Efficacy and Safety of AR101 in Peanut Allergy: Results from a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial (PALISADE)

Stacie M. Jones, MD¹, Kirsten Beyer, MD², A. Wesley Burks, MD³, Thomas B. Casale, MD⁴, Jonathan O’B. Hourihane, MD⁵, Annette Marcantonio⁶, Andrea Vereda, MD, PhD⁶, Brian P. Vickery, MD³,⁶, Rezi Zawadzki, DrPH⁶, and Daniel C. Adelman, MD⁶,⁷

¹ Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, AR; ² University Hospital Charité, Berlin, Germany; ³ Department of Pediatrics, University of North Carolina, Chapel Hill, North Carolina, USA, Chapel Hill; ⁴ University of South Florida, Morsani College of Medicine, Tampa, FL; ⁵ University College Cork, Cork, Ireland; ⁶ Aimmune Therapeutics, Brisbane, CA; ⁷ University of California, San Francisco, San Francisco, CA
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Cincinnati OH

Baker, James  
Portland OR

Ben-Shoshan, Moshe  
Montreal QC

Bird, Drew  
Dallas TX

Brooks, Gregory  
Bellevue NE

Carr, Tara F.  
Tucson AZ

Carr, Warner  
Mission Viejo CA

Casale, Thomas  
Tampa FL

Cheema, Amajan  
Mississauga ON

Chinthrajah, Sharon  
Palo Alto CA

Chong, Hey and Green, Todd  
Pittsburgh PA

Ciaccio, Christina E.  
Chicago IL

Davis, Carla  
Houston TX

Dorsey, Morna  
San Francisco CA

Fritz, Stephen  
Eagle ID

Greos, Leon  
Centennial CO.

Jeong, David  
Seattle WA

Johnston, Douglas  
Charlotte NC

Jones, Stacie  
Little Rock AR

Kachru, Rita  
Santa Monica CA

Kim, Edwin  
Chapel Hill NC

Lanser, Bruce J.  
Denver CO

Leickly, Frederick  
Carmel IN

Leonard, Stephanie  
San Diego CA

Lieberman, Jay  
Memphis TN

Mansfield, Lyndon  
El Paso TX

Matz, Jonathan  
Baltimore MD

Ohayon, Jason  
Hamilton ON

Pongracic, Jacqueline  
Chicago IL

Portnoy, Jay and Dinakar, Chitra  
Kansas City MO

Rachid, Rima  
Boston MA

Ratner, Paul  
San Antonio TX

Rupp, Ned  
Charleston SC

Sanders, Georgiana  
Ann Arbor MI

Sharma, Hemant  
Washington DC

Sher, Ellen  
Ocean NJ

Sher, Lawrence  
Rolling Hills Estates CA

Shreffler, Wayne  
Boston MA

Siri, Daren  
Normal IL

Spiegel, Jonathan  
Philadelphia PA

Stillerman, Allan  
Plymouth MN

Sussman, Gordon  
Toronto ON

Tilles, Stephen  
Seattle WA

Varshney, Pooja  
Austin TX

Wang, Julie  
New York NY

Welch, Michael J  
San Diego CA

Windom, Hugh  
Sarasota FL

Wood, Robert  
Baltimore MD

Yang, William  
Ottawa ON

Beyer, Kirsten  
Berlin DE

Bindels-Jensen, Carsten  
Odense DK

Blumchen, Katharina  
Frankfurt DE

Du Toit, George  
London UK

Dobois, Anthony EJ  
Groningen NL

Fernandez-Rivas, Maria Montserrat  
Madrid ES

Hourihane, Jonathan  
Cork IE

Ibanez, Maria Dolores  
Madrid ES

Muirar, Antonella  
Padua IT

Nilsson, Caroline  
Stockholm SE

Oude Eberink, Hanneke  
Groningen NL

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Manchester UK

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PALISADE
Peanut ALlergy Oral Immunotherapy Study of AR101 for DEsensitization

• International, multicenter, randomized, double-blind, placebo-controlled, Phase 3 study of AR101 in peanut-allergic individuals

• Key Enrollment Criteria:
  – Sensitization to peanut with clinical reactivity at ≤ 100 mg of peanut protein in a screening DBPCFC (i.e., tolerating no more than 30 mg at baseline)
  – Excluded for recurrent or chronic GI symptoms of any etiology, severe or poorly controlled asthma, or severe anaphylaxis occurring within 60 days of screening

• Prespecified primary analysis: children aged 4-17 years

AR101 is an investigational oral biologic drug product used for Characterized Oral Desensitization ImmunoTherapy (CODIT™) that contains the protein profile found in peanuts and is manufactured to current Good Manufacturing Practices (cGMP) specifications
Study Overview & Schematic

Participating countries (66 centers): US, Canada, Denmark, Germany, Ireland, Italy, Netherlands, Spain, Sweden, UK

Entry DBPCFC at Screening

Double-Blind OIT Updosing Phase (in Clinic)

~6 Month Double-Blind Maintenance Phase

Exit DBPCFC

Key Inclusion Criterion:
Tolerate ≤ 30 mg†

3:1 Randomization AR101 to Placebo

Day 1

3 mg

300 mg

2 weeks at each dose level; adjustments permitted

Primary Efficacy Endpoint:
Tolerate 600 mg†

Secondary Endpoints:
• Safety
• Immune Δs

Prophylactic use of symptomatic therapies (e.g., H1 and/or H2 blockers) was prohibited throughout the study. Rescue use was allowed.

†600 mg of peanut protein is approximately equal to two peanut kernels

www.clinicaltrials.gov: NCT02635776
Baseline Characteristics: 4-17 year olds

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>AR101 patients (n=372)</th>
<th>Placebo patients (n=124)</th>
<th>Totals (n=496)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>208 (56%)</td>
<td>76 (61%)</td>
<td>284 (57%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-11 years</td>
<td>238 (64%)</td>
<td>89 (72%)</td>
<td>327 (66%)</td>
</tr>
<tr>
<td>12-17 years</td>
<td>134 (36%)</td>
<td>35 (28%)</td>
<td>169 (34%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Caucasian</td>
<td>292 (78%)</td>
<td>97 (78%)</td>
<td>389 (78%)</td>
</tr>
<tr>
<td>Other</td>
<td>80 (22%)</td>
<td>27 (22%)</td>
<td>107 (22%)</td>
</tr>
<tr>
<td><strong>Baseline peanut sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR) SPT average wheal (mm)</td>
<td>11 (9, 14.5)</td>
<td>12 (9, 15.3)</td>
<td>11 (9, 15)</td>
</tr>
<tr>
<td>Median (IQR) Peanut-specific IgE (kUA/L)</td>
<td>69 (19, 194)</td>
<td>75 (29, 251)</td>
<td>71 (20, 202)</td>
</tr>
<tr>
<td>Median (IQR) maximum tolerated dose (mg)</td>
<td>10 (3,30)</td>
<td>10 (3,30)</td>
<td>10 (3,30)</td>
</tr>
<tr>
<td><strong>History of pre-study peanut anaphylaxis</strong></td>
<td>269 (72%)</td>
<td>89 (72%)</td>
<td>358 (72%)</td>
</tr>
<tr>
<td>Previous or present asthma</td>
<td>198 (53%)</td>
<td>65 (52%)</td>
<td>263 (53%)</td>
</tr>
<tr>
<td>Multiple food allergies</td>
<td>245 (66%)</td>
<td>80 (65%)</td>
<td>325 (66%)</td>
</tr>
</tbody>
</table>
Participant Disposition: 4-17 year olds

Screened (n=750)

Failed Screening (n=251)

AR101 (n=372)

Withdrawn (n=76, 20.4%)
Updosing (n=62)
Maintenance (n=14)

Completed Study: 80% (n=296)

Completed Study: 94% (n=116)

Placebo (n=124)

Withdrawn (n=8, 6.4%)
Updosing (n=6)
Maintenance (n=2)

Safety Population (N=496*)

Completer Population (N=412)

*3 were randomized in error; 496 exposed to ≥ 1 dose of study product
Efficacy of AR101 in 4-17 year olds: ITT Population (N=496)
Assessed at Exit DBPCFC

- Single Highest Dose (mg): 300, 600, 1000
- Cumulative Dose (mg): 443, 1043, 2043

*Δ* between groups = 63.2% (95%CI:53.73) *p*<0.00001

### Primary Endpoint

#### Highest Tolerated Dose (mg)

- **Placebo:**
  - Single Highest Dose: 300 mg, 8% responders
  - Cumulative Dose: 443 mg

- **AR101:**
  - Single Highest Dose: 600 mg, 67% responders
  - Cumulative Dose: 1043 mg

  - Single Highest Dose: 1000 mg, 50% responders
  - Cumulative Dose: 2043 mg

* *p*<0.00001 for H0:Treatment Difference = 15%
Highest Tolerated Single Challenge Dose: ITT Population

Median dose tolerated in Entry and Exit Peanut Challenges

- **AR101**
  - Baseline: 10
  - Exit: 1000

- **Placebo**
  - Baseline: 10
  - Exit: 30
Symptom Severity at Exit Peanut Challenge - Completers
DBPCFC Results as Evaluated by an Independent Blinded Assessor

<table>
<thead>
<tr>
<th>Epinephrine Use†</th>
<th>AR101</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>268 (91%)</td>
<td>54 (47%)</td>
</tr>
<tr>
<td>1</td>
<td>25 (8%)</td>
<td>43 (37%)</td>
</tr>
<tr>
<td>2</td>
<td>3 (1%)</td>
<td>17 (15%)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>0</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

†p<0.0001 for overall between-group difference

Key Findings
Compared to placebo, the AR101 group:
1. Developed fewer moderate and severe symptoms;
2. Required more peanut exposure to elicit the onset of symptoms;
3. Was more likely to complete the challenge; and
4. Needed less epinephrine.
Key Safety Events - Safety Population

- Approximately 99% of AR101-treated participants and 95% of placebo participants had a treatment-emergent (i.e., post-randomization) adverse event (AE)

- 9 SAEs in 8 AR101 participants (2.2%) and 1 SAE in 1 placebo participant (0.8%)
  - In the AR101-treated participants:
    - 5 events were unrelated to study drug; 4 were related
    - 5 events led to discontinuation
    - 1 event was severe and related - anaphylaxis early in maintenance; high baseline pslgE

- No deaths, life-threatening AEs, or suspected unexpected serious adverse reactions (SUSARs)

- 16 participants (4%) in the AR101 group discontinued the trial due to chronic/recurrent GI AEs
  - 1 AR101 participant was diagnosed with EoE and withdrew, with resolution of symptoms
  - 2 other participants had symptoms and negative EGDs

- 54 AR101 participants (14.5%) and 6 placebo participants (3.2%) had a treatment-emergent systemic hypersensitivity reaction
  - 98.2% of these events were graded mild or moderate
  - 10 AR101 participants (2.7%) discontinued as a result of these events
## Study Discontinuations: 4-17 year olds

<table>
<thead>
<tr>
<th>Discontinuations</th>
<th>AR101 (n=372)</th>
<th>Placebo (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawals not due to AEs</td>
<td>30 (8.0)</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Withdrawals due to AEs, total and by category</td>
<td>46 (12.4)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>• Acute / Chronic / Recurrent GI&lt;sup&gt;1&lt;/sup&gt;</td>
<td>25 (6.7)</td>
<td>0</td>
</tr>
<tr>
<td>• Systemic hypersensitivity reactions&lt;sup&gt;2&lt;/sup&gt;</td>
<td>10 (2.7)</td>
<td>2 (1.6)&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Respiratory system</td>
<td>4 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>• Cutaneous</td>
<td>3 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>• Other&lt;sup&gt;4&lt;/sup&gt;</td>
<td>4 (1.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

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1: Includes one case of EoE; 2 additional participants had negative endoscopies and no additional cases of EoE were identified in the study
2: Of these, 7 were investigator-identified anaphylaxis events (1 severe)
3: 2 systemic reactions during up-dosing attributed to study product
4: Includes one discontinuation for each: acute viral illness, eye pruritus, headache, and an unknown factor
Immune Modulation by AR101

**Peanut IgE**
- AR101
- Placebo
- \( p = 0.5^* \)

**Peanut IgE/IgG₄ ratio**
- AR101
- Placebo
- \( p < 0.0001^* \)

**Peanut SPT**
- AR101
- Placebo
- \( p < 0.0001^* \)

*\( p \) value refers to a between-group comparison of the change from Baseline to Exit using an ANCOVA model.
Summary and Conclusions

- In this highly allergic population, 67% of AR101-treated participants successfully tolerated 600 mg of peanut protein at the exit food challenge, compared to 4% in placebo group.

- The median tolerated dose improved 100-fold in AR101-treated participants from entry to exit food challenge; symptom severity and epinephrine use at exit were blunted.

- SAEs, and withdrawals due to GI or hypersensitivity events affected <5%; no deaths or SUSARs.

- Overall the safety profile of AR101 was similar to previous studies of oral immunotherapy:
  - The frequency and severity of hypersensitivity AEs was as expected.
  - The 6.7% rate of GI-related withdrawals, and one case of EoE, were lower than expected.

- PALISADE was the largest peanut allergy trial ever conducted; the first to use an independent blinded assessor; and first to accept participants with severe or life-threatening history.

- The data suggest that AR101 could potentially be useful in the treatment of peanut allergy in a highly sensitive population of children and adolescents.