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. It is also associated with life-threatening reactions, based upon their relationship to the physiology underlying the symptom.\(^5\) Another important caregiver-expressed outcome of peanut allergy immunotherapy is reduction in severity of allergic reactions.\(^5\)

Investigational epicutaneous immunotherapy with Viaskin\textsuperscript{™} Peanut (DBV712) 250 \(\mu\)g, a patch containing 250 \(\mu\)g 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;\(^2\) 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 \(\mu\)g 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 \(\mu\)g 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 \(\mu\)g, \(n = 222\); 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 \(\mu\)g-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 \(\mu\)g (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 \(\mu\)g and placebo (\(p = .946\)) and differed significantly at M12 (\(p = .016\)) (Table 1). Additionally, 20.7% of subjects in the Viaskin Peanut 250 \(\mu\)g 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 \(\mu\)g 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 \(\mu\)g group compared with the placebo group (Table 2).

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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.

**FUNDING INFORMATION**

The study was funded by DBV Technologies.

**ACKNOWLEDGEMENT**

The authors would like to acknowledge the contribution of all the PEPITES investigators and research staff and thank the patients and their families for participation in the clinical trial.

**CONFLICTS OF INTEREST**

Philippe Bégin reports research support to his institution from DBV Technologies during the conduct of this study, personal fees from Novartis, Pfizer, Sanofi, DBV Technologies, ALK, and Aralez outside the submitted work and research support from Novartis, Regeneron, and Sanofi outside the submitted work. J. Andrew Bird reports research support to his institution from DBV Technologies during the conduct of this study.

### 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 |
|---------------------------------------------------------------|
| **AOS** | Viaskin Peanut 250 µg (n = 222) | Placebo (n = 109) | **P-value** |
|----------|---------------------------------|-----------------|-------------|
| Month 0 DBPCFC | | | |
| n 222 | 109 | .931c |
| 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 | | | <.001c |
| n 222 | 109 | |
| 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 | .946c |
| 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 | | | .016c |
| n 222 | 109 | |
| 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.

aSkin: 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.

bWheezing, cardiovascular, laryngeal, vomiting, and diarrhea.

cTwo-sided exact P-value from Cochran-Armitage trend test.

dViaskin Peanut 250 µg vs placebo, p = .019; Fisher exact test.

eViaskin 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    |
| None                                  | 7 (4.7)                         | 2 (6.1)          |         |
| Mild                                  | 34 (22.8)                       | 4 (12.1)         |         |
| Moderate                               | 81 (54.4)                       | 16 (48.5)        |         |
| Severe                                 | 27 (18.1)                       | 11 (33.3)        |         |
| ED at M12 = ED at M0                   |                                 |                  | .033    |
| n                                     | 48                              | 36               |         |
| 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                     |                                 |                  | <.001   |
| n                                     | 25                              | 40               |         |
| 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.

The table shows the maximum severity of objectively measured symptoms among subjects receiving Viaskin Peanut 250 µg vs placebo, with a two-sided exact P-value from the Cochran-Armitage test or Fisher’s exact test for each severity category. The table includes comparisons of edema (ED) at month 12 by treatment group, with severity categories ranging from none to severe, and indicates statistically significant differences between treatment groups.

Support from DBV Technologies during the conduct of this study, research support from NIH-NIAID, Genentech, Astellas, Aimmune Therapeutics, DBV Technologies, and Food Allergy Research and Education outside the submitted work and consulting fees from Food Allergy Research and Education, Pharm-Olam International LTD, Pfizer, Aimmune, Prota Therapeutics, Allergy Therapeutics, AllerGenis, Abbott Nutrition International, DBV Technologies, and Novartis. Dianne E. Campbell is a part-time employee of DBV Technologies and reported receiving grant support from the National Health and Medical Research Council of Australia and personal fees from AllerGenis, Westmead Fertility Centre, and Financial Markets Foundation for Children. David M. Fleischer received research support from his institution to Aimmune Therapeutics and DBV Technologies and is a member of the Medical Advisory Board for the Food Allergy & Anaphylaxis Connection Team (FAACT), Medical Advisory Council for the National Peanut Board, the Adverse Reactions to Food Committee (former chair 2017–2019) for the AAAAI, and Food Allergy Committee for the ACAAI; has received royalties from UpToDate and is a consultant to AllerGenis, Aquestive, Aravax, Danone, DBV Technologies, Genentech, Intrommune, Nasus, and Nurture Inc (Happy Family Organics). Hugh A. Sampson receives consulting fees from DBV Technologies, Siolta Therapeutics, and N-Fold Therapeutics and received stock options from DBV Technologies and grants to his institution from the National Institutes of Health. Jonathan M. Spergel reports board membership from the American Partnership for Eosinophilic Disorders and the International Food Protein-Induced Enterocolitis Syndrome Association; consultancy fees from DBV Technologies, Sanofi/Regeneron, and Medscape; speaker fees from Abbott; and grants to his institution from the National Institutes of Health and End Allergies Together and Aimmune Therapeutics. Todd D. Green, Katharine J. Bee, and Romain Lambert are employees of DBV Technologies.

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