

Evaluation of daily patch application duration for epicutaneous immunotherapy for peanut allergy

David M. Fleischer, M.D.,¹ Jonathan M. Spergel, M.D., Ph.D.,² Edwin H. Kim, M.D.,³ Dianne E. Campbell, M.D., Ph.D.,^{4,5} Todd D. Green, M.D.,^{4,6} Katharine J. Bee, Ph.D.,⁴ Romain Lambert, M.S.,⁴ Terrance Ocheltree, Ph.D.,⁷ and Hugh A. Sampson, M.D.^{4,8}

ABSTRACT

Background: Epicutaneous immunotherapy is a potential novel immunotherapy that utilizes unique cutaneous immunologic properties. In a phase III, randomized, double-blind, placebo controlled clinical trial, an epicutaneous patch (DBV712) with 250 µg of peanut protein applied once daily for 12-months was statistically superior to placebo in desensitizing children with peanut allergy (ages 4–11 years) (N = 356).

Objective: To assess the relationship between the hours of daily application time and the efficacy of DBV712 250 µg.

Methods: DBV712 250 µg was applied to 30 nonallergic volunteers for various durations from 2 to 24 hours and then assayed for residual peanut protein. Patch application data from the phase III clinical trial were analyzed post hoc according to prespecified responder rates and changes in the eliciting dose (ED), as measured by the geometric mean (GM) ED ratio (12 months/baseline).

Results: Following application, there was a marked decrease in peanut protein on the patches from 2 to 12 hours. After 12 hours, the median peanut protein recovered was below quantification limits. The median daily patch application duration in subjects from the phase III clinical trial was 21.1 hours (DBV712 250 µg) and 22.4 hours (placebo). Ninety-five percent of the treated population achieved >10 hours per day mean application. Response rates and GM ED ratios were similar among subjects across a range of application durations; e.g., in those with a mean duration of >10 hours, the response rate was 36.6% and the GM ED ratio was 3.8, comparable with 42.6% and 4.0, respectively, in those with a mean duration of >20 hours. In DBV712 250 µg subjects with >16 hours mean application duration (84.5% of the treated population), the response rate was 38.8% versus 13.4% for placebo (difference, 24.4% [95% confidence interval, 15.5–34.0%]; $p < 0.001$).

Conclusion: An evaluation of residual peanut protein on patches following application and post hoc analysis of phase III data strongly suggest that allergen delivery is attained with 12–16 hours of daily patch application time, sufficient to drive clinically meaningful desensitization to peanut after 12 months.

(Allergy Asthma Proc 41:278–284, 2020; doi: 10.2500/aap.2020.41.200045)

Investigational epicutaneous immunotherapy (EPIT) is a novel form of immunotherapy that utilizes the unique immune properties of the skin to deliver allergen directly to antigen-presenting cells (APC) in the epidermis and dermis, which in turn initiates a process of desensitization.^{1–3} Delivery of the allergen to the

epidermis is achieved by an epicutaneous patch system that creates a condensation chamber, with a roof of occlusive film electrostatically coated with peanut protein, held above the skin by a circular crown of adhesive foam (Fig. 1). This chamber allows natural transepidermal water loss and perspiration to

From the ¹Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado; ²Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; ³University of North Carolina School of Medicine, Chapel Hill, North Carolina; ⁴DBV Technologies, Montrouge, France; ⁵Children's Hospital at Westmead, Sydney, Australia; ⁶University of Pittsburgh Medical Center Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; ⁷Certara, Princeton, New Jersey; and ⁸Icahn School of Medicine at Mount Sinai, New York, New York

D.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 Intrimmune Therapeutics; has received honorarium for lectures from DBV Technologies, and receives royalties from UpToDate. J.M. Spergel reports consultancy fees from DBV Technologies, Sanofi/Regeneron, Kaleo, and Novartis; speaker fees from Abbott and Regeneron; royalties from UpToDate, and grants to his institution from DBV Technologies, Aimmune Therapeutics, Sanofi/Regeneron, the National Institutes of Health (NIH), Food Allergy Research and Education (FARE), and End Allergies Together. E.H. Kim reports consultancy with Aimmune Therapeutics, DBV Technologies, AllerGenis, Allakos, Ukko,

ExVivo Labs, and Vibrant America; clinical medical advisory board membership with DBV Technologies; and receipt of grant funding from the NIH/National Institute of Allergy and Infectious Diseases (NIAID), the NIH/National Center for Complementary and Integrative Health, FARE, and the Wallace Research Foundation. T. Ocheltree reports consultancy for DBV Technologies. H.A. Sampson is an employee of DBV Technologies, reports receiving consultancy fees from N-Fold Therapeutics, grant funding from the NIH/NIAID, and royalties from Elsevier. D.E. Campbell, T.D. Green, K.J. Bee, and R. Lambert are employees of DBV Technologies

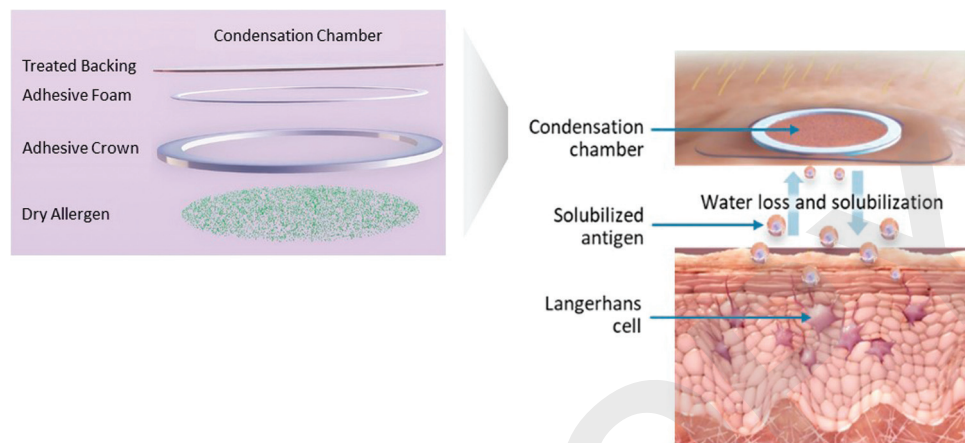
The study was sponsored by DBV Technologies Medical Creative Partners (formerly CréaBio Rhône-Alpes) assisted in the recruitment of participants for the SOLAR study. Stef Koppelman, Ph.D., a consultant for DBV Technologies, provided input to the study methodology. Aurélie Peillon, an employee of DBV Technologies, provided statistical support

Address correspondence to David M. Fleischer, M.D., Children's Hospital Colorado, 13123 E 16th Ave, Box B518, Aurora, CO 80045

E-mail address: david.fleischer@childrenscolorado.org

Copyright © 2020, OceanSide Publications, Inc., U.S.A.

Figure 1. The DBV712 epicutaneous patch. The DBV712 epicutaneous patch system includes a condensation chamber consisting of an occlusive film (treated backing) electrostatically coated with dry allergen that is separated from the skin by an adhesive crown. This chamber allows natural transepidermal water loss and perspiration to solubilize the peanut proteins, which are then captured by epidermal antigen-presenting cells, including Langerhans cells.



solubilize the proteins, and increases permeability of the outer layer of the epidermis, allowing for efficient delivery of allergen to epidermal APCs. Once the allergen is captured by the resident APCs, it is then transported to regional lymph nodes *via* the lymphatic system, allowing the allergen to largely bypass the systemic circulation.⁴ While traditional drug desensitization and food oral immunotherapy protocols are thought to rely upon disarming mast cells and basophils, at least in the early phase, mechanistic studies suggest that EPIT-induced immunomodulation is dependent on epigenetic modifications and the generation of a unique long-lived population of allergen-specific T regulatory cells.^{3,5}

EPIT with DBV712 250 µg peanut protein (~1/1000 of one peanut) applied once daily for 12 months has been shown to be efficacious in peanut-allergic children ages 4–11 years in a randomized, double-blind, placebo controlled pivotal phase III trial, Peanut EPIT Efficacy and Safety (PEPITES) study.⁶ Clinical trial outcomes across the DBV712 development program have been assessed using changes in peanut eliciting dose (ED) over the course of treatment in comparison with subjects receiving placebo during a double-blind placebo controlled food challenge (DBPCFC), consistent with recommendations by the U.S. Food and Drug Administration.^{6–8} In PEPITES, the prespecified primary endpoint compared responder rates between treatment groups: 35.3% and 13.6% for DBV712 250 µg ($n = 238$) and placebo ($n = 118$), respectively, with a difference of 21.7% and a p value of <0.001 ; the 95% confidence interval (CI) of the active/placebo difference was 12.4%–29.8%, not meeting the $\geq 15\%$ threshold prespecified for a positive trial result, although the clinical relevance of this remains to be determined.⁶ Sixty-three percent of subjects experienced an improvement in ED following treatment, with the odds of improving more than four times more likely with treatment. Increasing the ED should reduce the

risk of reaction to accidental ingestion, a primary goal of potential therapies for families of food-allergic children.⁹ Indeed, based on quantitative risk assessment (QRA) analysis by using real-world consumption and peanut contamination data, subjects in the PEPITES study treated with DBV712 250 µg for 12 months are predicted to experience up to a 93% relative risk reduction in accidental ingestion reactions as a result of peanut-contaminated packaged goods and restaurant meals.^{10,11} These analyses demonstrate that there are clinically meaningful implications of increasing an ED that are likely to be highly relevant to peanut-allergic patients and their families.

Throughout the DBV-sponsored phase II and phase III studies of DBV712 250 µg, the recommended duration of patch application in children on the interscapular region of the back has been 24 ± 4 hours. Evidence from animal studies demonstrated that, following application of the epicutaneous patch, allergen capture and internalization by epidermal APCs was observed within the first 2 hours of patch application, with ~80% of epidermal APCs showing evidence of allergen acquisition by 6 hours.⁴ Analysis of data suggest that a full 24 hours of adhesion may not be necessary to derive therapeutic benefit. However, unlike a transdermal patch, the uptake of miniscule amounts of the active medicinal product (peanut protein) from the DBV712 250-µg patch cannot be quantified within APCs, and traditional pharmacokinetic and pharmacodynamic relationships are not applicable. Thus, an evaluation of clinical trial data was completed to assess the relationship between the daily application duration (hours) and desensitization, as measured by changes in ED.

Objective

The objectives were to assess the timing of the protein release from DBV712 250 µg and to evaluate the

treatment effect based on wear time. In order to achieve these, we undertook two separate avenues of investigation presented herein. The first study was an *in vivo* assessment of residual peanut protein on patches after varying durations of application across a 24-hour time period, conducted in healthy volunteers (SOLAR study). Additionally, we undertook a detailed *post hoc* analysis of daily patch application duration and changes in ED by using data collected during the phase III PEPITES clinical trial.

METHODS

SOLAR Study

The SOLAR study was a phase I, single-site, clinical study designed to evaluate protein release by assessing the amount of residual peanut protein present on DBV712 250- μ g patches at different time points following application on the skin of adult healthy volunteers. Thirty adult (18–25 years old), healthy, non-atopic volunteers were recruited to participate at the CréaBio Rhône-Alpes research center within Givors Hospital in Givors, France. The clinical phase consisted of two consecutive days at the study center and a follow-up visit 4 weeks after the clinical phase. All subjects underwent a peanut skin prick test (SPT) and a serum peanut immunoglobulin E (IgE). Ethics approval for the study was granted. The study was conducted in accordance with the International Council for Harmonization Good Clinical Practice Guidelines, the Declaration of Helsinki, and all applicable regulatory requirements.

Subjects were required to be regularly consuming peanut and to have no history of IgE-mediated peanut allergy, with peanut-specific IgE ≤ 0.1 kU_A/L and negative SPT to undiluted peanut extract. Other major exclusion criteria included any other food or aeroallergen allergy, dermatologic disease, or antihistamine treatment within 6 months of the screening visit.

Each subject had a total of 10 patches applied over the study duration: eight DBV712 250- μ g patches and two placebo patches (without peanut protein), applied for a maximum duration of 24 hours. Eight patches (six DBV712 250 μ g and two placebo) were applied to the back (intrascapular region), and two (both DBV712 250 μ g) were applied to the arm (medial and lateral aspect of the nondominant upper arm). The application sites on the back were identical to those used in the phase II and III clinical trials. Patches on the back were removed after 2, 6, 12, and 16 hours (one patch each), and 24 hours (two patches), while patches on the arm and placebo patches were removed after 24 hours. For the $t = 0$ analysis, patches were directly assayed without application.

At each time point, the patches were removed and temporarily stored on dry ice before being transferred at -20°C for intermediate storage and before shipment

to a centralized facility (Bertin Pharma, Gif-sur-Yvette, France). The patches were assayed for residual peanut protein content remaining in the patch chamber (total peanut protein by the Bradford assay and peanut allergen Ara h 6 by enzyme-linked immunosorbent assay). Ara h 6 was selected as the most appropriate peanut component to measure because it is methodologically more straightforward to accurately analyze, with Ara h 6 having fewer isoforms than Ara h 2. Additionally, both are clinically relevant and potent peanut components that induce IgG4 during EPIT with DBV712 250 μ g.¹² Of the two active and control patches applied on the back for 24 hours, one was randomly selected for assay for each subject. The lower limit of quantification (LLOQ) was 35 μ g for total peanut protein and 0.9 μ g for Ara h 6. Values for total protein and Ara h 6 below the LLOQ were imputed as 35 μ g and 0.9 μ g, respectively.

PEPITES Study, Post Hoc Analysis

The study design and clinical assessments of the phase III PEPITES clinical trial have been previously published in detail.⁶ In brief, 356 subjects ages 4–11 years (median 7 years in both active and placebo arms) were randomized 2:1 to receive daily DBV712 250 μ g or placebo for 12 months in a double-blind, randomized controlled trial. To be included in the study, all subjects needed to react on DBPCFC, based on a standardized scoring system requiring a sufficient level of objective signs of an IgE-mediated reaction, to an ED of ≤ 300 mg. The prespecified primary study endpoint was based on achieving a Month 12 ED of either ≥ 300 mg (for those entering with an ED of ≤ 10 mg) or ≥ 1000 mg (for those entering with an ED of > 10 mg and ≤ 300 mg) at the DBPCFC.

A subject diary was completed daily during the 12-month study period. Subjects' parents or 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 specified as either "personal convenience, patch fell off, discomfort, or other." If the patch detached within 2 hours of application, the parents and caregivers were instructed to replace it.

A *post hoc* analysis of phase III data according to the average daily duration (hours) was performed. Subjects with at least 28 patches recorded in the diary were considered, as per the study protocol and prespecified study analysis plan. When the daily duration was unable to be calculated (*e.g.*, missing data), the duration was imputed as 0 hours. The geometric means (GM) of baseline and Month 12 ED (back-transformed

Table 1 Residual total peanut protein remaining in the patch chamber over time when applied to the back

Total Peanut Protein	Time Applied to Back (Active)				
	2 hr (n = 30)	6 hr (n = 30)	12 hr (n = 30)	16 hr (n = 30)	24 hr (n = 30)*
Patches analyzed (n)	30	28	30	29	30
Mean $\pm$ standard deviation, μg per patch	168.9 $\pm$ 59.1	92.1 $\pm$ 52.9	43.0 $\pm$ 15.9	36.2 $\pm$ 6.1	35.2 $\pm$ 0.9
Median, μg per patch	199.5	92.0	35.0 [#]	35.0 [#]	35.0 [#]
Q1, Q3, μg per patch	137.0, 213.0	35.0, 129.0	35.0, 47.0	35.0, 35.0	35.0, 35.0

*The primary endpoint.

[#]The total peanut protein lower limit of quantification = 35 μg /patch; the values below the lower limit of quantification were replaced by 35 μg . The total peanut protein upper limit of quantification = 235 μg /patch; values above the upper limit of quantification were replaced by 235 μg . The total peanut protein content was 261 μg /patch.

means of log-transformed ED values) as well as the corresponding ratio were calculated for subjects with >10, >12, >14, >16, >18, and >20 hours. In the case of withdrawal, the subjects were considered as nonresponder (missing = failure) with a baseline ED carried forward at Month 12.

RESULTS

SOLAR Study

Thirty-two subjects were screened, and two were excluded for having a serum peanut-specific IgE level >0.1 kU_A/L. The remaining 30 subjects met inclusion criteria, with negative peanut SPT and undetectable peanut-specific IgE levels; 16 of 30 (53.3%) were female, and the mean $\pm$ standard deviation age at inclusion was 21.2 $\pm$ 2 years (range, 18–25 years). Overall, 30 active patches from these 30 subjects were assayed for each duration of application on the back (2, 6, 12, 16, and 24 hours) and medial and lateral aspects of the upper arm (24 hours) as well as 30 placebo patches from the back (24 hours); of the 210 patches, 3 were unable to be assayed for residual protein content because of technical issues.

The amount of residual total peanut protein present on the patch decreased from 2 to 12 hours of application on the back (Table 1 and Fig. 2). After 6 hours, the median amount of peanut protein remaining on the patch was 92 μg (from 261 μg at baseline). After 12 hours, the median amount of residual total peanut protein on the patch was below the LLOQ of the assay of 35 μg . Further hours of application time, 16 or 24 hours, confirmed the observation at 12 hours (*i.e.*, below the LLOQ). The quantities of peanut protein remaining after 24 hours on the arm were similar relative to the back.

Ara h 6 levels followed a similar trend. Quantities tended to decrease from 2 to 12 hours of application,

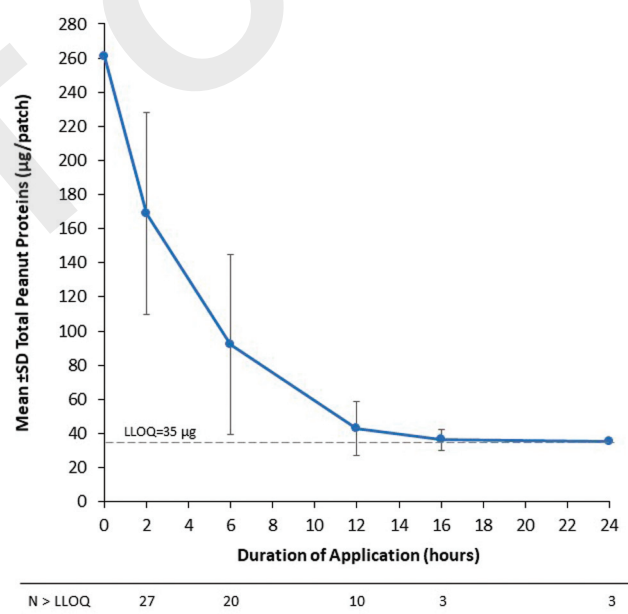


Figure 2. Mean total peanut proteins remaining in the chamber of patches applied on the back over time. The mean amount of residual total peanut protein remaining in the patch chamber was assessed at 2, 6, 12, 16, and 24 hours after application to the back. The time 0-hour value was determined by assessing the initial protein content on the patch before placement. Samples with unquantifiable total peanut proteins were assigned the lower limit of the quantification value of 35 μg . LLOQ = lower limit of quantification; N = number of patches with quantifiable peanut proteins at each time point.

followed by a plateau between 12 and 24 hours of application. There was a strong correlation ($R^2 = 0.9186$) between the two assay methods, supporting similar kinetics of release of both total peanut protein and Ara h 6 from the patch.

Table 2 Response rate and geometric mean eliciting dose according to average duration of daily patch application

Average Daily Duration of Application*	N		Responder Rate, % [#]				Geometric Mean ED DBV712 250 µg		
	DBV712 250 µg (n)	Placebo (n)	DBV712 250 µg (%)	Placebo (%)	Difference in Responder Rate (95% CI)	p	Baseline, mg	Month 12, mg	Ratio Month 12/ Baseline (95% CI)
>10 hr	224	116	36.6	13.8	22.8 (13.2–31.1)	<0.001	79.0	301.8	3.8 (3.0–4.9)
>12 hr	217	116	37.3	13.8	23.5 (13.9–31.9)	<0.001	80.5	314.5	3.9 (3.1–5.0)
>14 hr	214	113	37.4	14.2	23.2 (13.4–31.7)	<0.001	82.5	316.3	3.8 (3.0–4.9)
>16 hr	201	112	38.8	13.4	25.4 (15.5–34.0)	<0.001	84.0	328.6	3.9 (3.0–5.0)
>18 hr	184	109	39.7	13.8	25.9 (15.6–34.8)	<0.001	84.3	332.9	3.9 (3.0–5.1)
>20 hr	148	99	42.6	13.1	29.4 (18.3–39.1)	<0.001	89.2	354.5	4.0 (3.0–5.3)

N = number of subjects with at least 28 patches applied; PEPITES = Peanut EPIT Efficacy and Safety; ED = eliciting dose; CI = confidence interval.

*Patches without a calculated duration were imputed as 0 hours.

[#]Predefined response criteria in the PEPITES study.

PEPITES Study Post Hoc Analysis

Data from the PEPITES phase III study were analyzed *post hoc* to gain a comprehensive understanding of the relationship between the duration of daily patch application and measures of response to treatment. Of the 356 subjects in PEPITES, 355 subjects entered at least one record into the 12-month diary. The median (quartile [Q]1, Q3) percentage of days without patch application was 3% (1.1%, 7.4%) for subjects receiving DBV712 250 µg (*n* = 238) and 3% (1.1%, 6.3%) for placebo subjects (*n* = 117). The median (Q1, Q3) number of patches applied over the 12-month study period was 363 (345, 372) for DBV712 250 µg subjects and 362 (349, 370) for placebo subjects.

Overall, 352 of 356 subjects had 12-month diary data that met the criteria for analysis for the duration of application (see the methods section). The average duration of patch application across all subjects was within or close to the recommended wear time of 24 ± 4 hours. From the 12-month subject diary, the median (Q1, Q3) average duration of daily patch application was slightly lower in the DBV712 250-µg group than in the placebo group: 22.2 (19.9, 22.9) hours per day versus 23.0 (22.5, 23.4) hours per day. Even with worse case imputation (missing data are counted as 0 hours), the median (Q1, Q3) average duration of patch application remained >20 hours, 21.1 (18.3, 22.3) hours in the DBV712 250-µg group versus 22.4 (21.5, 23.0) hours in the placebo group.

The study population was assessed by mean hours of patch application over the 12-month period (Table 2). The responder rate in 95% (224/236) of the DBV712

250-µg arm ranged from 36.6% (>10 hours) to 42.6% (>20 hours) based on the mean daily application duration. In DBV712 250 µg-treated subjects with >16 hours mean duration of application, representing 85.2% (201/236) of the treated population, the response rate was 38.8% (78/201) compared with 13.4% (15/112) for placebo with a treatment difference of 25.4 points (*p* < 0.001) and a 95% CI of 15.5–34.0%.

To better assess the treatment response across the whole population, we measured ED fold changes by the GM ED ratio comparing 12 months with baseline. Fold changes in GM ED ranged from 3.8 to 4.0 across all the subjects who had mean daily patch application durations between >10 and >20 hours, with a lower bound of the 95% CI exceeding 3.0 for all subgroups. Additionally, as seen in Fig. 3, GM ED fold changes were similar in the groups with mean daily patch application of >12 to ≤16 hours (*n* = 16) and of >16 hours (*n* = 201): 3.8 (95% CI, 1.4–10.4) and 3.9 (95% CI, 3.0–5.0), respectively.

DISCUSSION

Investigational EPIT is a novel form of immunotherapy, which has been shown to induce significant desensitization to peanut in peanut-allergic children during phase II and phase III double-blind, randomized controlled trials using a daily application of an ultralow dose of peanut protein (~1/1000 of one peanut) via the skin.^{6,7} The DBV-sponsored phase II and phase III study protocols recommended a daily application time of 24 ± 4 hours each day, and once-a-day

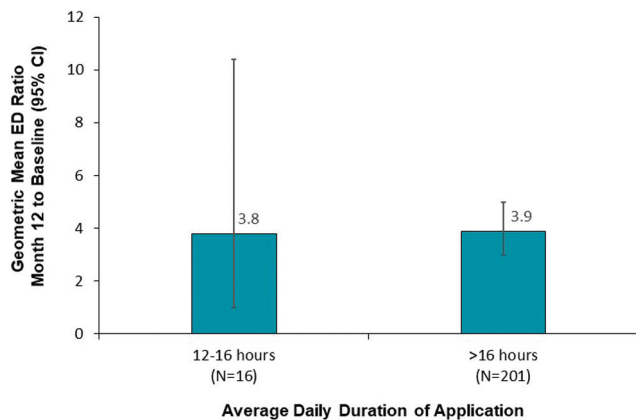


Figure 3. Treatment response according to GM ED ratio (Month 12/baseline [95% confidence interval {CI}]) by average daily duration of application in subjects treated with DBV712 250 µg. Response to treatment in DBV712 250 µg-treated subjects was assessed as the ratio of the GM ED from Month 12 compared with baseline, according to 12–16 hours and >16 hours of patch application. The GMs of baseline ED and Month 12 ED were back-transformed means of log-transformed ED values. In the case of withdrawal, subjects were considered as nonresponder (missing = failure), with a baseline ED carried forward at Month 12. When the daily duration was unable to be calculated (e.g., missing data), the duration was imputed as 0 hours. GM ED with 95% CI are shown. GM = geometric mean; ED = eliciting dose.

dosing at a consistent time of day may be beneficial for some patients and families for behavioral and compliance reasons. The two distinct data sets presented here, however, suggest that a daily application time of at least 12–16 hours may be sufficient both to allow peanut protein to be absorbed from the epicutaneous system and to induce a treatment response.

The results of the SOLAR study clearly showed that the majority of peanut protein has been released from the epicutaneous system within the first 12 hours of application. More than 60% of the initial dose is no longer on the film of the patch chamber after 6 hours and, after 12 hours, the median amount was below the LLOQ of the assay.

We compared and correlated the SOLAR study results with the *post hoc* analysis of the phase III randomized, double-blind, placebo controlled PEPITES study. Here, 95% of the study population receiving active treatment achieved a mean daily application time of >10 hours over the course of 12 months. The fold change in ED from the end of study to baseline showed consistent results for each subgroup, ranging from 3.8 to 4.0. Moreover, for all subjects who obtained a mean daily duration of application time of >16 hours, not only was the responder rate and ED fold change significantly different from that of placebo, but 85.2% of the study population

receiving treatment also met the criteria of having a lower bound of the 95% CI of >15% greater than that of placebo.

Limitations of the current study include that the SOLAR study was conducted on young adults not children, who are the current target population for therapy. While epidermal permeability in adults may be different from that in children ages 4–11 years, given data from several studies demonstrating that transepidermal water loss decreases during childhood, we do not have reason to suspect that protein solubilization would occur any less rapidly in children.^{13,14} Also, as detailed above, the SOLAR study specifically investigates residual peanut on the patch as a proxy for the amount of peanut antigen absorbed through the skin. Measurement of the specific amount of peanut absorbed by APCs would be ideal but would be practically and ethically problematic in humans, requiring numerous serial skin biopsies; animal data do provide a high degree of circumstantial evidence, where allergen capture and internalization by epidermal APCs was observed within the first 2 hours of patch application, with ~80% of epidermal APCs showing evidence of allergen acquisition by 6 hours in the mouse model when using epicutaneous peanut.⁴ In addition, while treatment benefit is similar in terms of GM ED fold changes in the >12 to ≤16 hours ($n = 16$) versus the >16 hours ($n = 201$) mean daily application duration groups (Fig. 3), the PEPITES study was not designed to compare varying application durations, and these *post hoc* results should be interpreted with this in mind.

CONCLUSION

The concept of shared decision-making with respect to potential food allergy immunotherapies has justifiably received increased attention recently, concurrent with the significant progress in desensitization that has been made over this century.^{15,16} Conversations around potential treatment options should involve a thorough assessment of the overall benefit: risk profile, including factors such as efficacy, safety, and practicality. Clinical trial protocols with DBV712 250 µg have demonstrated high compliance and low numbers of withdrawals due to adverse events and have not required any dosing modifications or restrictions around exercise or illness.^{6,7} While efficacy in a clinical trial is defined based on ideal/controlled circumstances, effectiveness refers to real-world performance.¹⁷ In conclusion, the results presented here and previously suggest that DBV712 250 µg may provide a practical and effective approach to peanut allergy immunotherapy in children ages 4–11 years and that a daily application time of at least 12–16 hours could be sufficient to achieve this goal.

REFERENCES

1. Bird JA, Sánchez-Borges M, Ansotegui IJ, Ebisawa M, Ortega Martell JA. Skin as an immune organ and clinical applications of skin-based immunotherapy. *World Allergy Organ J*. 2018; 11:38.
2. Wang J, Sampson HA. Safety and efficacy of epicutaneous immunotherapy for food allergy. *Pediatr Allergy Immunol*. 2018; 29:341–349.
3. Tordesillas L, Mondoulet L, Blazquez AB, Benhamou P-H, Sampson HA, Berin MC. Epicutaneous immunotherapy induces gastrointestinal LAP⁺ regulatory T cells and prevents food-induced anaphylaxis. *J Allergy Clin Immunol*. 2017; 139:189–201.e4.
4. Dioszeghy V, Mondoulet L, Dhelft V, Ligouis M, Puteaux E, Benhamou P-H, et al. Epicutaneous immunotherapy results in rapid allergen uptake by dendritic cells through intact skin and downregulates the allergen-specific response in sensitized mice. *J Immunol*. 2011; 186:5629–5637.
5. Kulis MD, Patil SU, Wambre E, Vickery BP. Immune mechanisms of oral immunotherapy. *J Allergy Clin Immunol*. 2018; 141:491–498.
6. Fleischer DM, Greenhawt M, Sussman G, Bégin P, Nowak-Wegrzyn A, Petroni D, et al. Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: the PEPITES randomized clinical trial. *JAMA*. 2019; 321:946–955.
7. Sampson HA, Shreffler WG, Yang WH, Sussman GL, Brown-Whitehorn TF, Nadeau KC, et al. Effect of varying doses of epicutaneous immunotherapy vs placebo on reaction to peanut protein exposure among subjects with peanut sensitivity: a randomized clinical trial. *JAMA*. 2017; 318:1798–1809.
8. Food and Drug Administration Center for Biological Evaluation and Research (CBER). Allergenic Products Advisory Committee Briefing Document. Clinical development of allergen immunotherapies for the treatment of food allergy. January 21, 2016 [cited 2020 Apr 21]. Available from: <https://www.fda.gov/media/95961/download>.
9. Greenhawt M, Marsh R, Gilbert H, Sicherer S, DunnGalvin A, Matlock D. Understanding caregiver goals, benefits, and acceptable risks of peanut allergy therapies. *Ann Allergy Asthma Immunol*. 2018; 121:575–579.
10. Remington BC, Krone T, Kim EH, Bird JA, Green TD, Lack G, et al. Estimated risk reduction to packaged food reactions by epicutaneous immunotherapy (EPIT) for peanut allergy. *Ann Allergy Asthma Immunol*. 2019; 123:488–493.e2.
11. Remington BC, Campbell DE, Green TD, Fleischer DM, Koppelman S. Modeled quantitative risk reduction through epicutaneous immunotherapy for peanut allergy: restaurant meal preparation with shared cooking utensils and equipment. Presented at American Academy of Allergy, Asthma, and Immunology (AAAAI) Congress 2020 [cited 2020 Apr 21]. Available from: <https://education.aaaaai.org/aaaai-virtual-poster-hall/aaaai-virtual-poster-hall>.
12. Koppelman SJ, Peillon A, Agbotounou W, Sampson HA, Martin L. Epicutaneous immunotherapy for peanut allergy modifies IgG₄ responses to major peanut allergens. *J Allergy Clin Immunol*. 2019; 143:1218–1221.e4.
13. Kong F, Galzote C, Duan Y. Change in skin properties over the first 10 years of life: a cross-sectional study. *Arch Dermatol Res*. 2017; 309:653–658.
14. Mack MC, Chu MR, Tierney NK, Ruvolo E Jr, Stamatas GN, Kollias N, et al. Water-holding and transport properties of skin stratum corneum of infants and toddlers are different from those of adults: studies in three geographical regions and four ethnic groups. *Pediatr Dermatol*. 2016; 33:275–282.
15. Duca B, Patel N, Turner PJ. GRADE-ing the benefit/risk equation in food immunotherapy. *Curr Allergy Asthma Rep*. 2019; 19:30.
16. Greenhawt M, Shaker M, Winders T, Bukstein DA, Davis RS, Oppenheimer J, et al. Development and acceptability of a shared decision making tool for commercial peanut allergy therapies. *Ann Allergy Asthma Immunol*. 2020; S1081–1206: 30076–30074.
17. Singal AG, Higgins PDR, Waljee AK. A primer on effectiveness and efficacy trials. *Clin Transl Gastroenterol*. 2014; 5:e45. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.