

EVALUATION OF DAILY PATCH APPLICATION DURATION FOR EPICUTANEOUS IMMUNOTHERAPY FOR PEANUT ALLERGY

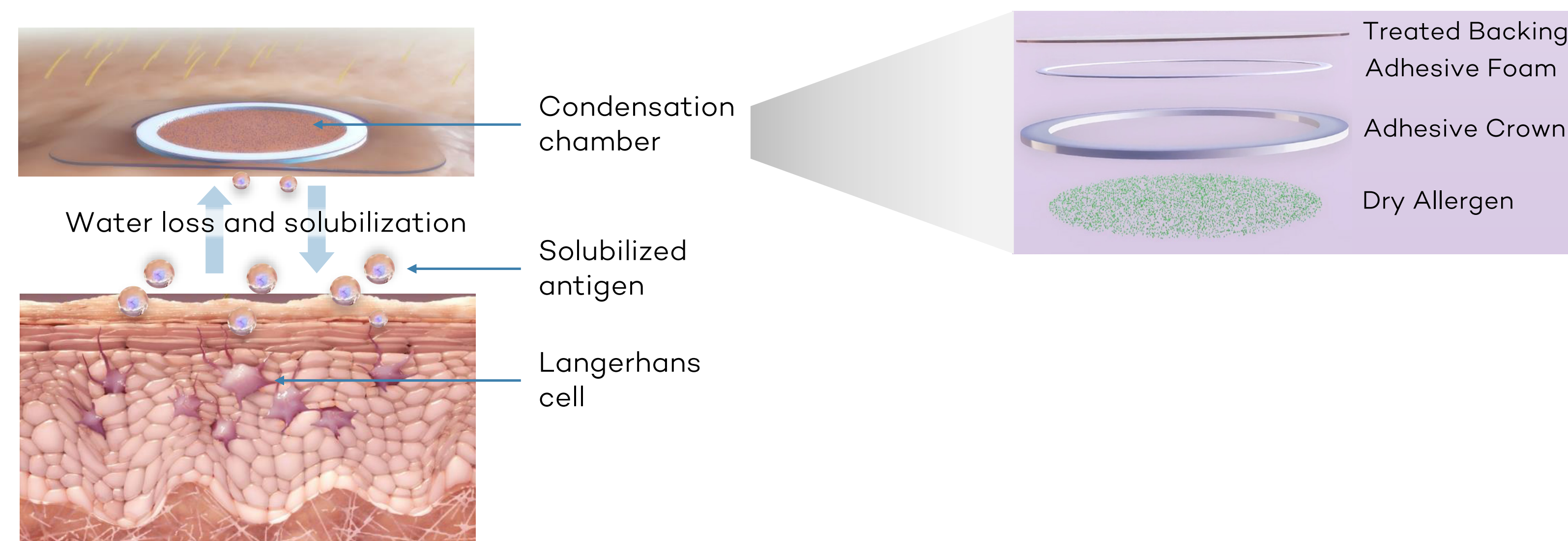
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RATIONALE

- 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) (**Figure 1**)¹
 - This patch system includes a condensation chamber, which consists of an occlusive film that is electrostatically coated with peanut protein, which allows for transepidermal water loss and perspiration to solubilize peanut protein¹
 - Mechanistic studies suggest that the solubilized allergen is captured by skin dendritic cells (antigen-presenting cells [APC]) and trafficked to lymph nodes, where it is thought that a long-lived population of regulatory T cells are generated^{1,2}
- DBV712 250 µg for peanut allergy has undergone investigation in multiple controlled clinical trials, including the Phase 3, double-blind, placebo-controlled PEPITES study in peanut-allergic children aged 4–11 years³
 - In PEPITES, DBV712 250 µg applied once daily for 12 months was shown to be statistically superior based on changes in the peanut eliciting dose (ED) in response to a double-blind, placebo-controlled food challenge (DBPCFC)³
- The recommended patch duration in PEPITES and other DBV712 250 µg clinical trials has been 24 ± 4 hours; however, preclinical data suggest that allergen capture by APCs takes place within the first 2 hours of patch application and that ~80% of antigen capture and internalization occurs by 6 hours¹⁻³
- Therefore, clinical trial data from PEPITES were analyzed to assess the relationship between the duration of daily DBV712 250 µg patch application and efficacy

Figure 1. DBV712 250-µg Epicutaneous Patch System



OBJECTIVES

- To determine the timing of protein release from the DBV712 250 µg patch (in vivo Phase 1 study [SOLAR])
- To evaluate the impact of daily wear time on the treatment effect of DBV712 250 µg (post hoc analysis of PEPITES)

METHODS

Timing of Protein Release (SOLAR Study)

- Healthy, non-atopic, adult volunteers aged 18–25 years (N=30) received DBV712 250 µg patch applications at a single center
- Each subject received a total of 10 patches: 8 DBV712 250 µg and 2 placebo patches
 - Six DBV712 250 µg and 2 placebo patches were applied to the intrascapular region of the back, and 2 DBV712 250 µg patches were applied to the nondominant arm
 - Of the 6 DBV712 250 µg patches applied to the back, 4 were removed 2, 6, 12, and 16 hours after application (1 from each time point) and 2 were removed 24 hours after application
 - The 2 placebo patches on the back and the 2 active patches on the arm were removed 24 hours after application
- After removal, patches were assayed for residual peanut protein remaining on the patch—total protein and peanut allergen Ara h 6—by a centralized facility (Bertin Pharma, Gif-sur-Yvette, France)
 - The lower level of quantification (LLOQ) for total peanut protein was 35 µg/patch

PEPITES Study and Post Hoc Analysis

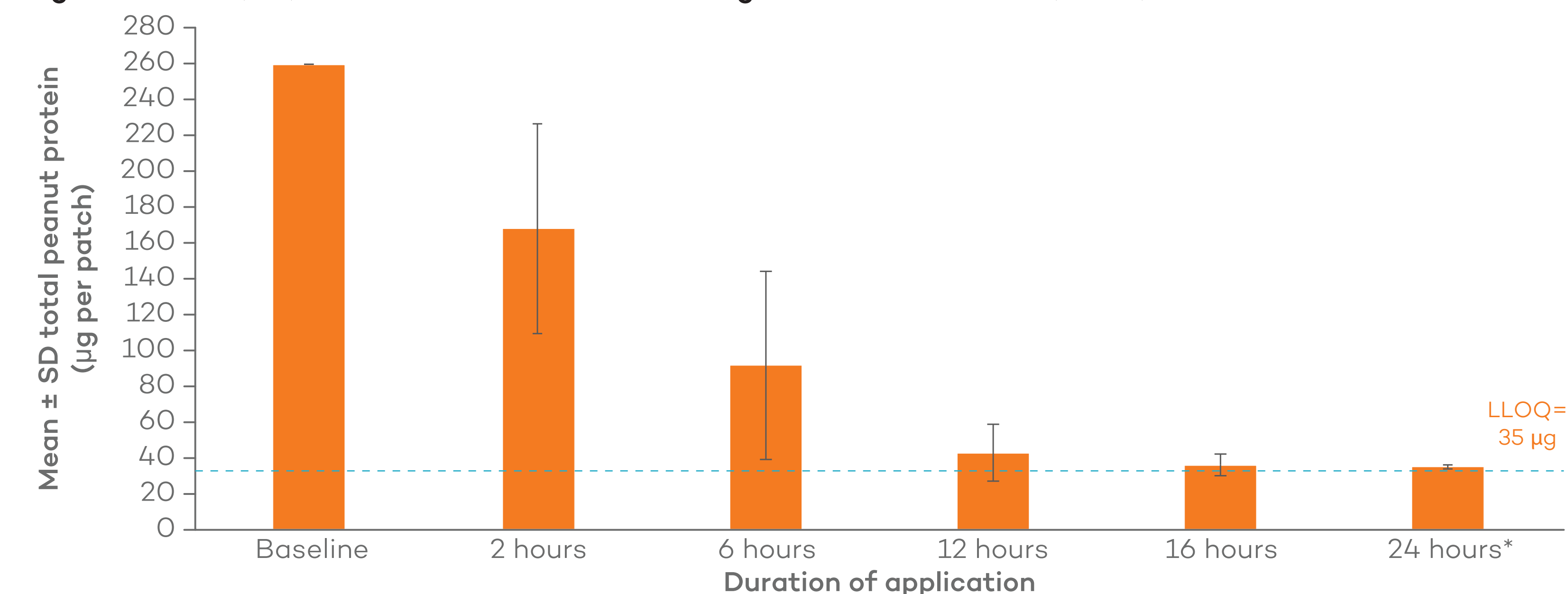
- In PEPITES, 356 subjects aged 4–11 years were randomized to DBV712 250 µg (n=238) or placebo (n=118). Subjects underwent a DBPCFC to be included in the study and to define the ED³
- The prespecified primary endpoint was the responder rate, defined as the proportion of subjects achieving an ED at Month 12 of ≥300 mg (for those who entered 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)³
- 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
- A post hoc analysis to assess the relationship between response rate (by primary outcome and by change in geometric mean [GM] of ED) and average daily patch duration was conducted for subjects with at least 28 patches recorded in their diaries
 - Missing data were imputed as 0 hours duration
 - GM ED at baseline and Month 12, as well as corresponding ratios, were calculated for subjects with >10, >12, >14, >16, >18, and >20 hours of average daily patch duration

RESULTS

SOLAR Study

- Of 210 active patches applied, 207 were suitable for assay of total residual peanut protein
- The total peanut protein at baseline (mean) was 261 µg/patch
- Mean residual total peanut protein from the patch decreased from 2 to 12 hours of application on the back and was below the LLOQ thereafter (**Figure 2**)
- Protein levels remaining on patches applied to the arm were similar to those applied to the back at 24 hours (*data not shown*)
- Ara h 6 levels showed a similar pattern to total protein, and the correlation (R²) between the 2 assays was 0.9186, suggesting similar kinetics of release for total peanut protein and Ara h 6 (*data not shown*)

Figure 2. Mean (SD) Total Peanut Protein Remaining on Patch Over Time (N=30)



Samples with unquantifiable total peanut proteins were assigned the LLOQ value of 35 µg. *Primary endpoint. LLOQ=lower limit of quantification; N=number of patches with quantifiable peanut proteins at each time point; SD=standard deviation.

PEPITES Study Post Hoc Analysis

- Of the 356 subjects in PEPITES, 352 (DBV712 250 µg: n=236, placebo n=116) had evaluable diary data for inclusion in the duration of patch application post hoc analysis
 - Median (Q1, Q3) daily duration of patch application was 21.1 (18.3, 22.3) hours in the DBV712 250 µg group and 22.4 (21.5, 23.0) hours in the placebo group
 - At least 10 hours/day of patch duration was achieved by 95% of the total treated population (n=340/356)
 - A daily patch duration of >16 hours was achieved by 85.2% (n=201/236) of subjects in the DBV712 250 µg group

- Responder rates in the DBV712 250 µg group ranged from 36.6% to 42.6% and differed significantly (P<0.001) from placebo-treated subjects across all average daily patch durations between >10 and >20 hours (**Table 1**)
 - Of subjects with a daily patch duration of >16 hours, the responder rate of the DBV712 250 µg group was 38.8% (n=78/201) compared with 13.4% (n=15/112) for the placebo group (treatment difference: 25.4 [P<0.001]; 95% CI, 15.5–34.0)
- Corresponding GM ED ratios (Month 12/baseline) ranged from 3.8 to 4.0 across all average daily patch durations between >10 and >20 hours
 - The GM ED ratios were similar for subjects with daily mean patch durations of 12–16 hours (n=16; 3.8 [95% CI, 1.4–10.4]) and of >16 hours (n=201; 3.9 [95% CI, 3.0–5.0])

Table 1. Responder Rate and GM ED 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	PLACEBO	DBV712 250 µg	PLACEBO	DIFFERENCE IN RESPONDER RATE (95% CI)	P	BASELINE, mg	MONTH 12, mg	RATIO MONTH 12/BASELINE (95% CI)
>10 hours	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 hours	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 hours	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 hours	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 hours	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 hours	148	99	42.6	13.1	29.4 (18.3–39.1)	<0.001	89.2	354.5	4.0 (3.0–5.3)

*Patches without a calculated duration were imputed as 0 hours. †Predefined response criteria in the PEPITES study. ED=eliciting dose; CI=confidence interval; N=number of subjects with at least 28 patches applied.

CONCLUSIONS

- The results of the phase 1 SOLAR analysis demonstrated that the majority of peanut protein is released from the epicutaneous patch system within the first 12 hours of application, after which time the protein remaining on the patch is below the LLOQ
- The post hoc analysis of the PEPITES data was consistent with the peanut protein release profile, with responder rates ranging from 36.6% for daily patch durations of >10 hours to 42.6% for daily patch durations of >20 hours. GM ED ratios were similar across all subgroups of daily patch duration, ranging from 3.8 to 4.0
- Taken together, these findings suggest that allergen delivery is attained within at least 12–16 hours of daily patch application time, which seems to be sufficient to drive clinically meaningful desensitization to peanut after 12 months of treatment

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ACKNOWLEDGMENTS:

This study was sponsored by DBV Technologies. Editorial support for the preparation of this poster was provided by International Meetings & Science (IMSci) and funded by DBV Technologies.