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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Reduction in peanut reaction severity during oral challenge after 12 months of epicutaneous immunotherapy

To the Editor,

Peanut allergy, one of the most common food allergies, can result in severe and potentially life-threatening reactions.[1,2] Immunotherapy aims to reduce the likelihood of allergic reactions due to accidental allergen ingestion, a noted treatment goal of caregivers, by increasing the threshold eliciting dose (ED).[3-5] Another important caregiver-expressed outcome of peanut allergy immunotherapy is reduction in severity of allergic reactions.[5]

Investigational epicutaneous immunotherapy with Viaskin™ Peanut (DBV712) 250 μg, a patch containing 250 μg of peanut protein (~1/1000 one peanut), demonstrated statistically significant superiority to placebo in desensitizing peanut-allergic children aged 4 to 11 years after 12 months of daily treatment in the phase 3 PEPITES trial and treatment-associated improvement in food allergy quality of life.[3,4,6] In PEPITES, double-blind placebo-controlled food challenges (DBPCFCs) were conducted according to PRACTALL guidelines at month 0 (M0, baseline) and month 12 (M12) using a standardized blinded food matrix.[3] DBPCFCs were stopped when sufficient objective signs or symptoms met prespecified stopping criteria and required treatment[3]; the peanut protein dose resulting in stopping was considered the subjects' ED. Reaction severity was assessed based on prespecified PRACTALL symptoms; severity for each symptom was graded by the investigator (none [0], mild [1], moderate [2], or severe [3]) at each dosing increment. Written and informed consent and assent (where applicable, depending upon the country) were obtained from the caregiver and subject, respectively.

To examine the potential role of Viaskin Peanut 250 μg in reducing allergic reaction severity, a post hoc analysis of PEPITES was conducted comparing the severity of allergic symptoms elicited during the DBPCFCs at M0 and M12 between subjects who received Viaskin Peanut 250 μg and placebo. Maximum symptom severity was assessed among all assessable organ systems (AOS) as the primary endpoint (which included objective symptoms in skin, upper respiratory, lower respiratory, objective gastrointestinal, and cardiovascular/neurologic systems) and in 5 specific symptom domains (wheezing, cardiovascular, laryngeal, vomiting, and diarrhea) as a sensitivity analysis (to target symptoms more commonly associated with life-threatening reactions, based upon their relationship to the physiology underlying the symptom) as well as by subjects' M12 ED status (increased, decreased, or unchanged). Analyses included all randomized subjects who underwent at least the peanut M12 DBPCFC (Viaskin Peanut 250 μg, n = 222; placebo, n = 109).

At M0, the proportion of subjects with mild, moderate, or severe objective signs/symptoms for AOS was similar between treatment groups (p =.931) (Table 1). In contrast, there was a significant between-group difference (p <.001) in the distribution of symptom severity at M12. Nearly twice as many Viaskin Peanut 250 μg-treated subjects (31.1%) as placebo-treated subjects (16.5%) had maximum symptom severity scores of "none" or "mild." The proportion of subjects with a maximum severity score of "severe" was also lower in subjects who received Viaskin Peanut 250 μg (16.2%) compared with placebo (27.5%; p =.019).

For the 5-domain sensitivity analysis, the proportion of subjects with mild, moderate, or severe signs/symptoms was similar at M0 in subjects treated with Viaskin Peanut 250 μg and placebo (p =.946) and differed significantly at M12 (p =.016) (Table 1). Additionally, 20.7% of subjects in the Viaskin Peanut 250 μg group had severity scores of "none" compared with 11.0% in the placebo group (p =.031).

To investigate possible confounding effects of ED on severity, the maximum symptom severity was also analyzed by subjects' M12 ED status. The proportion of subjects with maximum severity scores of "severe" remained lower in subjects who received Viaskin Peanut 250 μg versus placebo regardless of whether their ED increased, decreased, or was unchanged. Subgroup analysis demonstrated a significant difference among those whose ED decreased (increasing their reaction risk) or remained unchanged in the Viaskin Peanut 250 μg group compared with the placebo group (Table 2).

Limitations of the findings include those inherent in any post hoc analysis, although all data used in the analysis were collected prospectively, in accordance with the study protocol. Although it is possible that there is the potential for variability between assessors related to grading allergic reactions during DBPCFC, the blinded randomized nature of the study design is likely adequate to control for such variability. In addition, a strict well-known PRACTALL system was utilized, requiring prespecified stopping criteria based on objective reaction signs. Finally, although all assessors at DBPCFC were blinded to treatment allocation, some may have had knowledge of the subjects, gained during prior study visits. It is unclear to what extent, if any, this would have influenced the results of this analysis.

Overall, this post hoc analysis of prospectively collected prespecified data demonstrates that in addition and independent of increasing reactivity threshold in peanut-allergic children aged 4 to 11 years, Viaskin Peanut 250 μg may also reduce the severity of allergic reactions to accidental peanut ingestion, meeting two important caregiver-stated goals of peanut allergy immunotherapy.

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CONFLICTS OF INTEREST

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TABLE 1 Maximum severity of objective signs/symptoms[a] to peanut by treatment group at baseline and month 12 for AOS and 5 symptom domains[b]

Maximum severity of objective symptoms	Viaskin Peanut 250 μg (n = 222)	Placebo (n = 109)	*P*-value
AOS			
Month 0 DBPCFC			
n	222	109	.931[c]
None	0	0	
Mild	35 (15.8)	12 (11.0)	
Moderate	101 (45.5)	61 (56.0)	
Severe	86 (38.7)	36 (33.0)	
Month 12 DBPCFC			
n	222	109	<.001[c]
None	14 (6.3)	2 (1.8)	
Mild	55 (24.8)	16 (14.7)	
Moderate	117 (52.7)	61 (56.0)	
Severe[d]	36 (16.2)	30 (27.5)	
5 Symptom Domains[b]			
Month 0 DBPCFC			
n	222	109	.946[c]
None	33 (14.9)	12 (11.0)	
Mild	83 (37.4)	48 (44.0)	
Moderate	79 (35.6)	38 (34.9)	
Severe	27 (12.2)	11 (10.1)	
Month 12 DBPCFC			
n	222	109	.016[c]
None[e]	46 (20.7)	12 (11.0)	
Mild	103 (46.4)	50 (45.9)	
Moderate	63 (28.4)	39 (35.8)	
Severe	10 (4.5)	8 (7.3)	

Abbreviations: AOS, assessable organ systems; DBPCFC, double-blind placebo-controlled food challenge.

[a]Skin: erythematous rash (and % of rash area concerned), pruritus, urticaria/angioedema; Upper respiratory: sneezing/itching, nasal congestion, rhinorrhea, laryngeal; Lower respiratory: wheezing; Gastrointestinal: diarrhea, vomiting; Cardiovascular; Eyes: conjunctivitis.

[b]Wheezing, cardiovascular, laryngeal, vomiting, and diarrhea.

[c]Two-sided exact *P*-value from Cochran-Armitage trend test.

[d]Viaskin Peanut 250 μg vs placebo, $p = .019$; Fisher exact test.

[e]Viaskin Peanut 250 μg vs placebo, $p = .031$; Fisher exact test.

TABLE 2 Maximum severity of clinically significant reactions to peanut by treatment group at month 12 by ED status

Maximum severity of objective symptoms	Viaskin Peanut 250 μg (n = 222)	Placebo (n = 109)	*P*-value
Month 12 DBPCFC			
ED increase at M12			
n	149	33	.139[a]
None	7 (4.7)	2 (6.1)	
Mild	34 (22.8)	4 (12.1)	
Moderate	81 (54.4)	16 (48.5)	
Severe[b]	27 (18.1)	11 (33.3)	
ED at M12 = ED at M0			
n	48	36	.033[a]
None	1 (2.1)	0	
Mild	10 (20.8)	3 (8.3)	
Moderate	28 (58.3)	20 (55.6)	
Severe	9 (18.8)	13 (36.1)	
ED decrease at M12			
n	25	40	<.001[a]
None	6 (24.0)	0	
Mild	11 (44.0)	9 (22.5)	
Moderate	8 (32.0)	25 (62.5)	
Severe	0	6 (15.0)	

Note: For subjects who stopped the challenge before the onset of symptoms, ED was imputed as the value of the last ingested dose.

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge;ED, eliciting dose.

[a]Two-sided exact *P*-value from Cochran-Armitage trend test.

[b]Viaskin Peanut 250 μg vs placebo, $p = .061$; Fisher's exact test.

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