P339

Presented at the
Annual Scientific Meeting of the American College of Allergy, Asthma, and Immunology (ACAAI)
Boston, MA • October 26–30, 2017

International Comparisons of Patient Characteristics in a Phase 3 Study of AR101 for Peanut Allergy

Ellen Zigmont,[1] Rezi Zawadzki,[1] Kirsten Beyer,[2] A. Wesley Burks,[3] Thomas Casale,[4] Jonathan O'B Hourihane,[5] Stacie M. Jones,[6] Andrea Vereda,[1] Brian P. Vickery,[1,3] Daniel C. Adelman[1]

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

BACKGROUND

- Peanut allergy is a common and serious condition, which often affects children and is frequently associated with severe reactions, including life-threatening anaphylaxis
- Double-blind placebo-controlled food challenge (DBPCFC) is considered the gold standard in diagnosis of food allergy[1,2]
- PALISADE is a recent phase 3, international, randomized, placebo-controlled study conducted in North America (NA) and Europe (EU), which included screening DBPCFCs of eligible subjects (Clinicaltrials.gov Identifier: NCT02635776)

OBJECTIVE

- To evaluate reactivity during DBPCFC, epinephrine use, and clinical and immunologic characteristics in an international population of subjects with a clear history of peanut allergy

METHODS

- Eligible subjects aged 4–55 years with a clear clinical history of immunoglobulin E (IgE)-mediated peanut allergy, a positive peanut skin prick test (SPT), and/or positive peanut-specific IgE (pslgE), underwent a screening DBPCFC up to 144 mg (cumulative dose) peanut protein based on the PRACTALL guidelines[3]
- The 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
  - —The DBPCFCs progressed through the dose levels (1-, 3-, 10-, 30-, and 100-mg doses of peanut protein) in an unaltered sequence, without repeating any dose.
  - —DBPCFC stopping criteria were prespecified in the protocol, based on the PRACTALL guidelines,[3] and required the presence of 1 or more investigator-determined dose-limiting symptoms (DLSs), which were generally objective
  - —Investigators graded the severity of allergic symptoms during DBPCFCs
- Subjects who had a DLS at or before the 100-mg (144-mg cumulative) challenge dose of peanut protein were eligible for the PALISADE study
  - —Only subjects who completed the 2-day DBPCFC with no reaction to placebo were considered to have evaluable DBPCFC results and included in this analysis

RESULTS

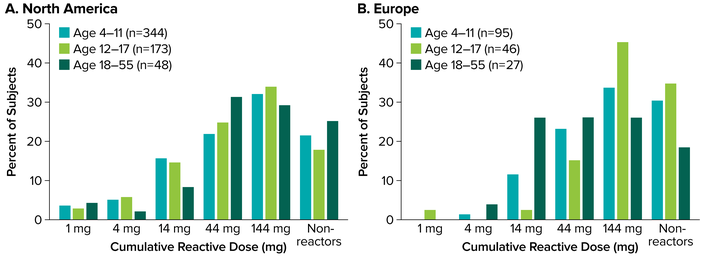
All Subjects

Table 1. Demographics of the Subjects With Evaluable DBPCFC Results

Characteristics, n (%)		North American Population (n=565)	European Population (n=168)
Sex	Male	346 (61)	99 (59)
	Female	219 (39)	69 (41)
Age	4–11 years	344 (61)	95 (57)
	12–17 years	173 (31)	46 (27)
	18–55 years	48 (9)	27 (16)
Allergic rhinitis		438 (78)	94 (56)
Asthma		290 (51)	82 (49)
Atopic dermatitis		352 (62)	89 (53)
Other food allergy		390 (69)	84 (50)

- Of the 761 subjects with a clear clinical history of peanut allergy undergoing the screening DBPCFC, 733 had evaluable results (96%; NA, n=565; EU, n=168). (**Table 1**)

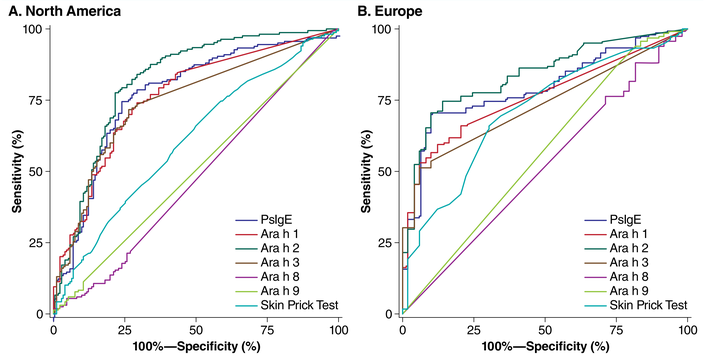
Figure 1. Distribution of Responses to the Screening DBPCFC by Age for NA vs EU



DBPCFC, double-blind placebo-controlled food challenge; EU, Europe; NA, North America.

- 448 (79%) NA subjects and 118 (70%) EU subjects reacted at or before a cumulative dose of 144 mg peanut protein ("reactors"), whereas 117 (21%) NA and 50 (30%) EU subjects failed to react at any dose level ("nonreactors") (**Figure 1**)

Figure 2. Predictors of Reaction During Screening DBPCFC for NA (n=565) vs EU (n=168)



- In both the NA and EU populations, based on receiver operating characteristic curve analysis, the best indicator to discriminate reactors from nonreactors was Ara h 2-specific IgE, followed by pslgE (**Figure 2**)

Reactors Only

- 60% of NA and 56% of EU reactors were aged 4–11 years; 32% and 25% were aged 12–17; whereas 8% and 19% were aged 18–55

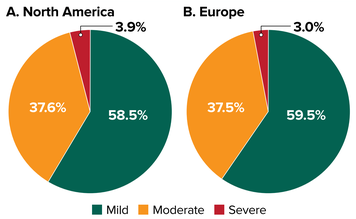
Table 2. Immune Parameters Among Reactors to the Screening DBPCFC by Population

Parameters, mean (SE), n	North America	Europe	*P* value
Skin Prick Test [mm[a]]	13.0 (0.3), 447	11.1 (0.3), 118	0.0009
pslgE [kU/L]	160.3 (11.7), 442	108.7 (20.2), 116	<0.0001
Ara h 2 IgE [kU/L]	83.6 (5.8), 441	49.6 (8.1), 116	<0.0001
Ara h 3 IgE [kU/L]	16.9 (1.5), 436	11.8 (2.6), 116	0.0005
Ara h 8 IgE [kU/L]	2.5 (0.5), 440	5.5 (1.9), 115	NS
Ara h 9 IgE [kU/L]	0.6 (0.1), 428	0.5 (0.1), 115	NS

[a]Wheal diameter above neg control. DBPCFC, double-blind placebo-controlled food challenge; NS, nonsignificant; pslgE, peanut-specific immunoglobulin E; SE, standard error.

- NA vs EU populations showed significant differences in immune parameters among reactors to the screening DBPCFC (**Table 2**)

Figure 3. Severity of DLSs for NA vs EU



DLSs, dose-limiting symptoms; EU, Europe; NA, North America.

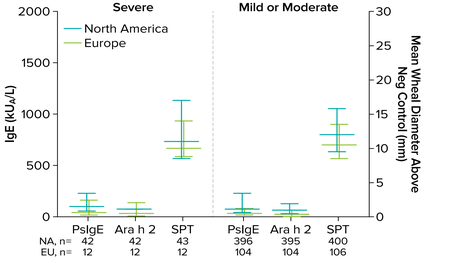
Table 3. DLSs Occurring in Reactors During Screening-DBPCFC by Symptom Group

Symptom Group, n (%)	North America (n=448)	Europe (n=118)	Total (n=566)
Gastrointestinal	368 (82)	103 (87)	471 (83)
Skin	277 (62)	69 (59)	346 (61)
Upper respiratory	166 (37)	76 (64)	242 (43)
Lower respiratory	165 (37)	46 (39)	211 (37)
Cardiovascular	17 (4)	8 (7)	25 (4)
Other	22 (5)	12 (10)	34 (6)

DBPCFC, double-blind placebo-controlled food challenge; DLSs, dose-limiting symptoms.

- 96% of NA and 97% of EU subjects experienced either mild or moderate symptoms (**Figure 3**; **Table 3**)

Figure 4. Immune Parameters by Severity of Worst Symptom During the Screening DBPCFC[a] for NA vs EU

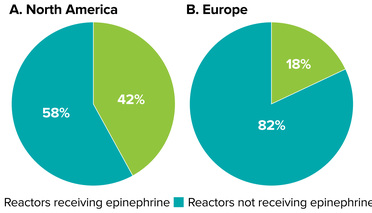


[a]Medians and interquartile range shown. DBPCFC, double-blind placebo-controlled food challenge; SPT, skin prick test.

- PslgE, 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 4**)

Epinephrine Use

Figure 5. Reactors by Epinephrine Use for NA vs EU



- 42% NA and 18% EU reactors received epinephrine as rescue medication during the screening DBPCFC (*P*<0.001) (**Figure 5**)

Table 4. Characteristics of Epinephrine Use by Population

Characteristic		North America	Europe
Amount of epinephrine use, %[a]	1 dose	84	71
	2 doses	15	29
	3 doses	1	0
Reactive dose where epinephrine was used, %[a]	1 mg	5	0
	3 mg	4	0
	10 mg	12	10
	30 mg	31	52
	100 mg	47	38
Symptoms by epinephrine use and group term, %[a]	Gastrointestinal	89	81
	Skin	69	81
	Lower respiratory	44	71
	Upper respiratory	42	71
	Cardiovascular	3	14
	Other	7	24
Subjects at each severity level receiving epinephrine, %	Mild	45	15
	Moderate	55	32
	Severe	70	69
Other rescue medication use, %[b]	Antihistamine	86	76
	Bronchodilators	11	20
	Corticosteroids	25	36
	H2 blockers, antacids, PPI	24	1
	Other	6	7

[a]Denominator is number of subjects using epinephrine per region (NA, n=189, EU, n=21). [b]Denominator is number of subjects who received rescue medication (NA, n=448, EU, n=118). PPI, proton pump inhibitor.

- Characteristics of epinephrine use to treat the DBPCFC reaction in NA and EU are shown in **Table 4**

CONCLUSIONS

1. This international cohort was similar demographically, clinically, and immunologically (with NA subjects having slightly higher Ara h 1, Ara h 2, and pslgE levels), and reacted to the screening DBPCFC similarly.
2. Despite this, NA and EU subjects were treated with rescue medication, and in particular epinephrine, differently during the screening DBPCFC. This could be due to differences in the perception of systemic symptoms or the practical indications for epinephrine use.
3. Based on these data, we hypothesize that epinephrine use is not a sufficient proxy for reaction severity, that regional practice variations drive differences in the use of rescue medications, and that early treatment with epinephrine could potentially avert the need for a second dose. However, more careful study will be needed to address these hypotheses.

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 ID: NCT02635776) was sponsored by Aimmune Therapeutics. Editorial assistance was provided by The Curry Rockefeller Group, LLC, Tarrytown, NY, which was funded by Aimmune Therapeutics.

Disclosures **EZ, RZ, AV, BPV, DCA:** Employment: Aimmune Therapeutics. **KB:** Research support: Aimmune, DBV, InfectoPharm, Thermo Fisher, Danone, Hipp, Hycor; Advisory board fees: Aimmune; Lecture honoraria/consultation fees: Aimmune, Thermo Fisher, Danone, Hycor, Meda, Nestle, ALK, Novartis, Bausch & Lomb, Allergopharma, HAL, Med Update, Infectopharm. **AWB:** Advisory board fees: Aimmune; Research support, consultation fees, and/or lecture honoraria: FARE, Wallace Research Foundation, Aimmune, Epiva, Genentech, Regeneron, Stallergenes, PPD, Allertein, Sanofi US. **TC:** Grant support and advisory board fees from Aimmune paid to university employer. **JO'BH:** Grant support: City of Dublin Skin and Cancer Hospital, National Children's Research Centre, Ireland, DBV Technologies; Advisory board fees: Aimmune; Lecture honoraria: Thermo Fisher, Nutricia, Servier. **SMJ:** Advisory board fees: Aimmune.

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