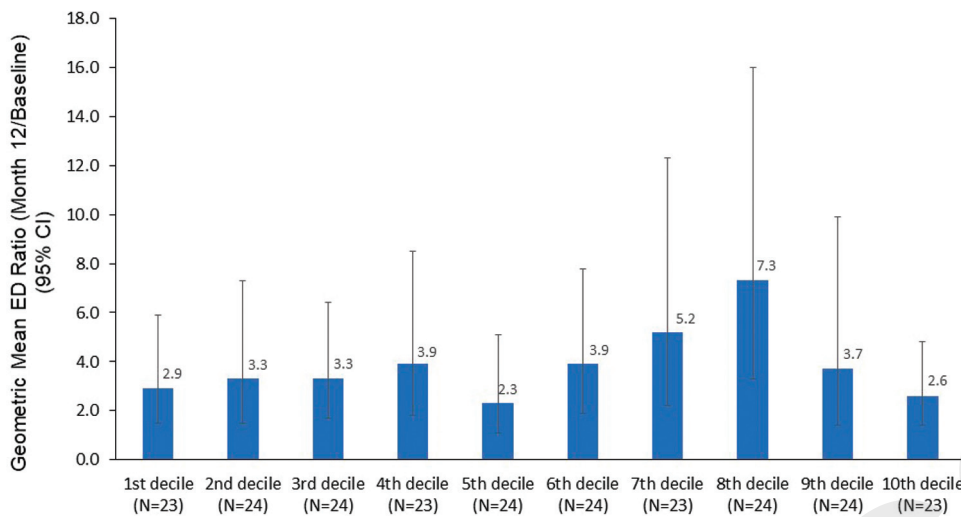


Figure 2. Geometric Mean Eliciting Dose Ratio (Month 12/Baseline) According to Deciles of Patch Detachment in Subjects Treated with DBV712 250 µg (N = 236). Response to treatment in DBV712 250 µg-treated subjects was assessed as the ratio of the geometric mean ED from Month 12 compared to baseline, according to the percentage of patches detached. Subjects were stratified into deciles based on the proportion of detached patches. CI = confidence interval; ED = eliciting dose.

Patch Adhesion and Treatment Response

As described in the Methods section, the PEPITES population was divided into deciles based upon the percentage of patches that detached before the recommended daily duration over the whole 12-month treatment period. Table 3 and Table 4 present the percentage of patches that detached by deciles (1st to 10th), corresponding baseline characteristics, and treatment responses for multiple parameters for the DBV712 250 µg and placebo groups, respectively. For both populations, median baseline peanut-sIgE, Ara h 2, and itch score increased with increasing patch detachment decile, while mean baseline ED decreased with increasing patch detachment deciles. Treatment response as assessed by the PEPITES prespecified primary outcome did not appear to be directly associated with the proportion of patch detachments for DBV712 250 µg subjects within the 1st to 8th patch detachment deciles (80% of the population receiving treatment) (Table 3). For example, those subjects in the 8th decile, who had patch detachment rates of 16.1%–25.3%, had a responder rate of 37.5%, while the 2nd and 3rd deciles had the same 37.5% responder rate, with the percentage of detached patches ranging from 1.2%–2.5% and 2.5%–4.6%, respectively (Table 3).

Response to treatment, as measured by fold changes in ED from baseline to Month 12 was observed across all deciles, including those with the highest rates of patch detachment. For example, DBV712 250 µg-treated subjects with the highest percentage of detached patches (9th and 10th deciles) had multiple fold-increases in GM ED (3.7 and 2.6, respectively) that were similar to those in the deciles with the lowest percentage of detached patches (1st and 2nd deciles: 2.9 and 3.3, respectively) (Table 3, Fig. 2). Furthermore, confidence intervals of the fold change in ED for all deciles were above 1, including deciles 9 (1.4–9.9) and 10 (1.4–4.8) (Table 3, Fig. 2). In addition, there was no

discernable difference in the active arm between median peanut-sIgG4 relative change over the treatment period in those subjects with highest and lowest patch detachment rates, or with lowest median hours of patch application duration (Table 3). The placebo group demonstrated no trends or tendencies in fold changes in ED (Month 12 to baseline ratio), predefined responder rate, or changes in median peanut-sIgG4 relative to the patch detachment deciles (Table 4).

Factors Influencing Patch Adhesion

The level of baseline peanut-sIgE trended higher from the 1st decile to the 10th decile (Table 3). This peanut-sIgE relationship was mirrored by higher IgE against Ara h 2, a peanut component which is well known to correlate with clinical allergy to peanut. In contrast, there was a steady trend of lower baseline ED from the 1st decile to the 10th decile. These data suggest that subjects that tended to have the highest rates of patch detachment are also those with the greatest sensitivity (i.e., lowest ED) and highest sensitization (i.e., highest peanut-sIgE) to peanut protein at baseline. The mean itching scores tended to be higher in the highest detachment deciles, which along with higher baseline peanut-sIgE and lower baseline ED, could indicate a greater overall sensitivity and local reactivity to peanut protein in those subjects experiencing highest patch detachment.

Within the group of subjects treated with DBV712 250 µg, we were unable to find any strong association between baseline atopic dermatitis or SCORAD scores and rates of patch detachment. The presence of atopic dermatitis at baseline tended to be lower in those within the highest patch detachment deciles, with 39.1% of subjects in the 10th decile vs 50.0%–66.7% of subjects in deciles 1–9, suggesting that this baseline factor is not driving higher patch detachment rates. Overall, compliance (calculated based on the number

of patches dispensed versus the number returned) was high and comparable across all deciles (97.2%–100.0%), and did not differ for those with the highest rates of patch detachment (98.6% in the 10th decile). Of the patches recorded as detached prior to the recommended duration in DBV712 250 µg-treated subjects, 13.4% of patches were reported by subjects as being deliberately removed due to discomfort. The median percentage of patches removed prematurely due to discomfort was similar across the deciles, ranging from 0.0%–1.3%, including in the 10th decile (0.3%), suggesting this was not a driving factor for patch detachment.

In subjects who received DBV712 250 µg, median daily duration of patch application was above 20 hours per day across the 1st to 7th deciles of subjects by patch detachment (Table 3), and there was no discernable association between higher detachment rates and lower median daily application duration for these subjects. However, subjects in the 10th decile had appreciably lower median daily duration of application: 12.3 hours (using worst case imputation where missing reports were considered as 0 hours) compared to 17.9 or more hours across the other deciles. This was similarly observed in those subjects receiving placebo, but to a lesser extent (Table 4).

As shown in Table 4, there was a low percentage of detachment in the placebo group across all deciles, and in the majority of subjects (i.e., deciles 1 to 9), patch detachment occurred infrequently. However, similar to the DBV712 250 µg arm, the placebo subjects with highest detachment rates tended to have the lowest baseline ED values and highest peanut-sIgE levels. Although the overall itching scores were lower (relative to the DBV712 250 µg arm), the same trend of higher itching in these most sensitive subjects was observed.

DISCUSSION

Epicutaneous immunotherapy using DBV712 is a novel approach to the management of food allergy and the first therapy of its kind to be under review for approval by the US Food and Drug Administration. While EPIT utilizes a patch, it does not have the same defining properties as transdermal (TD) patches and many principles that characterize use of TD patches (e.g., application time and pharmacokinetic/pharmacodynamic relationships) do not apply to DBV712. While there are patients who respond more and less robustly to any therapy, here we show treatment benefit across the entire cohort treated with DBV712 250 µg.

As recently reported, DBV712 daily application time of at least 12–16 hours/day appears to be adequate for sufficient amounts of peanut protein to be delivered to the skin and to effect desensitization.⁵ The objective of the current report was to further investigate what

baseline and in-study factors influenced treatment response and to assess whether patch detachment, as another measure of application time, had an influence on efficacy measures. Herein, we show that higher baseline ED and lower baseline peanut-sIgE were the variables most highly predictive (1st and 2nd, respectively) of treatment response, as measured by higher ED at Month 12. A minority of subjects were identified with low baseline ED and particularly high baseline peanut-sIgE (a subgroup of subjects who are the most sensitive to peanut protein) who have both lower pre-specified responder rates (by the primary outcome measure) and higher patch detachment rates. In this subgroup, baseline characteristics appeared to drive the lower responder rates; and while the higher detachment rate may have been a contributing factor, a broader assessment of efficacy measured by fold changes in ED revealed similar DBV712 250 µg treatment effects across the population, irrespective of patch detachment rates.

The median daily duration (hours) was markedly lower in subjects receiving either DBV712 250 µg or placebo who were in the highest decile for patch detachment (10th decile, 12.3 and 18.2 hours, respectively) relative to the other respective deciles. The observation that the 10th decile of the placebo arm is characterized as a sensitive subgroup of subjects (i.e., low baseline ED and high baseline peanut-sIgE), consistent with those of the active arm (10th decile), is not likely due to coincidence, but rather confirmation of the role that these baseline parameters play in patch detachment. It is likely, but not proven, that patch detachment in this particularly sensitive subgroup may relate to enhanced itch and scratching at the patch application site, with higher itching scores contributing, at least in part, to the higher detachment percentage in this subgroup.

Induction of specific IgG4 is one of the most reliable immunologic hallmarks of exposure to subcutaneous and oral immunotherapies,^{6,7} and the rise in peanut-specific IgG4 seen across all patch detachment deciles, from 1st to 10th, supports an exposure of adequate duration to drive an immunomodulatory effect of EPIT with DBV712 250 µg across the study population.

SCORAD and age were the 4th and 5th variables, respectively, in the multivariate analysis most highly predictive of higher ED at Month 12, and it is perhaps not surprising that these also emerged. Patients with increased atopic dermatitis severity, as reflected by higher SCORAD results, have been noted to have elevated transepidermal water loss and altered skin barrier function (not related to filaggrin mutations).^{8–10} It may be that these subjects are more efficiently hydrating the peanut patch protein and absorbing allergen delivered with EPIT, although further investigation is required. We previously noted a higher predefined

responder rate in patients treated with DBV712 250 µg among subjects with ongoing atopic dermatitis at baseline versus those without (43.6% versus 29.2%), though the treatment effect versus placebo was similar in the two groups and the interaction p-value was non-significant at 0.8.¹¹ Although the body of literature is not extensive, younger food-allergic patients have generally demonstrated more robust responses to therapy;¹² indeed, this was observed in the DBV712 Phase 2 study, although the study was not designed to assess an age-dependent response.¹³ It has also been hypothesized in the context of peanut oral immunotherapy (OIT) that the immune system and the allergic response may be more modifiable early in life.¹²

Limitations of the current analysis include the post-hoc nature and that the Phase 3 study was not primarily designed to compare response according to geometric mean ED or across deciles of patch detachment. Assessing changes in ED by fold changes provides greater granularity in understanding treatment response, however it may overestimate the clinical impact of those subjects who start from a very low ED, and likewise underestimate the significance of doubling or tripling an ED from 1000 mg to 2000 or 3000 mg. However, quantitative risk assessment (QRA) modeling using US consumption and contamination data suggests that even changes from 10 mg to 100 mg may be clinically relevant in terms of reduction of risk of reactions to accidental exposure to undeclared peanut in packaged foods.¹⁴ Factors were included in the multivariate regression analysis that occurred within the study, rather than at baseline, which is not optimal. However, the two major factors identified were baseline parameters, not in-study factors. In addition, by actively soliciting information on premature patch detachment through daily questioning and reporting in the 12-month subject diaries and raising attention to this among subjects/caregivers, we may have overestimated patch detachments, which may be different and possibly lower in “real world” use.

DBV712 provides a completely different approach to desensitization, applying only 1/1000 of the protein contained in a single peanut kernel each day, with a simple, easy to use dosing regimen that does not require lifestyle modification. Like any other therapy, there will be potential outliers that experience greater or lesser responses. However, the data presented here suggest that for the majority of subjects, patch detachment does not impact the treatment response, and therapeutic benefit is still derived even in the minority of subjects who are characterized as being highly sensitive to peanut protein (by highest baseline peanut-sIgE and lowest baseline ED). These highly sensitive peanut allergy subjects, whose baseline characteristics were associated with treatment-modifying effects, with

baseline peanut-sIgE levels over >100 kU_A/L, are recognized as a subgroup who also tend to be more challenging to manage and less likely to achieve success with therapies such as OIT. Indeed, OIT in these subjects may carry a higher risk for adverse effects, and highly sensitive subjects may not tolerate even the very low initial up-dosing schedules required in OIT.^{15–17} Therefore, the ease of use and low rates of serious adverse events,⁴ coupled with clinically meaningful increases in ED, may present a favorable benefit: risk relative to other therapies such as OIT, which may present greater challenges in this subgroup. Further data arising from the 3- and 5-year open-label extension study will help to further examine accrual of additional benefits from ongoing treatment in these subgroups.

Our analysis suggests that baseline characteristics that profile the most highly sensitive and highly sensitized individuals drive a significant proportion of the patch detachments, and the association with reduced predefined responder rates may be a consequence of these characteristics rather than the adhesive properties of DBV712. Overall, across the baseline sensitivity factors and detachment rates of the entire group, the benefit:risk profile following 12 months of treatment with DBV712 250 µg is viewed as positive.

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