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University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Predicting probability of tolerating discrete amounts of peanut protein in allergic children using epitope-specific IgE antibody profiling

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Dianne E. Campbell | Hugh A. Sampson

ARTICLE SUMMARY

- Existing diagnostic testing is not predictive of severity or the threshold dose of clinical reactivity, and many patients still require an Oral Food Challenge (OFC). While OFCs are very useful for making an allergy diagnosis and determining clinical reactivity, they often cause anaphylaxis, which can increase patient anxiety. and are time and resource intensive.[1]
- An extensive validation was performed across 5 cohorts (all with confirmed oral food challenge results) across six different countries. Cohorts used: BOPI, OPIA, CAFETERIA, CoFAR6, and PEPITES with specimens from Australia, UK, US, Ireland, and Germany.
- This paper reports the first validated algorithm using two key peanut specific IgE epitopes to predict probabilities of reaction to different amounts of peanut in allergic subjects and may provide a useful clinical substitute for peanut oral food challenges.
- Using the algorithm, subjects were assigned into "high", "moderate", or "low" dose reactivity groups. On average, subjects in the "high" group were 4 times more likely to tolerate a specific dose, compared to the "low" group.[1] For example, 88% of patients in the high dose reactivity group were able to tolerate ≥ 144 mg of peanut protein whereas only 29% were able to tolerate the same amount in the low dose reactivity group.[1-2]

CLINICAL CONSIDERATIONS

- The new epitope test offers more granular information to help clinicians stratify treatment and peanut avoidance plans for their patients.
- See below for summary of clinical considerations based on threshold reactivity level.[1]

allergenis peanut diagnostic result	clinical considerations[1]
likely allergic – low dose reactor	• inform or avoid oral food challenge to reduce risk of anaphlyaxis • confirm strict avoidance of peanut • consider immunotherapy to reduce risk of reaction
likely allergic – moderate dose reactor	• consider a single oral food challenge (30 to 100 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider immunotherapy to reduce risk of reaction
likely allergic – high dose reactor	• consider a single oral food challenge (100 to 300 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider starting immunotherapy at higher doses to shorten time to maintenance dose
unlikely allergic	• oral food challenge to rule out the diagnosis of peanut allergy

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ORIGINAL ARTICLE

Food Allergy and Gastrointestinal Disease

Open-label follow-on study evaluating the efficacy, safety, and quality of life with extended daily oral immunotherapy in children with peanut allergy

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Abstract

Background: The benefit of daily administration of Peanut (*Arachis hypogaea*) Allergen Powder-dnfp (PTAH)—formerly AR101—has been established in clinical trials, but limited data past the first year of treatment are available. This longitudinal analysis aimed to explore the impact of continued PTAH therapeutic maintenance dosing (300 mg/day) on efficacy, safety/tolerability, and food allergy-related quality of life.

Methods: We present a subset analysis of PALISADE-ARC004 participants (aged 4–17 years) who received 300 mg PTAH daily for a total of ~1.5 (Group A, $n = 110$) or ~2 years (Group B, $n = 32$). Safety assessments included monitoring the incidence of adverse events (AEs), accidental exposures to food allergens, and adrenaline use. Efficacy was assessed by double-blind, placebo-controlled food challenge (DBPCFC);

Abbreviations: AE, adverse event; ARC004, PALISADE follow-on study; DBPCFC, double-blind placebo-controlled food challenge; FAIM, food allergy independent measure; FAQLQ, food allergy quality of life questionnaire; MWD, mean wheal diameter; PALISADE, peanut allergy oral immunotherapy study of AR101 for desensitization in children and adults; PTAH, peanut (Arachis hypogaea) allergen powder-dnfp; QoL, quality of life; SPT, skin prick test.

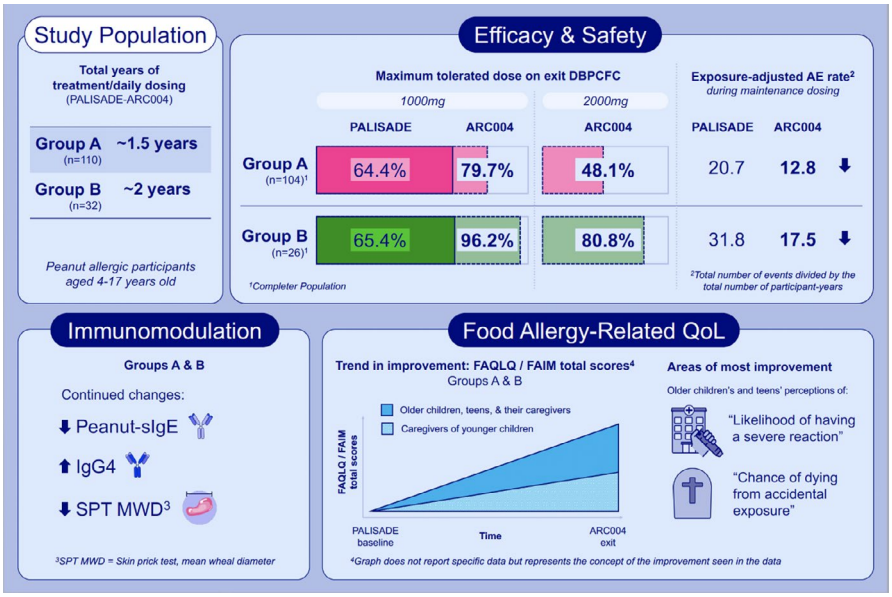
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skin prick testing; peanut-specific antibody assays; and Food Allergy Quality of Life Questionnaire (FAQLQ) and Food Allergy Independent Measure (FAIM) scores.

Results: Continued maintenance with PTAH increased participants' ability to tolerate peanut protein: 48.1% of completers in Group A (n = 50/104) and 80.8% in Group B (n = 21/26) tolerated 2000 mg peanut protein at exit DBPCFC without dose-limiting symptoms. Immune biomarkers showed a pattern consistent with treatment-induced desensitization. Among PTAH-continuing participants, the overall and treatment-related exposure-adjusted AE rate decreased throughout the intervention period in both groups. Clinically meaningful improvements in FAQLQ and FAIM scores over time suggest a potential link between increased desensitization as determined by the DBPCFC and improved quality of life.

Conclusions: These results demonstrate that daily PTAH treatment for peanut allergy beyond 1 year leads to an improved safety/tolerability profile and continued clinical and immunological response.

KEYWORDS
desensitization, food allergy, oral immunotherapy, peanut allergy, quality of life



GRAPHICAL ABSTRACT

Daily administration of Peanut (*Arachis hypogaea*) Allergen Powder-dnfp (formerly AR101) beyond the 1-year PALISADE trial (total treatment of ~1.5 or ~2 years) increased participants' ability to tolerate peanut protein. This was paralleled by a pattern of immunomodulation consistent with desensitization and an improved safety/tolerability profile. Treatment beyond 1 year was associated with clinically meaningful improvements in self-reported and caregiver-reported food allergy-related quality of life.

Abbreviations: AE, adverse event; ARC004, PALISADE Follow-on Study; DBPCFC, double-blind placebo-controlled food challenge; FAIM, Food Allergy Independent Measure; FAQLQ, Food Allergy Quality of Life Questionnaire; MWD, mean wheal diameter; PALISADE, Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults; PTAH, Peanut (Arachis hypogaea) Allergen Powder-dnfp; QoL, quality of life; SPT, skin prick test.

1 | INTRODUCTION

Peanut allergy (PA) affects approximately 1.6% to 2.0% of the population in Western countries.[1-3] It typically manifests in early childhood,[4] persists into adulthood,[5] and is associated with a relatively high risk of accidental exposure and severe allergic reactions, including anaphylaxis.[6,7] Standard management of PA includes strict avoidance of peanut and use of rescue medications—including adrenaline auto-injection—as treatment for allergic reactions following accidental exposure.[8] The demands of PA self-management

often cause stress and anxiety for patients and for caregivers and may result in substantial impairment of food allergy-related quality of life (FAQoL).[9]

Peanut (*Arachis hypogaea*) Allergen Powder-dnfp (PTAH, formerly known as AR101) is a first-in-class standardized oral biologic drug recently approved in the United States and Europe to mitigate allergic reactions that may occur with accidental exposure to peanuts in individuals 4–17 years of age with a confirmed diagnosis of peanut allergy.[10] The active ingredient in PTAH consists of defatted lightly roasted peanut flour characterized by a number of tests including high-performance liquid chromatography, enzyme-linked immunosorbent assay, and assay for protein content. This characterization includes a determination of the relative potency of the Ara h 1, Ara h 2, and Ara h 6 antigens and content uniformity for product release. Additional protein determinations, which include these antigens as well as Ara h 3 and Ara h 8, have been conducted to demonstrate that they are consistently present in a lot of peanut material used. The defatting process supports storage conditions, enables a more robust pharmaceutical processing, and may remove some of the peanut flavor.[11]

Two phase 3, randomized, placebo-controlled trials have evaluated daily PTAH in children and adolescents with PA: PALISADE (NCT03201003)[12] and ARTEMIS (NCT02635776).[13] In the PALISADE trial, participants from North America and Europe aged 4–55 years (N = 551) received PTAH or placebo for up to 12 months; the primary analysis population consisted of participants aged 4–17 years (N = 496).[12] The PALISADE trial demonstrated that once-daily OIT with PTAH increased participants' ability to tolerate peanut protein[12]; these findings were confirmed in the European phase 3 ARTEMIS trial again in individuals aged 4–17 years (N = 175).[13]

Participants completing the PALISADE trial, which showed that daily dosing of PTAH (300 mg) was well tolerated with no new safety concerns,[14] could enrol in the follow-on, open-label ARC004 study (NCT02993107). Although the clinical benefit of daily administration of PTAH had been established in PALISADE, ARTEMIS, and ARC004, there were limited data beyond 1 year of treatment. The post hoc longitudinal exploratory analysis of participant data from the start of PALISADE through the end of ARC004 was designed to assess whether the efficacy and tolerability of daily PTAH improved over time, over approximately 1.5 to 2 years of treatment, as well as to evaluate the effects of PTAH on FAQoL.

2 | METHODS

2.1 | Trial design and participants

Details of the PALISADE and ARC004 trials were previously reported.[12,14] Participants who completed PALISADE and received PTAH treatment and tolerated ≥300 mg peanut protein (443 mg cumulative) at PALISADE exit double-blind, placebo-controlled food challenge (DBPCFC), as well as those who were assigned to placebo, could elect to enter the ARC004 trial after providing written informed consent or assent, as appropriate. Participants received daily therapeutic maintenance dosing (300 mg/day) for 28 weeks (Group A) or 56 weeks (Group B), accounting for a total of ~1.5 and

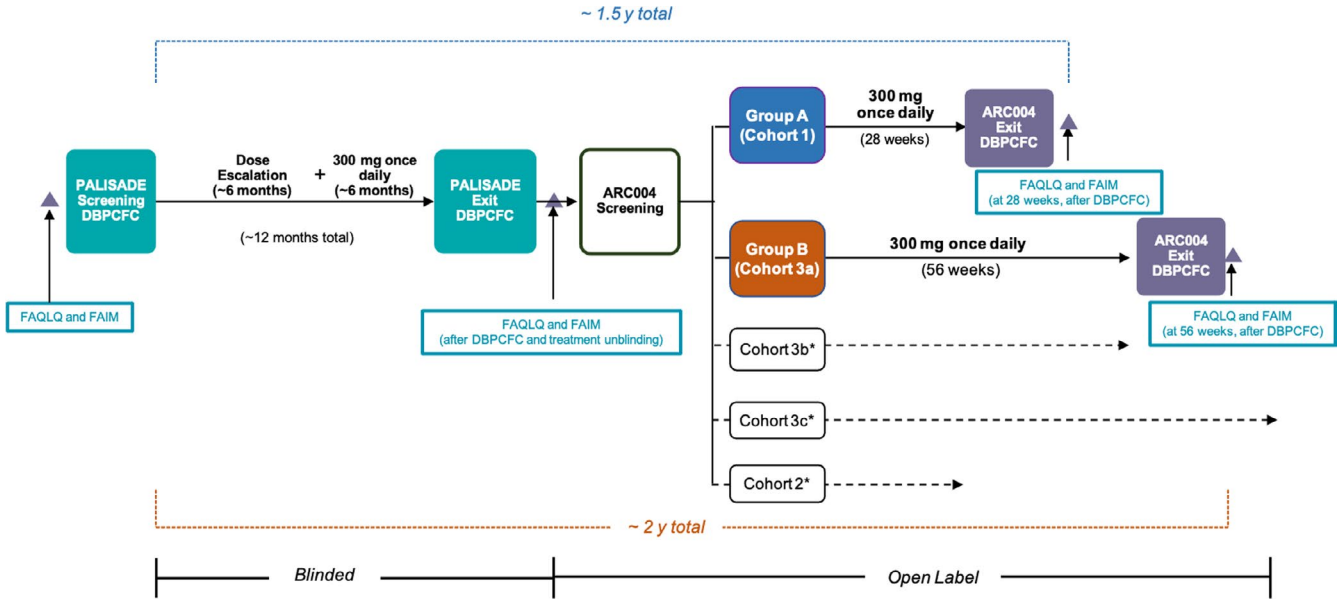


FIGURE 1 Treatment protocol. *Group A in this analysis was ARC004 Cohort 1 which continued daily PTAH treatment for an additional 28 weeks. Participants in Group B of this analysis were randomly assigned to daily PTAH treatment for an additional 56 weeks in ARC004 (Cohort 3a). Cohorts 2, 3B, and 3C represented the non-daily dosing cohorts. Cohort 2 initially received 300 mg every other day (4 weeks) and then 300 mg 138 twice weekly (24 weeks). Cohorts 3B and 3C initially received daily doses of 300 mg (28 weeks), followed by 300 mg every other day (4 weeks), and 300 mg twice weekly (duration of twice-weekly treatment varied).[14] Cohorts 2, 3B, and 3C are not discussed further in this paper. DBPCFC, double-blind, placebo-controlled food challenge; FAIM, Food Allergy Independent Measure; FAQLQ, Food Allergy Quality of Life Questionnaire; y, years

2 years of treatment, respectively, including PALISADE (Figure 1). Participants included in this analysis were 4–17 years of age at the time of entry to ARC003. Key inclusion and exclusion criteria are detailed in Table S1.

Efficacy was assessed by DBPCFC. Additional outcome measures included skin prick testing (SPT); peanut-specific antibody assays; and scores on the Food Allergy Quality of Life Questionnaire (FAQLQ) and Food Allergy Independent Measure (FAIM).[15,16] DBPCFCs were conducted at PALISADE screening (up 100 mg peanut protein, 144 mg cumulative) and exit (up to 1000 mg peanut protein, 2043 mg cumulative), and at ARC004 exit (up to 2000 mg peanut protein, 4043 mg cumulative). SPT and blood sample collections for peanut-specific antibody assays were performed at PALISADE entry and end of updosing, and at PALISADE and ARC004study exit/early discontinuation. The FAQLQ and FAIM were administered at PALISADE screening (before the entry DBPCFC), at PALISADE exit/ARC004 screening (after the DBPCFC and unblinding), and after the exit ARC004 DBPCFC (Figure 1).

Safety assessments included monitoring the incidence of adverse events (AEs)—including allergy symptoms, hypersensitivity reactions, systemic allergic reactions, and anaphylaxis. The protocol definition in PALISADE and ARC004 for anaphylaxis was consistent with both the US National Institute of Allergy and Infectious Diseases criteria and the Food Allergy and Anaphylaxis Network criteria. Severity was graded on a three-point scale, as recommended by the European Academy of Allergy and Clinical Immunology[17]. The term systemic allergic reaction was used to describe anaphylactic reaction events of any severity, and the term anaphylaxis was used to distinguish severe anaphylactic reaction events. Accidental exposures to food allergens and adrenaline use were also monitored and are reported here.

2.2 | Efficacy endpoints

The main efficacy endpoints included desensitization to peanut protein assessed as the proportion of participants tolerating each dose of peanut protein in the DBPCFCs, the single highest administered dose, the maximum severity of symptoms at each challenge dose, and the incidence of adrenaline use as a rescue medication during the DBPCFCs.

2.3 | Safety endpoints

Safety measures recorded included the incidence of treatment-emergent AEs (TEAEs), both related and unrelated, including serious AEs, during the overall study period (from entry into PALISADE to exit from ARC004). Other safety measures included the incidence of systemic allergic reactions; use of adrenaline as a rescue medication; AEs leading to discontinuation; gastrointestinal (GI) AEs of clinical interest; and accidental food allergen exposure.

All treatment periods were summarized for each group: the initial dose escalation (IDE) and updosing periods of PALISADE, the 24-week therapeutic maintenance dosing period of PALISADE, and the ARC004 therapeutic maintenance dosing period (28 weeks for Group A, 56 weeks for Group B). Since the total length of exposure was different in the two groups, total participant-years exposure and exposure-adjusted event rates were calculated.

2.4 | Immunological parameter assessment

Peanut-specific immunoglobulin E (psIgE) and peanut-specific immunoglobulin G4 (psIgG4) levels were measured using a commercial automated immunoassay system (ImmunoCAP, Thermo Fisher Scientific).[18] Changes in psIgE, psIgG4, and psIgE/IgG4 ratio were measured, and the psIgE/psIgG4 ratio was calculated. Changes in mean wheal diameter (MWD) of the peanut SPT were evaluated.

2.5 | Food allergy-related quality of life

As an exploratory endpoint, FAQoL was assessed by longitudinal change in scores on the FAQLQ[16,19] and the FAIM,[15] administered at PALISADE baseline, PALISADE exit (after the DBPCFC and treatment unblinding), and after the ARC004 exit DBPCFC (at 28 weeks for Group A or 56 weeks for Group B; Figure 1). A developer-referenced minimal important difference (MID)—defined as a reduction in mean score of ≥0.5 from baseline to study exit—was considered a clinically significant indication of change in FAQoL.[16,19,20,21]

2.6 | Data analysis

The safety population—defined as all participants enrolled in Group A and Group B who received ≥1 dose of PTAH during ARC004—was the primary population for all safety analyses. The completer population included all participants in the safety population who had an evaluable peanut exit ARC004 DBPCFC and was the analysis population used for all efficacy analyses involving the food challenges.

Data were summarized using descriptive statistics by group as change from baseline (from PALISADE entry to ARC004 exit). No specific hypothesis testing or comparisons between treatment groups were performed. The baseline for evaluating change in efficacy endpoints was the result associated with PALISADE exit (except for changes in FAQoL, which were relative to PALISADE baseline). Means and 95% confidence intervals (CIs) were used to describe FAQoL parameters.

3 | RESULTS

3.1 | Participant disposition and baseline characteristics

This analysis includes 142 participants aged 4–17 years who received daily dosing of PTAH in PALISADE and ARC004 (110 participants were assigned to Group A and 32 to Group B). Baseline

TABLE 1 Baseline demographics and clinical characteristics at PALISADE entry

Characteristic	Group A ($n = 110$) ~1.5 years of treatment	Group B ($n = 32$) ~2 years of treatment
Demographics		
Median age, y (Q1, Q3)	10.0 (7.0, 12.0)	8.0 (6.0, 13,0)
Sex, n (%) Male	58 (52.7)	18 (56.2)
Race, n (%) White	87 (79.1)	25 (78.1)
Allergy History		
Months since PA diagnosis, Median (Q1, Q3)	96.7 (61.6, 132.1)	74.2 (42.9, 116.4)
Systemic allergic reactions to peanut during lifetime, n (%)		
0	36 (32.7)	9 (28.1)
1	44 (40.0)	15 (46.9)
2	17 (15.5)	6 (18.8)
3	8 (7.3)	1 (3.1)
>3	5 (4.5)	1 (3.1)
Allergic rhinitis	80 (72.7)	21 (65.6)
Asthma	47 (42.7)	15 (46.9)
Atopic dermatitis	67 (60.9)	23 (71.9)
Food allergies other than peanut n (%)	68 (61.8)	18 (56.3)
Single MTD at PALISADE entry, *n* (%)		
None	5 (4.5)	4 (12.5)
1 mg	8 (7.3)	1 (3.1)
3 mg	23 (20.9)	6 (18.8)
10 mg	28 (25.5)	8 (25.0)
30 mg	46 (41.8)	13 (40.6)
Baseline Immunoglobulin and SPT results	**Group A**	**Group B**
SPT MWD, mm	$n = 110$	$n = 32$
Median (Q1, Q3)	11.5 (9.0, 15.0)	10.3 (8.0, 15.5)
Total IgE, IU/ml	$n = 106$	$n = 31$
Median, (Q1, Q3)	352.0 (163.0, 725.0)	386.0 (129.0, 903.0)
psIgE, kUA/L	$n = 110$	$n = 32$
Median (Q1, Q3)	62.7 (20.1, 172.0)	44.3 (7.9, 214.5)
psIgG4, mgA/L	$n = 102$	$n = 32$
Median (Q1, Q3)	0.5 (0.2, 1.1)	0.5 (0.3, 0.8)
psIgE/IgG4 ratio	$n = 102$	$n = 32$
Median (Q1, Q3)	138.1 (35.4, 348.4)	130.8 (17.3, 353.8)

Abbreviations: IgE, immunoglobulin E; IgG4, immunoglobulin G4; MTD, maximum tolerated dose; MWD, mean wheal diameter; PA, peanut allergy; ps, peanut-specific; SPT, skin prick test; Systemic allergic reaction, all severities (MedDRA preferred term anaphylactic reaction); y, years.

characteristics as of entry into PALISADE of both groups are shown in Table 1. Baseline characteristics are consistent with the overall and remaining populations of PALISADE.[12]

At exit from ARC004, Group A had received daily PTAH for approximately 1.5 years and Group B for approximately 2 years. The disposition of participants is shown in Figure S1. The completer population ($n = 130$) consisted of 104 (94.5%) Group A participants and 26 (81.3%) Group B participants. Two participants in these cohorts turned 18 during PALISADE and were included in this analysis but not included in the primary analysis, already published[14] (Group A, $n = 110$ [Cohort 1 in ARC004, $n = 109$]; Group B, $n = 32$ [Cohort 3a in ARC004, $n = 31$]). Two participants in Group A and 1 in Group B withdrew because of an AE.

3.2 | Efficacy

The percentage of participants able to tolerate higher doses of peanut at the exit DBPCFC rose with longer duration of PTAH treatment. At ARC004 exit, 80.8% of participants who completed ~2 years of treatment (Group B) tolerated the highest challenge dose of 2000 mg without dose-limiting symptoms, versus 48.1% of those who completed ~1.5 years of treatment (Group A) (Figure 2, Table S2).

The percentage of participants requiring adrenaline as rescue medication during the exit DBPCFCs differed between PALISADE and ARC004 (Table S3). During the ARC004 exit DBPCFC, the percentage of participants who received adrenaline as rescue medication was 24.0% for those who completed ~1.5 years of treatment (Group A) and 3.8% for those who completed ~2 years of treatment (Group B; Table S3).

3.3 | Safety

Most participants experienced one or more treatment-emergent AEs, which include related and unrelated AEs. No deaths or life-threatening AEs occurred. The total number of treatment-emergent AEs decreased during the course of the intervention period (PALISADE and ARC004) (Table 2). Similar trends were seen for more frequently reported AEs, which were mostly gastrointestinal and respiratory in origin (Table S4). For example, the percentage of participants experiencing abdominal pain declined from 41.8% during PALISADE IDE and updosing to 10.0% during ARC004 therapeutic maintenance dosing in Group A; and from 53.1% to 15.6% in Group B (Table S4).

The overall exposure-adjusted AE rate (total number of events divided by the total number of participant-years) decreased throughout the intervention period in both groups (Table 2). Highest exposure-adjusted AE rates were observed during IDE and updosing and decreased during the therapeutic maintenance. The lowest exposure-adjusted AE rates were observed during the ARC004 therapeutic maintenance period, when participants were exposed to PTAH for longer (Table 2).

Exposure-adjusted treatment-related AEs decreased from 56.6 events per participant-year during PALISADE IDE and updosing to 4.7 during ARC004 maintenance in Group B (~2 years treatment); a similar decrease was seen in Group A (~1.5 years treatment) (Table 2). Among participants not reporting any treatment-related AE during the first 6 months of therapeutic maintenance (in PALISADE), 65.6% (40/61) of Group A participants and 84.6% (11/13) of Group B participants continued to report no treatment-related AEs during ARC004 (Table S5).

Systemic allergic reactions caused by any trigger, including PTAH, food, or other allergen, occurred in 4.5% of participants in Group A and in 9.4% of Group B during therapeutic maintenance in PALISADE, and in 6.4% of participants in Group A and 15.6% of Group B during ARC004. Throughout treatment (PALISADE and ARC004), a total of 15 participants (10.6%, 15/142) presented with treatment-related systemic allergic reactions. More than half of the treatment-related systemic allergic reactions reported in Group B (61.1%, $n = 11/18$) were repeated events within the same 2 subjects, with identifiable cofactors (Table S6). Two severe systemic allergic reaction events (anaphylaxis) related to PTAH occurred during continued therapeutic maintenance dosing (ARC004) in Group A, one of which led to the discontinuation of one participant (Table S6). The percentage of participants receiving at least one dose of adrenaline ranged from 4.5% to 12.5% across groups and dosing periods (Table 2). Most events for which adrenaline was administered were mild to moderate in severity and occurred away from the study site (Table S7). No participant received more than one dose of adrenaline per event (defined as within a 2-h window; Table S7).

The percentage of participants reporting accidental food exposures ranged from 4.5% to 21.9% (Table 2). Exposures to peanut outside of study dosing were reported by fewer than 8% of participants in either group over the course of PALISADE and by 6.4% of Group A and 18.8% of Group B during extended maintenance in ARC004.

3.4 | Immunological parameter assessment

Initial immune markers were assessed at PALISADE screening and end of updosing, and at exit visits for both PALISADE and ARC004. Serum levels of psIgE decreased from PALISADE screening to ARC004 exit whereas psIgG4 increased (Figure 3). Although lower mean serum levels of psIgE at ARC004 exit were observed in Group B compared with Group A, it must be noted that Group B had lower baseline psIgE levels. Reductions were observed in the ratio of peanut-specific IgE/IgG4 from screening to ARC004 exit (Figure 3). Mean peanut SPT wheal diameters decreased from screening to ARC004 exit (Figure 3), with the most important reduction after the PTAH updosing.

3.5 | Food allergy-related quality of life

FAQoL was assessed at PALISADE screening and PALISADE exit and ARC004 exit using age-appropriate FAQLQ and FAIM instruments completed by participants aged 8–12 and 13–17 years (self-report), and caregivers of all participants (proxy-report). Scores from screening and both exits are reported (Figures S4, S2–S4). Changes in scores ≥0.5 are considered as clinically meaningful (minimal important difference [MID]) for FAQoL.

At PALISADE baseline, the mean scores for all participants and caregivers were within the typical range for their age groups.[22] Self-report FAQLQ total and domain scores for children (aged 8–12 years, Figure 4, S4) and teenagers (aged 13–17 years, Figure 4, S2) showed similar, consistent improvements from PALISADE screening to ARC004 exit. Mean changes in total FAQLQ self-reported scores in Groups A and B, respectively, were −0.75 (95% CI: −1.21, −0.29) and −0.44 (95% CI: −1.74, 0.85) in children, and −0.64 (95% CI: −1.18, −0.11) and −0.80 (95% CI: −1.72, 0.12) in teenagers.

The percentage of children and teenagers demonstrating clinically meaningful improvement in the FAQLQ total and domain scores (≥0.5) generally rose with duration of PTAH treatment (Figure 5, Table S8). Caregiver-reported scores for younger children (aged 4–6 years) did not show improvement from baseline (Figure S3), in comparison with those of older children (aged 7–12 years, Figure S3) and teenagers (aged 13–17 years, Figure S2), which were similar to those reflected in the self-report child and teenager scores. The percentage of caregiver documented meaningful improvements in FAQLQ total and domain scores (≥0.5) of their children (aged 7–12 years) and teenagers (aged 13–17) increased progressively from PALISADE baseline to ARC004 exit (Figure 5, Table S8).

Self-reported FAIM domain scores generally showed either improvements or no change from PALISADE baseline to ARC004 exit in children (aged 8–12 years, Figure S4) and teenagers (aged 13–17 years, Figure S2). Similar results were obtained in caregiver-reported scores for children (aged 4–12 years, Figure S4) and teenagers (aged 13–17 years, Figure S2). With regard to the individual items of FAIM, the greatest improvements were seen in "likelihood of having a severe reaction" and "chance of dying from accidental exposure" in teenagers (aged 13–17) and caregivers of teenagers (aged 13–17, Figure S2). FAIM items "likelihood of having a severe reaction" and "chance of dying from accidental exposure" demonstrated the highest percentage of children (aged 8–12 years) and teenagers (aged 13–17 years) gaining clinically meaningful improvement (≥0.5) that increased with duration of PTAH treatment (Table S9). Results obtained from caregiver documented improvements for children (aged 4–12 years) and teenagers (aged 13–17 years) showed similar trends (Table S9).

4 | DISCUSSION

The PALISADE trial and subsequent ARC004 follow-on study provide a rigorous evaluation of the efficacy, safety, and immunologic effects of OIT for peanut-allergic individuals up to 2 years of treatment.[12,14] In addition to continued increased peanut protein tolerability and improved safety, peanut-allergic participants evaluated after ~1.5 and ~2 years of daily PTAH experienced continued improvements in FAQoL.

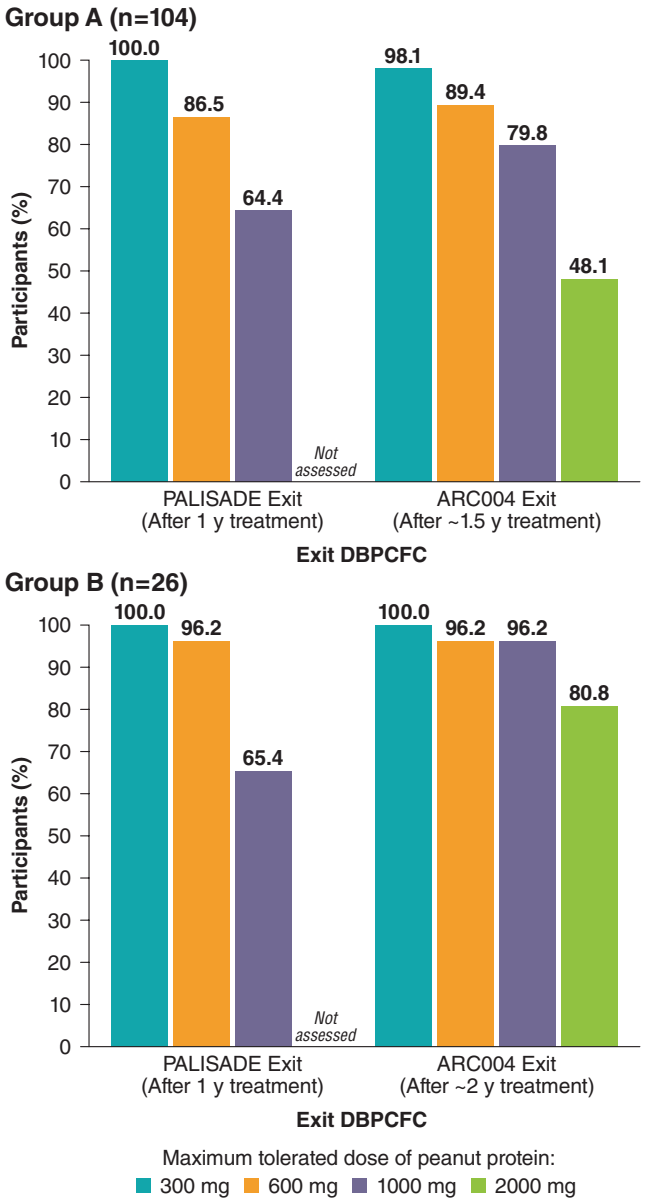


FIGURE 2 Efficacy of Continued PTAH Therapeutic Maintenance Dosing: Tolerated Doses at Exit DBPCFC in Group A and Group B (Completer Population). DBPCFC, double-blind, placebo-controlled food challenge; ITT, intent-to-treat

Peanut-allergic participants evaluated after ~1.5 and ~2 years of daily PTAH demonstrated an increased ability to tolerate peanut protein. Analyses of immune biomarkers showed that psIgE levels in both groups were elevated at baseline (PALISADE screening), increased during the updosing period, and returned to baseline at the end of 1 year treatment, but continue to decrease into the second year of treatment (Figure 3). If the immunomodulatory effects of continued administration of PTAH are similar to those seem with other forms of allergen immunotherapy,[23] we postulate that IgG4 levels are likely to fall with ongoing treatment as the immune response matures, shifting the initial effector response to PTAH to a more regulatory response that could signal the emergence of sustained remission. Such a pattern of immunomodulation is consistent with previous work demonstrating a decrease in T_H2A cells—a key subset of Th2 cells correlated with allergic disorders—and a shift toward a more regulatory phenotype in peanut-allergic individuals with OIT-induced desensitization.[23]

The changes in immune biomarkers are consistent with the clinical effects observed. Approximately two-thirds of participants in both groups tolerated 1000 mg of peanut protein at the PALISADE exit DBPCFC compared with 79.8% of participants in Group A and 96.2% in Group B at the ARC004 exit DBPCFC (Figure 2). These results were only minimally subject to completer bias, as 94.5% of Group A participants and 81.3% of those in Group B were completers. Additionally, the percentage of participants tolerating the highest dose of peanut protein (2000 mg) during the DBPCFC was higher in the group receiving treatment for ~2 years (80.8%) than in the one receiving treatment for ~1.5 years (48.1%). These results are consistent with the observation that the treatment benefits of allergen immunotherapy increase the longer the duration of treatment.

Measures of FAQoL also improved with increased duration of therapy. FAQLQ and FAIM scores over time showed clinically meaningful improvements from the start of PALISADE through to ARC004 exit, suggesting a link between increased desensitization and improved FAQoL beyond a study participation effect. Proxy FAQLQ scores reported by parents of younger children showed smaller changes, perhaps because parents need more time to process the effect of desensitization on the risk associated with accidental exposure and to "stand down" from a position of constant vigilance and stress. Of note, the greatest improvement was seen in FAIM item scores of teenagers and caregivers of teenagers, who would typically have greater autonomy in self-management. Although the FAQLQ and FAIM results in this study should be interpreted with caution due to the relatively small number of participants in each subgroup for these measures, and the exploratory nature of the analysis, these findings may indicate a reduction in stress and anxiety associated with the reduced risks of accidental exposure to peanut.[21,22] Follow-up studies with PTAH will be required to obtain further insights into changes over time.

As expected of any allergen immunotherapy, AEs were common in participants who received PTAH. Study withdrawals due to AE were predictably more frequent during PALISADE (43 of 372 treated participants aged 4–17 years [11.6%])[12] compared with ARC004 (3 of 142 treated participants [2.1%]) (Figure S1). Similarly, the exposure-adjusted AE rate was highest during the IDE and updosing periods, decreased during the maintenance periods, and continued to decrease with longer duration of treatment (Table 2). Many participants (Group A: 55.5%; Group B: 40.6%) experienced no treatment-related AEs during the first ~6 months of maintenance (in PALISADE); this trend continued during the additional 6 or 12 months of maintenance dosing (Table S5). This trend was also observed in the exposure-adjusted treatment-related AEs rates, which decreased considerably with extended treatment in both groups (Table 2). Treatment-related systemic allergic reactions following

TABLE 2 Summary of treatment-emergent AEs during PALISADE and ARC004 (safety population)

	Group A ($n = 110$) ~1.5 years of treatment			Group B ($n = 32$) ~2 years of treatment		
	PALISADE IDE & updosing	PALISADE therapeutic maintenance dosing	ARC004 Therapeutic maintenance dosing	PALISADE IDE & updosing	PALISADE therapeutic maintenance dosing	ARC004 therapeutic maintenance dosing
Participants with ≥1 AE, *n* (%)	104 (94.5)	97 (88.2)	91 (82.7)	32 (100.0)	29 (90.6)	27 (84.4)
Maximum AE severity, *n* (%)[†]						
Mild	49 (44.5)	60 (54.5)	58 (52.7)	8 (25.0)	20 (62.5)	15 (46.9)
Moderate	54 (49.1)	35 (31.8)	30 (27.3)	23 (71.9)	9 (28.1)	12 (37.5)
Severe	1 (0.9)	2 (1.8)	3 (2.7)	1 (3.1)	0 (0.0)	0 (0.0)
Participants with ≥1 Serious AE, *n* (%)	0 (0.0)	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Participants with ≥1 treatment-related AEs, *n* (%)	87 (79.1)	49 (44.5)	47 (42.7)	30 (93.8)	19 (59.4)	15 (46.9)
Participants with ≥1 systemic allergic reactions, *n* (%)[‡]	1 (0.9)	5 (4.5)	7 (6.4)	1 (3.1)	3 (9.4)	5 (15.6)
Participants discontinuing the trial due to AEs,[§] *n* (%)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)	0 (0.0)	1 (3.1)
Total exposure, participants-years	47.9	54.6	74.7	15.8	16.2	31.5
Number of AEs (Exp-adj event rate)[¶]	2712 (56.6)	1130 (20.7)	960 (12.8)	1303 (82.7)	516 (31.8)	553 (17.5)
Number of treatment-related AEs (Exp-adj event rate)[¶]	2125 (44.3)	739 (13.5)	416 (5.6)	892 (56.6)	348 (21.4)	147 (4.7)
Participants experiencing a reaction that required adrenaline, *n* (%)	5 (4.5)	6 (5.5)	7 (6.4)	4 (12.5)	2 (6.3)	4 (12.5)
Participants with accidental food allergen exposures, *n* (%)	14 (12.7)	5 (4.5)	15 (13.6)	5 (15.6)	2 (6.3)	7 (21.9)
Participants with peanut-related food allergen exposure, *n* (%)	8 (7.3)	3 (2.7)	7 (6.4)	2 (6.3)	0 (0.0)	6 (18.8)
Participants with non–peanut-related food allergen exposure, *n* (%)	7 (6.4)	2 (1.8)	8 (7.3)	3 (9.4)	2 (6.3)	2 (6.3)
Participants with food allergen exposures that required treatment, *n* (%)	13 (11.8)	3 (2.7)	11 (10.0)	5 (15.6)	1 (3.1)	3 (9.4)
Participants with food allergen exposures that required adrenaline, *n* (%)	2 (1.8)	0 (0.0)	4 (3.6)	0 (0.0)	0 (0.0)	1 (3.1)

[†]Participants with more than 1AE were counted only once by recording their highest severity adverse event.

[‡]Systemic allergic reactions of all severity, including anaphylaxis. For more granularity on severity and relatedness of systemic allergic reactions, please refer to Table S6.

[§]No participants in this analysis discontinued during PALISADE because completion of PALISADE was required for entry to ARC004. In Group A one participant was discontinued due to anaphylaxis (severe systemic allergic reaction) and another one due to moderate abdominal pain. In Group B, one participant was discontinued due to moderate hypersensitivity AE.

[¶]Exposure-adjusted event rates are defined as the total number of events divided by the total number of participant-years at risk during the period

Abbreviations: AEs, adverse events; GI, gastrointestinal; IDE, initial dose escalation; NA, not applicable.

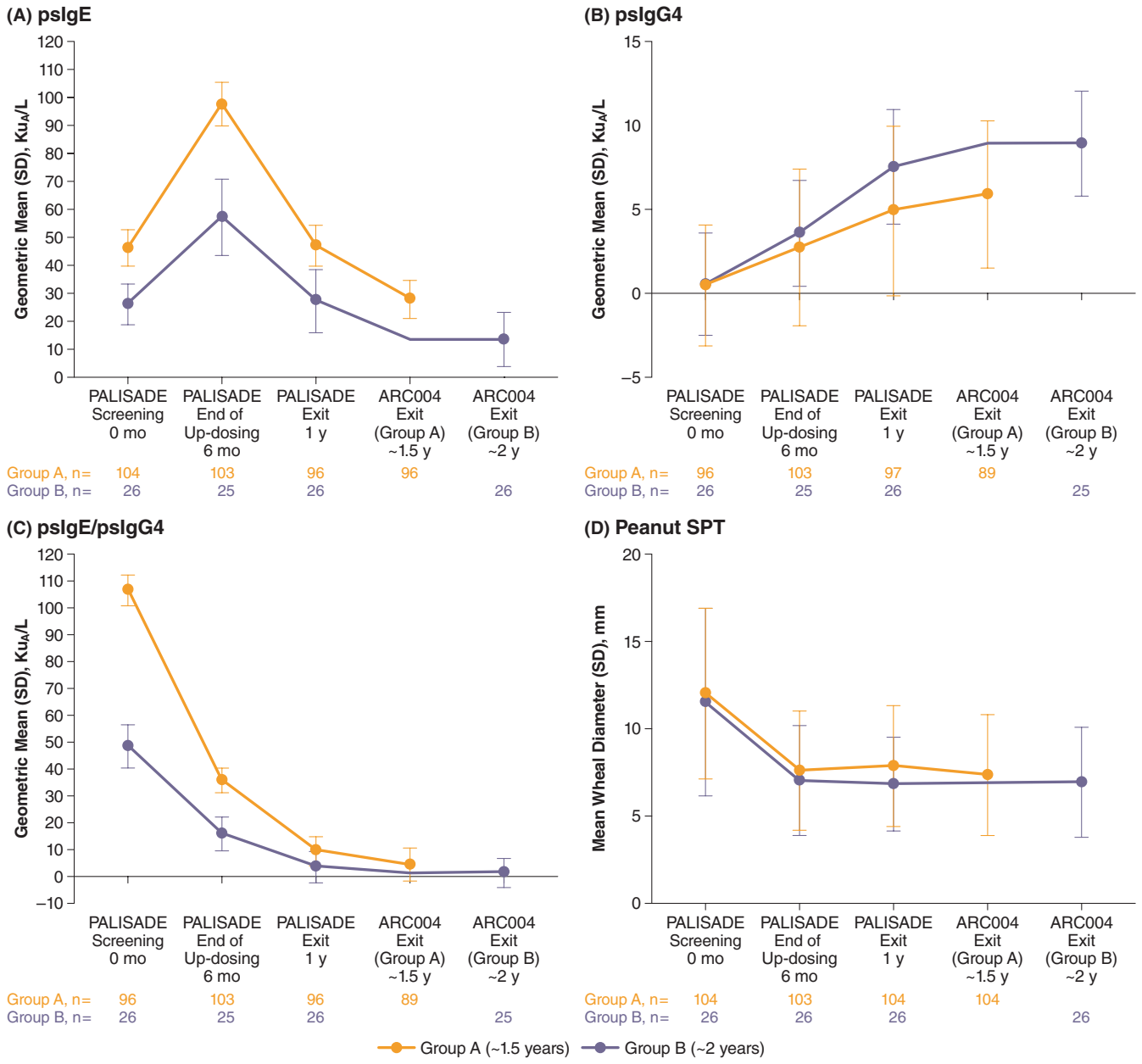


FIGURE 3 Changes in (A) psIgE levels, (B) psIgG4levels, (C) psIgE/IgG4 ratio (D) peanut SPT mean wheal diameter between baseline, end of updosing, and exit during PALISADE and ARC004 (Completer Population). IgE, immunoglobulin E; IgG4, immunoglobulin G4; ps, peanut-specific; SD, standard deviation, SPT, skin prick test

treatment beyond ~1 year were mostly attributable to a small number of participants. Specifically, 79% (15/19) treatment-related systemic allergic reactions experienced by participants from Group A and B during the ARC004 maintenance can be attributed to 5 participants, indicating that some patients might benefit of extra care and education on cofactor avoidance.

It is noteworthy that in both treatment groups (ie, Groups A and B), the rate of accidental food allergen exposures was higher during the open-label ARC004 therapeutic maintenance period than during the blinded PALISADE therapeutic maintenance phase. This finding may reflect decreased parental and personal vigilance despite ongoing study supervision and clinical advice to maintain peanut avoidance. It is reassuring to note that the ensuing reaction severity and adrenaline use were very low, further supporting the association of immunological changes with mitigation of the effects with peanut exposure.

The longitudinal study data summarized here suggest a correlation between the changes in the allergen immune response biomarkers and clinical benefits of continued OIT with PTAH and indicate that continued treatment is required for the maturation of the immune response to manifest fully. The low rates of serious/severe AEs and of AE-related discontinuations—coupled with the clinical benefits of markedly greater desensitization and improved QoL—indicate a favorable benefit-risk profile for long-term OIT with PTAH.

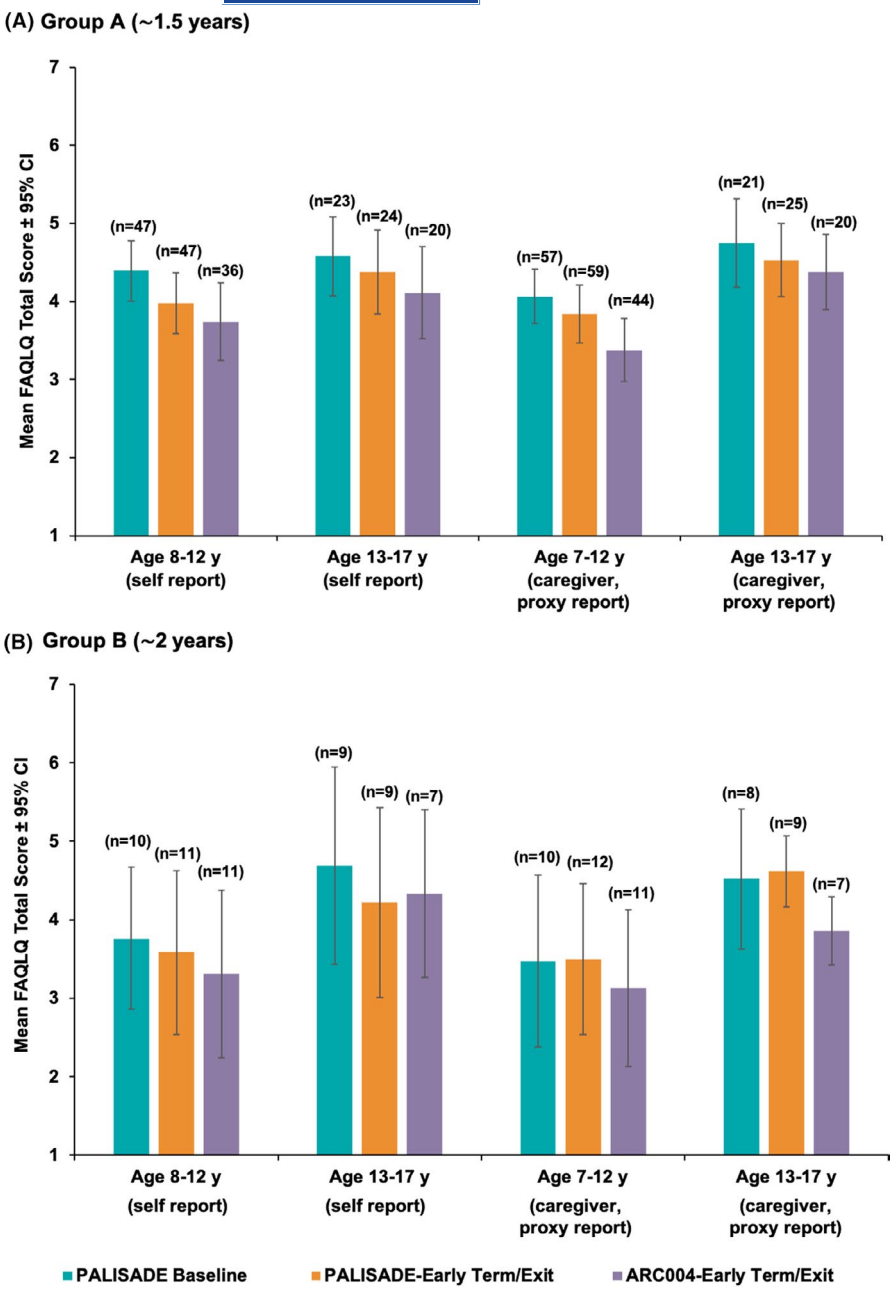


FIGURE 4 FAQLQ total score at PALISADE baseline, PALISADE exit, and ARC004 exit for (A) Group A and (B) Group B. CI, confidence interval; FAQLQ, Food Allergy Quality of Life Questionnaire; y, years

Other studies have reported improved safety, tolerability, and FAQoL using other PA oral immunotherapy peanut formulations.[24-26] A longitudinal analysis of PA oral immunotherapy over 104 and 156 weeks has been reported,[26] and a meta-analysis published in 2017 concluded that PA oral immunotherapy is effective in raising the threshold and improving a patient's QOL.[27,28] PTAH is the first commercially available product for peanut OIT and represents an important advancement in the management of PA.

Several limitations of this analysis must be acknowledged. The ARC004 extension study was open-label, and no statistical comparisons between Groups A and B were performed owing in part to the relatively small group sizes. The participants who opted for extended treatment with PTAH were self-selected, given that they completed PALISADE. Moreover, baseline demographic and clinical characteristics were similar between the ARC004 participants and the total PALISADE population.[12,14] The selection criteria for PALISADE (the source of the ARC004 population) also excluded individuals with poorly controlled asthma or gastrointestinal disorders. In addition, the data included in this analysis encompasses 2 trials with different methods. In PALISADE, treatment was double-blinded, while ARC004 involved open-label treatment, which could influence the efficacy and safety results in patients who are aware they are receiving active therapy. As exit challenges were performed by investigators who knew the patients had all taken active treatment for a long time, their criteria for use adrenaline may be different compared with the baseline PALISADE trial. The knowledge that all patients were on active treatment may have instilled a greater sense of safety and raised the threshold for administering adrenaline. Also, sustained awareness during the open-label extension study could be assumed to produce a far greater sense of

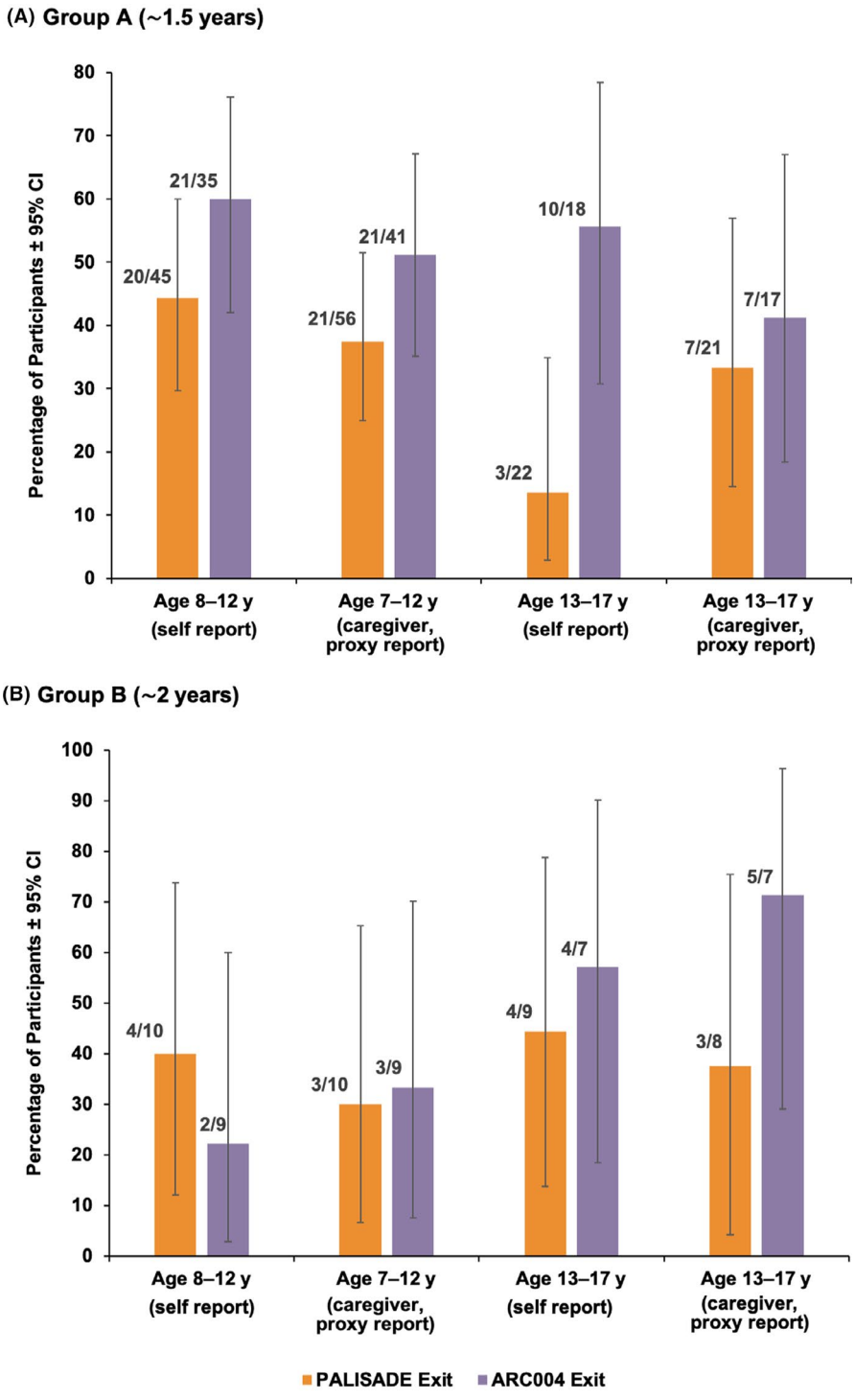


FIGURE 5 Percentages of participants whose FAQLQ total score changed (≥0.5) from PALISADE screening to PALISADE exit and ARC004 exit. (A) Children (aged 8–12 years, self-report), teenagers (aged 13–17 years, self-report), caregivers of children (aged 7–12 years, proxy-report) and teenagers (aged 13–17 years, proxy-report) in Group A. (B) Children (aged 8–12 years, self-report), teenagers (aged 13–17 years, self-report), caregivers of children (aged 7–12 years, proxy-report), and teenagers (aged 13–17 years, proxy-report) in Group B. FAQLQ, Food Allergy Quality of Life Questionnaire; y, years

confidence in the effect of therapy in participants relative to their assessment at the exit of PALISADE, which occurred immediately after unblinding. However, the improvements in safety and efficacy seen with increased duration of treatment are consistent with previous observations of allergen immunotherapy.[27-29] Finally, the careful monitoring of AEs in the trial setting may tend to overestimate the rate of AEs that patients would be aware of in real life.[12] Notwithstanding these limitations, this analysis provides much-needed insight into the long-term safety, tolerability, and efficacy of PTAH and of OIT in general.

5 | CONCLUSION

Continued daily therapeutic maintenance dosing with PTAH shows consistent safety and tolerability with a potential for lower frequency of AEs, ongoing immune response, and increased desensitization to peanut protein that improves over time. Mitigation of reactions due to accidental peanut exposure may have beneficial effects on FAQoL in peanut-allergic children and teenagers as well as their caregivers. The association between extended dosing with PTAH treatment and a trend toward improved FAQoL is intriguing

and warrants further investigation. Longer-term data on this cohort will continue to be gathered on participants enrolled in the follow-on ARC008 study (NCT03292484).

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CONFLICTS OF INTEREST

Montserrat Fernández-Rivas reports consultancies for Aimmune Therapeutics, DBV, Novartis, SPRIM; research funding from European Commission, MINECO and ISCIII of Spanish government; speakers bureau for ALK, Allergy Therapeutics, Diater, Fundacion SEAIC, GSK, HAL Allergy, Thermo Fisher Scientific. **Andrea Vereda** is an employee and stockholder of Aimmune Therapeutics. **Brian P Vickery** reports advisory board/consultant: Aimmune Therapeutics, AllerGenis, FARE, Reacta; site investigator: Aimmune Therapeutics, DBV, Genentech, Regeneron; research grants: FARE, NIAID. **Vibha Sharma** reports speaker fees from Aimmune Therapeutics outside the submitted work. **Caroline Nilsson** reports grants to institution and advisory board fees from Aimmune Therapeutics and Novartis and speakers fees from MEDA, ALK, Thermo Fisher, GSK. **Antonella Muraro** reports personal fees from DVB Technologies, Aimmune, Nestlé-Purina, Nestlé Health Institute, Mylan, and Nutricia outside the submitted work. **Jonathan O'B. Hourihane** reports advisory board fees, Aimmune Therapeutics; speakers bureau, Aimmune Therapeutics, DBV Technologies, Nutricia, Mead Johnson; grants to institution/research funding, and clinical trials within past 2 years, Aimmune Therapeutics, DBV Technologies. **Audrey DunnGalvin** reports personal fees from Aimmune Therapeutics and DBV Technologies outside the submitted work. **George du Toit** reports research grants to institution and advisory board fees from Aimmune Therapeutics. **Katharina Blumchen** reports consulting for Aimmune Therapeutics, DBV Technologies, Bencard Allergie, HAL Allergy; speakers bureau for Aimmune Therapeutics, DBV Technologies, HAL Allergy, Nutricia, Thermo Fisher Scientific, ALK, Allergopharma, Nestle; and conducting clinical trials for Aimmune Therapeutics, DBV Technologies, and Hipp. **Kirsten Beyer** reports advisory board/consulting fees from Aimmune Therapeutics, ALK, Bausch & Lomb, Bencard, Danone, DBV, Hycor, Infectopharm, Mabylon, Meda Pharma, Mylan, Nestle; speakers bureau for Aimmune Therapeutics, Allergopharma, Bencard, Danone, Di-Text, Hammer und Rall Media, Infectopharm, Meda Pharma, Med Update, Nestle, Nutricia; and research grants from Aimmune, ALK, Danone, DBV, Good Mills, Hipp, Hycor, Infectopharm, Nutricia, ThermoFisher, VDI. **Alex Smith** is an employee and stockholder of Aimmune Therapeutics. **Robert Ryan** an employee and stockholder of Aimmune Therapeutics. **Daniel C. Adelman** was an employee and stockholder of Aimmune Therapeutics at the time of the development of this work. He has patents pending for the following: US 16/542,198; PCT/US2019/046706; US 16/721,805; PCT/US2019/067634. **Stacie M. Jones** reports advisory board fees, Aimmune Therapeutics, FARE; personal fees, DBV Technologies; clinical trials grants, Aimmune Therapeutics, DBV Technologies, Astellas, Sanofi, Regeneron, FARE, Genentech, and NIH-NIAID.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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