EPITOPE Study Results: Phase 3, Randomized, Double-blind, Placebo-controlled Study of Epicutaneous Immunotherapy in Peanut-allergic Toddlers

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Disclosures

- Member, Joint Task Force on Allergy Practice Parameters
- Member of Nutricia, DBV, Novartis, Sanofi, Aquestive, Prota, Allergy Therapeutics, GSK, ALK-Abello, AstraZeneca
- Consultant, Aquestive
- Received honorarium from ImSci, MedLearning Group, RMSI, multiple state and local allergy societies, and the CSACI
- Member of the Medical Advisory team for the Allergy and Asthma Foundation of America and the International Association for Food Protein Enterocolitis (nonfinancial)
- Has received support from K08-HS024599 (Agency for Healthcare Research and Quality)
- Member of AAAAI Practice/Diagnostics/Therapeutics, Anaphylaxis, Adverse Reaction to Food, Vaccine committees
- Co-chair, AAAAI Primary Prevention of Food Allergy Working Group; Co-chair, AAAAI Oral Immunotherapy Office-based Practice Working Group
- Member, NIAID Expert Panel on early introduction of peanut to prevent peanut allergy
- Senior Associate Editor, *Annals of Allergy, Asthma, and Immunology*
- International Advisory Board, Lancet Child and Adolescent Health
- Editorial board: *Medscape Pediatrics; Infectious Diseases in Children, Pediatric Allergy and Immunology*
- Member, Scientific Advisory Council, National Peanut Board
- Member, EAACI Task Forces on Nutrition and Immunomodulation; Outcomes of Food Allergy Therapies
- Member, Core Outcome Measures for Food Allergy (COMFA) consortium, COST Action
- Member, Brighton Criteria Collaboration Case Definition for Anaphylaxis working group 2.0
Rationale

- There is currently no approved treatment for peanut allergy in children younger than 4 years, demonstrating a strong unmet need for an available treatment\(^1\).
- Studies have shown early oral introduction of peanuts in children could reduce the risk of developing peanut allergy, suggesting the immune system in infancy may be particularly responsive to immunomodulation\(^2\).

Epicutaneous immunotherapy (EPIT) with VP250 for peanut allergy\(^3,4\)

- EPIT with investigational VP250 is a novel patch-based approach involving administration of microgram quantities of peanut allergen to intact skin to induce desensitization.
- Single, daily patch applied to children’s backs; first patch applied at study site, subsequent applications at home.
- Each patch contains 250 µg peanut protein (~1/1000 of 1 peanut kernel); no up-dosing.
- No restrictions based on illness or daily activities required in clinical trial protocol.

Objective

- To assess the efficacy and safety of EPIT with VP250 among children 1 to <4 years of age with peanut allergy.

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Epicutaneous immunotherapy and Viaskin™ (VP250) are under clinical investigation and have not been approved for marketing by any health or regulatory authority.
EPITOPE Study Design: Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Trial

- Participants randomized 2:1 to VP250 or placebo daily for 12 months
- Month 0 and Month 12 DBPCFC conducted per PRACTALL guidelines\(^1\)
  - Eliciting dose (ED) = dose at which signs/symptoms met the prespecified stopping criteria

Phase 3 Global Study
- 362 peanut-allergic toddlers (aged 1 to <4 years)
- 51 sites in Australia, Canada, Europe, and US
- Key inclusion criteria: baseline ED \(\leq 300\) mg, sIgE \(>0.7\) kU/L, and SPT ≥6 mm

Primary Efficacy Endpoint
- Percent difference in responders between VP250 and placebo, defined as M12 ED:
  - \(\geq 1000\) mg (if baseline ED >10 mg)
  - \(\geq 300\) mg (if baseline ED \(\leq 10\) mg)

Additional Endpoints
- % reaching ED \(\geq 1000\) mg at M12
- % reaching CRD \(\geq 3444\) mg at M12
- Change in severity of symptoms elicited during DBPCFC from baseline to M12
- Safety as assessed by treatment-emergent adverse event rates, including anaphylaxis

CRD, cumulative reactive dose; DBPCFC, double-blind, placebo-controlled food challenge; sIgE, specific immunoglobulin E; SPT, skin prick test.

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Participant Flow and Characteristics

- **851 Children assessed for eligibility**
  - 489 Excluded
    - 415 Did not meet inclusion/exclusion criteria
    - 1 Physician decision
    - 59 Withdrawal by parent/guardian
    - 14 Other
  - 362 Randomized
  - 244 Randomized to VP250
  - 118 Randomized to placebo
    - 208 Completed study
      - 8 Adverse event
      - 2 Lost to follow-up
      - 2 Noncompliance
      - 1 Physician decision
      - 18 Withdrawal by parent/guardian
      - 5 Participants did not want to complete oral food challenge
    - 99 Completed study
      - 19 Discontinued study treatment
        - 1 Lost to follow-up
        - 2 Physician decision
        - 1 Protocol violation
        - 13 Withdrawal by parent/guardian
        - 2 Participants did not want to complete oral food challenge

<table>
<thead>
<tr>
<th>Category</th>
<th>VP250 (N=244)</th>
<th>Placebo (N=118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (Q1, Q3)</td>
<td>2.50 (1.75, 3.20)</td>
<td>2.40 (1.70, 3.10)</td>
</tr>
<tr>
<td>Age, category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>83 (34.0)</td>
<td>43 (36.4)</td>
</tr>
<tr>
<td>2 years</td>
<td>76 (31.1)</td>
<td>38 (32.2)</td>
</tr>
<tr>
<td>3 years</td>
<td>85 (34.8)</td>
<td>37 (31.4)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>165 (67.6)</td>
<td>84 (71.2)</td>
</tr>
<tr>
<td>Female</td>
<td>79 (32.4)</td>
<td>34 (28.8)</td>
</tr>
<tr>
<td>Peanut-specific IgE, kU/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>13.4 (4.04, 65.85)</td>
<td>14.75 (4.86, 52.11)</td>
</tr>
<tr>
<td>Range</td>
<td>0.8-971.0</td>
<td>0.7-1031.0</td>
</tr>
<tr>
<td>Peanut protein eliciting dose, mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>100 (30, 300)</td>
<td>100 (30, 300)</td>
</tr>
<tr>
<td>Range</td>
<td>1-300</td>
<td>1-300</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>39 (16.0)</td>
<td>27 (22.9)</td>
</tr>
<tr>
<td>Eczema/atopic dermatitis</td>
<td>194 (79.5)</td>
<td>96 (81.4)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>49 (20.1)</td>
<td>23 (19.5)</td>
</tr>
<tr>
<td>Food allergy(ies) other than peanut</td>
<td>161 (66.0)</td>
<td>81 (68.6)</td>
</tr>
</tbody>
</table>

- Baseline characteristics and demographics were balanced between treatment groups

IgE, immunoglobulin E; Q, quartile.

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Efficacy Results: Primary Endpoint

- At Month 12, a significantly larger percentage of participants achieved the **primary endpoint** in the **VP250 group vs placebo**, 67.0% vs 33.5%, respectively, with a **difference of 33.4%** (95% CI: 22.4, 44.5; \( P < 0.001 \))
Primary Efficacy Endpoint: Prespecified Sensitivity Analyses

- All prespecified sensitivity analyses regarding the primary endpoint were statistically significant and demonstrated the consistency of the treatment effect.

**Sensitivity Analysis (Intercurrent events*)**
- Primary Responder Endpoint
- 1 Missing Failure
- Imputation (1,2,5)
- 2 Multiple Imputation
- (1,2,5)
- 3 Multiple Imputation within arms (2,5)
- 4 Exclusion of subjects with intercurrent events (1,2,5)
- 5 Exclusion of subjects outside OFC window (4)
- 6 Per-protocol set

*Intercurrent events defined as: 1. early treatment discontinuation before 12 months; 2. participants refusing the peanut DBPCFC at Month 12; 3. peanut DBPCFC at Month 12 initiated but not finished; 4. DBPCFC at Month 12 falls outside the recommended time window; 5. discontinuation after 12 months with DBPCFC at Month 12 missing.

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Key Secondary Efficacy Endpoints: ED and CRD

- At Month 12, regardless of baseline ED, a statistically significantly larger percentage of participants in the VP250 vs placebo group achieved an ED ≥1000 mg or CRD ≥3444 mg.

**ED ≥1000 mg at Month 12**

- VP250 (N=244): 64.2% responders
- Placebo (N=118): 29.6% responders
- Δ = 34.7% (95% CI: 23.6, 45.7)
- P < 0.001

**CRD ≥3444 mg* at Month 12**

- VP250 (N=244): 37.0% responders
- Placebo (N=118): 10.0% responders
- Δ = 27.0% (95% CI: 17.9, 36.1)
- P < 0.001

CRD, cumulative reactive dose; ED, eliciting dose.

*At Month 12 DBPCFC, 1000 mg and 2000 mg doses added to DBPCFC for a maximum possible cumulative dose of 3444 mg. Participants with CRD ≥3444 mg include those who reached a CRD=3444 mg and participants who did not meet the stopping criteria at any dose during the M12 DBPCFC.

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Key Efficacy Endpoint: Reaction Severity

- Severity of reactions during DBPCFC was graded by the investigator according to PRACTALL\textsuperscript{2} scoring as 0 (absent), 1 (mild), 2 (moderate) or 3 (severe); distribution of maximum severity at baseline and Month 12 was compared between treatment groups.

- At baseline DBPCFC, the proportions of maximum reaction severity were balanced between groups.

- At Month 12, the distribution of maximum symptom severity was significantly shifted toward less severe symptoms in the VP250 group relative to placebo ($P<0.001$).

- This shift toward a reduction in reaction severity coincided with an increase in ED and a greater proportion of responders in the VP250 vs placebo group.

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


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Safety Results

• Most participants in both the VP250 and placebo arms experienced TEAEs, which consisted primarily of mild to moderate local skin reactions that decreased in frequency with time.

• Serious adverse events (SAEs) were reported by 8.6% in the VP250 group vs 2.5% in the placebo group, of which 1 SAE in the VP250 group was considered treatment-related.

• Anaphylaxis considered related to treatment was reported in 4 participants (1.6%), all in the VP250 arm.
  - All events were mild or moderate in severity.
  - Three (1.2%) participants were treated with a single dose of epinephrine, and 1 participant was treated with no epinephrine.

• Treatment compliance was high and comparable between groups, with an overall mean rate of 97.0%.
Safety Results (cont)

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<table>
<thead>
<tr>
<th>TEAEs Related to Investigational Product</th>
<th>VP250 (N=244)</th>
<th>Placebo (N=118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>244 (100%)</td>
<td>112 (94.9%)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>1 (0.4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Severe TEAE</td>
<td>57 (23.4%)</td>
<td>11 (9.3%)</td>
</tr>
<tr>
<td>Moderate TEAE</td>
<td>208 (85.2%)</td>
<td>59 (50.0%)</td>
</tr>
<tr>
<td>Mild TEAE</td>
<td>238 (97.5%)</td>
<td>110 (93.2%)</td>
</tr>
</tbody>
</table>

System organ class preferred term

| Administration-site conditions          | 243 (99.6%)   | 111 (94.1%)     |
| Skin and subcutaneous disorders        | 74 (30.3%)    | 25 (21.2%)      |
| Immune system disorders                | 7 (2.9%)      | 0 (0%)          |
| Anaphylactic reaction                  | 4 (1.6%)      | 0 (0%)          |
| Non-anaphylactic hypersensitivity reaction | 3 (1.2%) | 0 (0%)          |
| Eye disorders                          | 5 (2.0%)      | 0 (0%)          |
| Infections and infestations            | 3 (2.0%)      | 0 (0%)          |
| Gastrointestinal disorders             | 6 (2.5%)      | 0 (0%)          |
| Respiratory, thoracic, and mediastinal disorders | 11 (4.5%) | 1 (0.8%)        |
| Psychiatric disorders                  | 6 (2.5%)      | 0 (0%)          |
| Blood and lymphatic disorders          | 1 (0.4%)      | 1 (0.8%)        |
| Nervous system disorders               | 1 (0.4%)      | 1 (0.8%)        |

| TEAEs leading to temporary discontinuation | 31 (12.7%) | 2 (1.7%) |
| TEAEs leading to permanent discontinuation | 7 (2.9%) | 0 (0%)   |
| TEAEs leading to epinephrine use         | 3 (1.2%)    | 0 (0%)   |
| TEAEs leading to systemic or inhaled corticosteroid use | 6 (2.5%) | 1 (0.8%) |
| TEAEs leading to topical corticosteroid use | 233 (95.5%) | 70 (59.3%) |

- The most reported treatment-related TEAEs were application-site reactions, including erythema, pruritus, and swelling.
- Seven (2.9%) participants in the VP250 group and none in the placebo group discontinued due to treatment-related TEAEs.
Conclusions

- This pivotal, phase 3 trial of children 1 to <4 years of age with peanut allergy met its primary endpoint with significantly more participants meeting responder criteria in the VP250 group vs placebo (67.0% vs 33.5%, respectively; difference: 33.4%; 95% CI: 22.4, 44.5 [P<0.001])
- 12 months of daily EPIT with VP250 was associated with significant increases in ED and CRD, as well as decreases in reaction severity, compared to placebo
- The safety profile was consistent with prior VP250 studies and demonstrated that EPIT with VP250 was well tolerated with low rates (1.6%) of treatment-related anaphylaxis and low (2.9%) discontinuations due to treatment-related TEAEs
- This is the first study of peanut desensitization in children <4 years of age using a non-oral immunotherapy route; results from this study suggest VP250 may be a potential treatment option for young children with peanut allergy

CRD, cumulative reactive dose; TEAE, treatment-emergent adverse event.
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