The Efficacy of AR101, a Peanut-Derived Pharmaceutical for Oral Immunotherapy (OIT), is Maintained and Tolerability is Increased with Low-Dose Maintenance Therapy

This study was sponsored by Aimmune Therapeutics
Background

• Currently there is no FDA-approved therapy for peanut allergy which is rarely outgrown and prevalence is increasing, affecting >5 million patients in U.S. and EU today

• AR101 is a highly characterized, pharmaceutical-grade, peanut OIT formulation, standardized in its protein content and tested for Ara h1, h2, and h6, to provide consistent dosing of all peanut allergens

• In a previously reported double-blind, placebo-controlled Phase 2 study (ARC001), AR101 appeared to have an acceptable safety profile and desensitized 79% of subjects to 443 mg on an ITT basis and 100% of subjects on a completer basis
ARC002: An Open-label Phase 2b study

ARC002 consist of 2 parts (re-consent required between them)
• Part I – Maximum daily dose is 300 mg; efficacy and safety readouts

Objectives:
• Confirm the efficacy and safety findings of up-dosing in ARC001
• Evaluate the efficacy and safety of maintenance dosing at 300 mg/day

Endpoints:
1. Incidence of treatment-related adverse events
2. Percent of subjects desensitized during DBPCFC (post-up-dosing), defined as ingestion with no more than mild symptoms:
   • 300 mg (443 mg cumulative) of peanut protein
   • 600 mg (1043 mg cumulative) of peanut protein
   • 1000 mg (2043 mg cumulative) of peanut protein
• Satisfied the inclusion/exclusion criteria for ARC001

**Key inclusion criteria:**
• Ages 4 – 26 years
• History of peanut allergy
• Peanut-specific IgE ≥0.35 kU/L and/or SPT ≥3 mm
• Dose-limiting symptoms to ≤143 mg of peanut protein in ARC001 Screening DBPCFC

**Key exclusion criteria:**
• History of life-threatening anaphylaxis
• History of EGID
• Severe asthma or mild/moderate asthma if poorly controlled
ARC002 Study Design: Overview

ARC001

Placebo

ARC002: Placebo Crossover Subjects

Placebo Crossover:
Up-dosing Period ~22 wks
(schedule as per ARC001)

Plateau Period
~12 wks
(300 mg/day)

ARC001

Active

ARC002: Active Rollover Subjects

Plateau Period
~12 wks
(300 mg/day)

Part 2: Optional high-dose up-titration to 2000 mg and Extended Maintenance at 300 mg/d or 2000 mg/d, max.

Post-Up-dosing DBPCFC
Up to 600 mg
(1043 mg cumulative)

Post-Plateau DBPCFC
Up to 1000 mg
(2043 mg cumulative)
ARC002: Enrollment and Disposition

- Former ARC001
  - Placebo
    - Crossover
      - Placebo Crossover
        - Placebo Crossover
          - Placebo Crossover
            - Failed Post-Up-dosing FC: n = 1
              - GI adverse event (4)
              - Scheduling issues (1)
            - Up-Dosing Completers
              - Active Rollover Plateau Completers
                - N = 40
          - Active Rollover Plateau Completers
            - Former ARC001
              - Active
                - Active Rollover
                  - Active Rollover Plateau Completers
                    - N = 40
        - Active Rollover
          - Up-Dosing Completers
            - Early Discontinuation: n = 1
              - Scheduling issues
          - N = 23
    - N = 26
  - N = 26
- Declined: N = 2

- Failed Post-Up-dosing FC: n = 1
  - Early Discontinuation: n = 5
    - GI adverse event (4)
    - Scheduling issues (1)
### ARC002: Demographics (Safety/ITT)

<table>
<thead>
<tr>
<th></th>
<th>Placebo Crossover N=26</th>
<th>Active Rollover N=21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, Median</strong></td>
<td>8.5 years (5 to 14)</td>
<td>8.0 years (4 to 21)</td>
</tr>
<tr>
<td><strong>Gender, n</strong></td>
<td>16 male 10 female</td>
<td>14 male 7 female</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (4)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Black or African-American</td>
<td>2 (8)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>20 (77)</td>
<td>18 (86)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (8)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

**Treatment arms overall adequately balanced**
Placebo Crossover Subjects Experience Similar Desensitization Rate as Active Therapy Subjects at Post-Up-dosing DBPCFC (ITT)

- Placebo Crossover N=26
- Placebo (ARC001) N=29
- Active Crossover N=26
- Active (ARC001) N=29

Percent of Subjects Tolerating

- Placebo Crossover: 77% (n=20)
- Active Crossover: 79% (n=23)
- Placebo: 65% (n=17)
- Active: 62% (n=18)

Challenge Dose, mg
- 300
- 600

Cumulative Dose, mg
- 443
- 1043
Placebo Crossover Subjects Experience Similar Desensitization Rate as Active Therapy Subjects at Post-Up-dosing DBPCFC (Completers)

- Placebo Crossover: N=21
  - Percentage Tolerating: 95% (n=20)

- Active (ARC001): N=23
  - Percentage Tolerating: 100% (n=23)

- Placebo Crossover: N=21
  - Percentage Tolerating: 81% (n=17)

- Active (ARC001): N=23
  - Percentage Tolerating: 78% (n=18)

**Challenge Dose, mg**
- Placebo Crossover: 300 mg
- Active (ARC001): 600 mg

**Cumulative Dose, mg**
- Placebo Crossover: 443 mg
- Active (ARC001): 1043 mg
AR101 Significantly Reduced Symptom Severity and Epi Use at Post-Up-Dosing DBPCFC

**Placebo Crossover DBPCFC Symptoms Prior to Receiving AR101**

<table>
<thead>
<tr>
<th>Challenge dose, mg</th>
<th>Cumulative dose, mg</th>
<th>n=26</th>
<th>n=25</th>
<th>n=23</th>
<th>n=17</th>
<th>n=12</th>
<th>n=6</th>
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<tbody>
<tr>
<td>3</td>
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<td>10</td>
<td>13</td>
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<td>15</td>
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<tr>
<td>30</td>
<td>43</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>100</td>
<td>143</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>300</td>
<td>443</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>600</td>
<td>1043</td>
<td></td>
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</tbody>
</table>

Maximal Symptom Severity:
- None
- Mild
- Moderate
- Severe

**Epinephrine Use by Subject:**
- None: 15 (58%)
- 1 injection: 8 (31%)
- 2 injections: 3 (12%)

**Placebo Crossover DBPCFC Symptoms AFTER AR101 Up-dosing**

<table>
<thead>
<tr>
<th>Challenge dose, mg</th>
<th>Cumulative dose, mg</th>
<th>n=21</th>
<th>n=21</th>
<th>n=21</th>
<th>n=21</th>
<th>n=21</th>
<th>n=19</th>
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<tbody>
<tr>
<td>3</td>
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<tr>
<td>100</td>
<td>143</td>
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<td></td>
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</tr>
<tr>
<td>300</td>
<td>443</td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>600</td>
<td>1043</td>
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</tbody>
</table>

**Epinephrine Use by Subject:**
- None: 21 (100%)
- 1 injection: 0
- 2 injections: 0
Desensitization Is Maintained at the Post-Plateau FC in Both Groups (ITT)

<table>
<thead>
<tr>
<th>Challenge dose, mg</th>
<th>Cumulative dose, mg</th>
<th>Placebo Crossovers n=26</th>
<th>Active Rollovers n=21</th>
<th>All Subjects n=47</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>443</td>
<td>77</td>
<td>95</td>
<td>85</td>
</tr>
<tr>
<td>600</td>
<td>1043</td>
<td>65</td>
<td>90</td>
<td>77</td>
</tr>
<tr>
<td>1000</td>
<td>2043</td>
<td>50</td>
<td>62</td>
<td>51</td>
</tr>
</tbody>
</table>

Percent of Patients Tolerating
Desensitization Is Maintained at the Post-Plateau FC in Both Groups (Completers)

![Bar chart showing percent of patients tolerating different cumulative and challenge doses for Placebo Crossovers and Active Rollovers.](chart)

- **Placebo Crossovers n=20**
  - Challenge dose, mg: 300, 600, 1000
  - Cumulative dose, mg: 443, 1043, 2043
  - Percent of patients tolerating: 100, 95, 85

- **Active Rollovers n=20**
  - Challenge dose, mg: 300, 600, 1000
  - Cumulative dose, mg: 443, 1043, 2043
  - Percent of patients tolerating: 100, 90, 65

- **All Subjects n=40**
  - Challenge dose, mg: 300, 600, 1000
  - Cumulative dose, mg: 443, 1043, 2043
  - Percent of patients tolerating: 100, 90, 60
Safety: Numbers of subjects with AEs during 3-month Plateau Period reduced compared with Up-dosing Period

<table>
<thead>
<tr>
<th>Treatment Period:</th>
<th>Placebo Crossovers:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=26</td>
</tr>
<tr>
<td></td>
<td>Up-Dosing</td>
</tr>
<tr>
<td>Subjects with any AE, n (%)</td>
<td>25 (96)</td>
</tr>
<tr>
<td>Mild</td>
<td>12 (46)</td>
</tr>
<tr>
<td>Moderate</td>
<td>12 (46)</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (4)*</td>
</tr>
<tr>
<td>Treatment Related AE</td>
<td>19 (73)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>3 (12)^†</td>
</tr>
<tr>
<td>Anaphylaxis (non-SAE)</td>
<td>1 (4)^‡</td>
</tr>
<tr>
<td>SAE</td>
<td>0</td>
</tr>
</tbody>
</table>

*Unrelated to treatment, AE of gastroenteritis
†All involving GI AEs
‡mild anaphylaxis at 80 mg, subject completed up-dosing
## Placebo Crossovers: Safety in Up-Dosing vs Plateau (Exposure-Adjusted)

<table>
<thead>
<tr>
<th>Treatment Period: (Total Subject·Days)</th>
<th>Placebo Crossovers N = 26</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Up-Dosing (3749)</td>
</tr>
<tr>
<td><strong>Exposure-Adjusted AE Incidence or Events per Subject·Day</strong></td>
<td></td>
</tr>
<tr>
<td>Adverse Event</td>
<td>0.0568</td>
</tr>
<tr>
<td>Severe AE</td>
<td>0.0003</td>
</tr>
<tr>
<td>Related AE</td>
<td>0.0323</td>
</tr>
<tr>
<td>Related Severe AE</td>
<td>0</td>
</tr>
</tbody>
</table>

**Treatment Period**
- Up-Dosing: 3749
- Plateau: 1882
SPT Wheal Diameter, Increases in IgG4 and Decreases in IgE/IgG4 Ratio Were Similar Between Placebo Crossovers and Active Subjects (Completers)

**ARC002: Placebo Crossovers**

- Median Peanut Wheal, mm
  - Baseline: 10, Post-Up-Dosing: 5
  - $p = 0.0105$

- IgG4, kUa/L
  - Baseline: 2, Post-Up-Dosing: 4
  - $p = 0.0001$

- IgE/IgG4
  - Baseline: 120, Post-Up-Dosing: 40
  - $p = 0.0002$

**ARC001: Actives**

- Median Peanut Wheal, mm
  - Baseline: 15, Post-Up-Dosing: 5
  - $p < 0.0001$

- IgG4, kUa/L
  - Baseline: 3, Post-Up-Dosing: 6
  - $p < 0.0001$

- IgE/IgG4
  - Baseline: 120, Post-Up-Dosing: 30
  - $p < 0.0001$
Summary

• Placebo crossover, open label subjects confirmed findings from ARC001
  – Desensitization to 443 mg is achieved with ~22-week up-dosing period to 300 mg/d of AR101

• For those who completed approximately ~ 9 months of AR101 therapy (up-dosing and maintenance)
  – 100% tolerated 443 mg cumulative of peanut protein
  – 90% tolerated 1043 mg
  – 60% tolerated 2043 mg

• Preliminary evidence suggests that the safety and tolerability of AR101 improves during maintenance therapy relative to up-dosing
Conclusion and Next Steps

• AR101 appears to safely and effectively desensitize to peanut allergy in a controlled OIT regimen

• Next Steps
  – ARC002 Part II: Optional High-dose Up-Dosing and Extended Maintenance
    – Longer-term safety and tolerability
    – Longer-term changes in IgE and IgG4
  – PALISADE Phase 3 trial of AR101 (initiated 2015, enrolling)
Thank you for your attention

• Special thanks to study volunteers and their families

• Thanks also to the dedicated physicians, nurses, and staff at:
  – Allergy & Asthma Medical Group, San Diego - Mary Vales and Sarah Holland
  – Arkansas Children's Hospital - Denise Pearson
  – Boston Children’s Hospital - Heather Biehl and Sara Little
  – Children's Hospital of Philadelphia - Deirdre Burke
  – Children’s Medical Center of Dallas - Amy Arneson
  – Cincinnati Children's Hospital Medical Center - Lisa Clark
  – Icahn School of Medicine at Mount Sinai - Sally Noone
  – University of North Carolina School of Medicine - Jill French and Pamela Steele

The ARC001 study was sponsored by Aimmune Therapeutics, a company formerly known as Allergen Research Corporation (ARC)