Outcome of 583 Entry Double-Blind Placebo-Controlled Peanut Challenges During Screening for the PALISADE Phase 3 Oral Immunotherapy (OIT) Trial

Brian P Vickery[1,2], Kirsten Beyer[3], A Wesley Burks[1], Thomas Casale[4], Jonathan OB Hourihane[5], Stacie M Jones[6], Amr Radwan[2], Andrea Vereda[2], Daniel C Adelman[2], for the ARC003 Study Group

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]Aimmune Therapeutics, Brisbane, CA, [3]University Hospital Charite, Berlin, Germany, [4]Morsani College of Medicine, University of South Florida, Tampa, FL, [5]University College Cork, Cork, Ireland, [6]University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, AR

Aimmune™ Therapeutics
8000 Marina Boulevard, Suite 200
Brisbane, CA 94005-1884
Phone: (650) 614-5220
Fax: (650) 616-0075

ABSTRACT #L20

- **Rationale:** Standardized double-blind, placebo-controlled food challenges (DBPCFCs) can experimentally model the poorly understood relationship between threshold allergen sensitivity and reaction severity. 583 DBPCFCs were recently conducted during North American screening for PALISADE (Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults), a randomized, placebo-controlled, international Phase 3 trial of AR101 for peanut allergy
- **Methods:** Subjects aged 4-55 years with a clinical history of immunoglobulin E (IgE)-mediated peanut allergy underwent a baseline DBPCFC conducted according to Practical Issues in Allergology, Joint United States/European Union Initiative (PRACTALL) guidelines with up to 144 cumulative milligrams of peanut protein. Preliminary pre-randomization data were summarized with descriptive statistics
- **Results:** 583 subjects (62% male; mean age, 11.3 [standard deviation (SD) 7.1] years) underwent DBPCFC. Median [interquartile ranges (IQR)] peanut- and Ara h 2-specific IgEs (kU_A/L) were 56.6 [10.7-187] and 37.6 [7.4-98.9], and peanut skin prick tests (SPTs) were 11 mm [8.5-15]. 457 subjects (78%) experienced dose-limiting symptoms (DLS) at a cumulative median [IQR] 44 mg peanut protein [14-144], whereas 116 (20%) consumed all 144 mg without symptoms. 10 (2%) reacted to placebo. 228 doses of epinephrine were administered, with 162 subjects receiving 1 dose, 27 receiving 2, and 4 receiving 3. Three DBPCFC-related serious adverse events of anaphylaxis occurred; overall, 5% of DBPCFC symptoms were graded severe
- **Conclusions:** This unique dataset of DBPCFCs is the largest ever collected on peanut-allergic subjects in the clinical trial context and will be used to explore predictors of sensitivity and severity. While serious or severe reactions were rare, epinephrine utilization was quite common, suggesting that epinephrine use alone may not indicate DBPCFC severity. DBPCFCs can be conducted safely by trained allergists, and are a critically useful research tool

BACKGROUND

- Peanut allergy is a common and serious condition that often affects children and is commonly associated with severe reactions, including life-threatening anaphylaxis
- DBPCFC is considered the gold standard in diagnosis of food allergy[1,2]
- Standardized DBPCFCs can experimentally model the poorly understood relationship between threshold allergen sensitivity and reaction severity
- DBPCFCs were recently conducted during screening for PALISADE, a randomized, placebo-controlled, international Phase 3 trial of AR101 for peanut allergy[3]
- Preliminary pre-randomization North American data from PALISADE are summarized here

METHODS

- Eligible subjects aged 4-55 years with a clinical history of IgE-mediated peanut allergy and evidence of peanut sensitization underwent a screening DBPCFC
  - Screening DBPCFCs included both a peanut challenge (defatted peanut flour) and a placebo challenge (oat flour), both containing sensory-tested masking additives, on separate days after antihistamine washout of 5 half-lives
  - The screening DBPCFC was an abbreviated version of the DBPCFC described in the PRACTALL guidelines, and progressed through the dose levels (1, 3, 10, 30, and 100 mg doses of peanut protein) in an unaltered sequence, without repeating any dose. Doses were given at 20- to 30-minute intervals, but investigators could increase the interval to 60 minutes to observe emerging symptoms
  - DBPCFC stopping criteria were prespecified in the protocol, based on PRACTALL guidelines, and required the presence of 1 or more investigator-determined dose-limiting symptoms (DLS), which were generally objective
  - Investigators graded the severity of allergic symptoms during DBPCFCs using National Cancer Institute Common Toxicity Criteria grading scales previously modified and established by the Consortium of Food Allergy Research
  - The protocol used the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID-FAAN) criteria to establish the case definition of anaphylaxis,[4] and the European Academy of Allergy and Clinical Immunology (EAACI) grading scale to assign anaphylaxis severity[5]
- Subjects who had DLS at or before the 100-mg (144 mg cumulative) challenge dose of peanut protein were enrolled into the PALISADE study

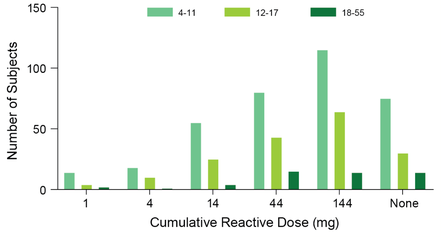
RESULTS

Table 1. North American Subject Demographics

Characteristic	Population (N=583)
Mean age Years (SD)	11.3 (7.1)
Male sex	62%
Peanut-specific IgE* Median (Q1, Q3), kU_A/L	56.6 (10.7, 187.0)
Ara h 2-specific IgE† Median (Q1, Q3), kU_A/L	37.6 (7.4, 98.9)
Peanut SPT wheal diameter Mean (range), mm	11.0 (8.5 to 15.5)

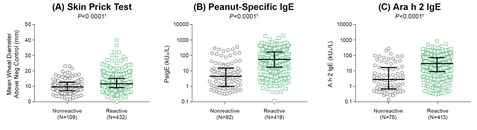
*n=543.
†n=513.

Figure 1. Cumulative Amount of Peanut Protein Causing Dose-Limiting Symptoms During the Screening DBPCFC, by Age (N=583)



- 457 subjects (78%) experienced DLS at a cumulative median [IQR] 44 mg of peanut protein [14-144] **(Figure 1)**
  - No correlation between age and sensitivity was found (not shown)
- 116 subjects (20%) did not experience DLS up to a cumulative reactive dose of 144 mg
- 10 subjects (2%) reacted to placebo

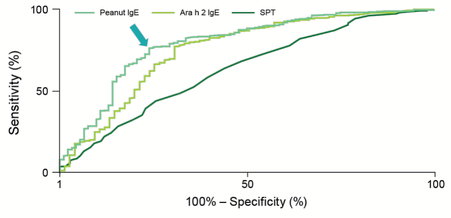
Figure 2. Immune Parameters Among Reactors and Nonreactors to the Screening DBPCFC*



*Medians and IQR shown.
†Mann-Whitney 2-tailed t-test.

- Median peanut wheal diameter, peanut-specific IgE, and Ara h 2-specific IgE were statistically significantly greater in reactive subjects compared with nonreactive subjects **(Figure 2A-C)**

Figure 3. Predictors of Reacting at or Before 144 mg Peanut Protein During the Screening DBPCFC



IgE Value	Sensitivity	95% CI	Specificity	95% CI	LR
>19.25	76.13	71.76%-80.14%	76.09	66.06%-84.37%	3.184

LR, likelihood ratio.

- Peanut-specific IgE demonstrated greater accuracy compared with Ara 2 h-specific IgE and peanut wheal diameter, for discriminating reactors from nonreactors to DBPCFC, based on receiver operating characteristic curve analysis **(Figure 3)**
- Peanut-specific IgE levels correlated positively with cumulative reactive dose [Spearman's rank correlation coefficient 0.2143, 95% CI 0.1301 to 0.2954] (not shown)

Table 2. Symptoms Occurring in ≥5% of Subjects During DBPCFC

Symptoms	Subjects Who Experienced an Adverse Event (N=580) n (%)	Adverse Events per Dose of FC* n (%)
Abdominal pain/cramping/discomfort	248 (42%)	391 (16%)
Pruritus/itching	213 (36%)	315 (13%)
Nausea	211 (36%)	290 (12%)
Mouth tingling/itching	192 (33%)	386 (16%)
Vomiting	160 (27%)	193 (8%)
Rhinorrhea/nasal congestion	114 (19%)	161 (7%)
Hives	111 (19%)	142 (6%)
Rash	110 (19%)	145 (6%)
Throat tightness/discomfort	94 (16%)	151 (6%)
Skin flushing	63 (11%)	75 (3%)
Cough	54 (9%)	74 (3%)
Sneezing	51 (9%)	66 (3%)
Wheezing	35 (6%)	38 (2%)
Conjunctivitis	30 (5%)	52 (2%)
Anaphylaxis	28 (5%)	5 (0.2%)

FC, food challenge.
*Total doses were 2437.

- 28 subjects (5%) were judged by the investigator to meet NIAID-FAAN criteria for anaphylaxis

Figure 4A. Symptom Severity During the Screening DBPCFC

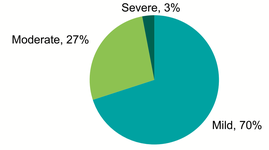


Figure 4B. Distribution of Reactive Doses Among Subjects Having a Severe Symptom (n=54) or Anaphylaxis (n=28) During the Screening DBPCFC

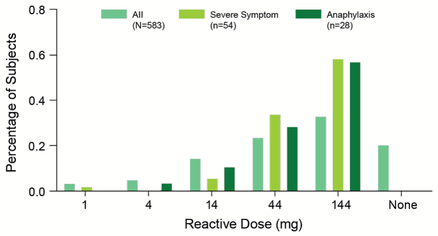
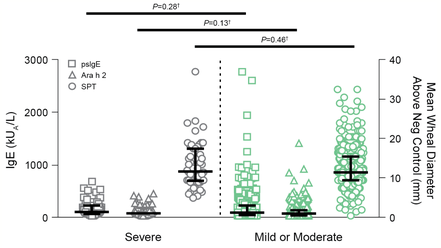


Figure 4C. Immune Parameters by Severity of Worst Symptom During the Screening DBPCFC*



*Medians and IQR shown.
Mann-Whitney 2-tailed t-test.

- Three subjects (0.5%) experienced serious adverse events related to the DBPCFC, all anaphylaxis (not shown)
- The distribution of reactive doses among subjects with severe symptoms and/or anaphylaxis was similar to the distribution among all subjects **(Figure 4B)**
- Peanut-specific IgE, Ara h 2-specific IgE, and peanut mean wheal diameters were not different in subjects with severe symptoms compared with subjects with mild or moderate symptoms **(Figure 4C)**

Table 3. Most Commonly Used Rescue Medications During the Screening DBPBFC

Medication	Uses (n)
Diphenhydramine	307
Cetirizine	271
Epinephrine	240
Prednisone	75
Ranitidine	64
Albuterol	61
Famotidine	54
Prednisolone	43

- 240 doses of epinephrine were administered, with 198 subjects receiving 1 dose, 37 receiving 2 doses, 4 receiving 3 doses, and 1 receiving 4 doses (not shown)

CONCLUSIONS

- Despite capping the highest dose of the screening DBPCFC at 100 mg, sensitivities were distributed across dose levels and age groups, independent of severity
- Peanut-specific IgE, Ara h 2-specific IgE, and peanut mean wheal diameters were significantly elevated in subjects reacting to the screening DBPCFC, compared with nonreactors
  - Of these 3, peanut-specific IgE provided the most utility to discriminate the 2 populations, at a threshold of 19.25 kU_A/L
- Sensitivity to peanut and severity of symptoms during screening DBPCFCs were not closely linked, and neither was associated with baseline immune parameters or age
- Whereas protocol-defined anaphylaxis was uncommon, most subjects did have multiple symptoms, and investigators frequently used epinephrine

IMPLICATIONS/FUTURE DIRECTIONS

- This unique dataset of DBPCFCs is the largest ever collected on peanut-allergic subjects in the clinical trial context and provides valuable data for future study
- The data suggest that
  1. DBPCFCs can be conducted safely by trained community allergists;
  2. Epinephrine use alone is not an adequate proxy for systemic or severe reactions occurring during DBPCFCs; and
  3. More work is needed to understand the determinants of, and relationship between, sensitivity and severity.

REFERENCES

1. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, et al. Standardization of food challenges in patients with immediate reactions to foods—position paper from the European Academy of Allergology and Clinical Immunology. *Allergy*. 2004;59(7):690-697.
2. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol*. 2012;130(6):1260-1274.
3. Clinicaltrials.gov website. Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE). https://clinicaltrials.gov/ct2/show/NCT02635776. Accessed January 20, 2017.
4. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117(2):391-397.
5. Muraro A, Roberts G, Clark A, et al. The management of anaphylaxis in childhood: position paper of the European Academy of Allergology and Clinical Immunology. *Allergy*. 2007;62(8):857-871.

ACKNOWLEDGEMENTS

We are grateful to the subjects and their families for their participation in this study. We appreciate the contributions of the investigators, coordinators, and other staff at each of the PALISADE study sites. This study (Clinicaltrials.gov NCT02635776) was sponsored by Aimmune Therapeutics.

2017 AAAAI Annual Meeting, Atlanta, Georgia, March 3-6, 2017. Abstract #L20.