AN EVALUATION OF FACTORS INFLUENCING RESPONSE TO EPICUTANEOUS IMMUNOTHERAPY FOR PEANUT ALLERGY IN THE PEPITES TRIAL

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RATIONALE

- Investigational epicutaneous immunotherapy (EPIT) with DBV712 250 µg for peanut allergy is a novel form of immunotherapy administered via a patch that contains 250 µg of peanut protein (~1/1000 of 1 peanut)[1]
  - The adhesive properties of the DBV712 250 µg patch system are designed to provide an acceptable level of attachment to reduce the risk of incidental detachment while also minimizing pain and damage to the skin upon removal
- The DBV712 250 µg patch has been studied in controlled clinical trials, including the Phase 3 randomized, placebo-controlled PEPITES study, which demonstrated statistically significant superiority to placebo in inducing desensitization to peanut allergy after 12 months of daily treatment in children 4–11 years of age[2]
  - Following patch application in PEPITES, there were no protocol-mandated restrictions to daily activities (eg, exercise, bathing) or required dose interruptions due to viral infections or asthma exacerbations, and compliance remained high (98.5%) throughout the study
- In order to optimize treatment in peanut-allergic individuals, it is important to further assess and understand the factors associated with response to DBV712 250 µg, such as patch adhesion

OBJECTIVE

- To investigate baseline and in-study factors influencing response to treatment with DBV712 250 µg, with a focus on patch adhesion, by post hoc analysis of PEPITES data

METHODS

PEPITES

- In PEPITES, 356 subjects aged 4–11 years were randomized to daily treatment with DBV712 250 µg (n=238) or placebo (n=118)[2]
- The prespecified primary endpoint was the responder rate based on double-blind, placebo-controlled food challenges, which was defined as the proportion of subjects achieving an eliciting dose (ED) at Month 12 of ≥300 mg (for those entering the study with an ED of ≤10 mg) or of ≥1000 mg (for those who entered the study with an ED >10 mg and ≤300 mg)[2]
- Subjects' parents or caregivers completed a daily diary for the 12-month study period, recording the date and time of patch application and removal
  - They also noted whether duration of application met protocol recommendations for 6 hours/day for Week 1, 12 hours/day for Week 2, and 24 ± 4 hours/day thereafter
  - They were instructed to report reasons for premature patch removal as either "personal convenience," "patch fell off," "discomfort," or "other"
  - Parents/caregivers were also instructed to replace the patch if it detached within 2 hours of application

Statistical Analysis: Multivariate Model

- Log-transformed Month 12 ED was the dependent variable for the post hoc multivariate model
- A total of 22 baseline and in-study variables were selected for evaluation in a univariate model, based on clinical relevance and potential impact on the Month 12 ED
- Baseline and in-study variables with a *P* value <0.15 were selected to be entered into the multivariate model; when several variables correlated, those with the smallest *P* values were selected
- Variables entered into the multivariate model were:
  - Average daily application duration
  - Mean of itching scores
  - Age
  - Sex
  - Baseline ED (log-transformed)
  - Baseline peanut-specific IgE (log-transformed)
  - SCORing Atopic Dermatitis (SCORAD) score (in category = 0; >0 and <15; ≥15)
- Forward selection was performed, and variables were retained in the multivariate model if their *P* value was ≤0.10 and already selected variables in the model remained at *P*≤0.10, which helped to eliminate confounding variables

Evaluation of the Role of Patch Adhesion and Treatment Response

- The DBV712 250 µg and placebo populations of PEPITES were divided into deciles based on the percentage of patches that detached before the recommended duration (24 ± 4 hours/day) during the 12-month period
  - The first decile included the 10% of subjects with the fewest patch detachments, while the 10th decile included the 10% with the highest percentage of patch detachments
- Multiple variables (median daily duration in hours, antibody levels, increase in ED, responder rates, and itching scores) were evaluated for each decile
- Fold changes from baseline in the geometric mean (GM) ED were assessed using the ratio of the 12-month ED to the baseline ED

RESULTS

Multivariate Analysis

- Five variables were found to be predictive of a higher ED at Month 12 **(Table 1)**
- Higher baseline ED and lower baseline peanut-specific IgE were the most predictive variables, followed by mean daily patch application duration, higher SCORAD, and younger age at baseline

Table 1. 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 IgE	−0.08820	0.02101	<0.0001	−0.24425
Average daily application duration	0.03035	0.00982	0.0022	0.17869
SCORAD 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.

Patch Adhesion and Treatment Response

- Percentage of patches that prematurely detached by decile, according to baseline characteristics and treatment response for subjects receiving DBV712 250 µg, are shown in **Table 2**
- Mean baseline ED tended to decrease with increasing deciles of patch detachment
- Median baseline peanut-specific IgE, Ara h 2, and itch score tended to increase with increasing patch detachment decile
- Across 80% of the population receiving DBV712 250 µg (first to eighth deciles), the prespecified primary outcome of response rate was not directly associated with increasing patch detachment
- As measured by fold changes in GM ED ratios (Month 12 ED/baseline ED), all subjects treated with DBV712 250 µg demonstrated treatment benefit across all deciles of patch detachment **(Figure 1)**
- There was no discernible difference in the DBV712 250 µg-treated group with regards to change in median peanut-specific IgG4 levels over the treatment period in those with highest and lowest detachment rates

Figure 1. Geometric Mean ED Ratio (Month 12/Baseline) (n=236)

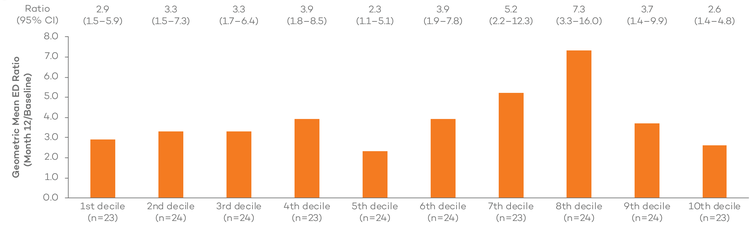

Table 2. Baseline Characteristics and Efficacy Outcomes According to Decile of Patches Detached in Subjects Randomized to Treatment With DBV712 250 µg (n=236)

DECILE	N	% PATCHES DETACHED RANGE	MEDIAN DAILY DURATION (HOURS)*	MEDIAN sIgE AT BASELINE (kU_A/L)	MEDIAN sIgE ARA H 2 AT BASELINE (kU_A/L)	MEDIAN IgG4 RELATIVE CHANGE (%)*	GEOMETRIC MEAN ED			RESPONDER RATE AT M12 (%)*	MEAN ITCHING SCORE‡
							BASELINE (mg)	M12 (mg)	RATIO M12 TO BASELINE (95% CI)		
1st	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
2nd	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
3rd	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
4th	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
5th	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
6th	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
7th	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
8th	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
9th	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
10th	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

CI=confidence interval; ED=eliciting dose; M=month; N=number of subjects with at least 28 patches applied; sIgE=peanut-specific IgE.
*Patches without calculated duration were imputed as 0 hours. †Relative change in median IgG4 calculated by 100 × (M12 − baseline)/baseline. ‡Responder rate using missing = failure imputation.
§Mean itching score during first 6 months of 12-month diary; scores ranged from 0–3 (0=none, 1=mild, 2=moderate; 3=severe).

Factors Influencing Patch Adhesion

- Subjects with the highest rates of patch detachment tended to have the greatest sensitivity to peanut protein and highest sensitization at baseline, as evidenced by the lowest EDs and the highest peanut-specific IgE **(Table 2)**
  - In addition, mean itching scores tended to be higher in the higher detachment deciles, suggesting greater sensitivity and local reactivity to peanut protein in those with the highest patch detachment
  - Similar trends were observed in the placebo-treated group (*data not shown*)
- No strong associations were seen between baseline atopic dermatitis or SCORAD scores and rates of patch detachment (*data not shown*)
- Compliance ranged from 97.2% to 100% across all deciles, including 98.6% in those within the tenth decile
- Median duration of patch application was more than 20 hours/day across the first to seventh deciles in DBV712 250 µg-treated subjects

CONCLUSIONS

- Higher baseline ED and lower baseline peanut-specific IgE were the variables most predictive of higher Month 12 ED following treatment with DBV712 250 µg
- For at least 80% of treated subjects, patch detachment did not appear to impact treatment response
- An increase in peanut-specific IgG4 was observed across all deciles of patch detachment, supporting the view that exposure to DBV712 250 µg was of adequate duration in the treated population to drive an immunomodulatory response
- A minority of subjects who were highly sensitive to peanut at baseline had lower prespecified responder rates and higher patch detachment rates, yet still benefited from treatment with DBV712 250 µg based upon fold changes in ED

REFERENCES

1. Fleischer DM, et al. *Allergy Asthma Proc.* 2020;41:1-10. **2.** Fleischer DM, et al. *JAMA.* 2019; 321:946–955.

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