Original Article

Continuous and Daily Oral Immunotherapy for Peanut Allergy: Results from a 2-Year Open-Label Follow-On Study

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What is already known about this topic? The phase 3 PALISADE trial established the safety and efficacy of daily oral immunotherapy with Peanut (*Arachis Hypogaea*) allergen powder-dnfp (PTAH, formerly AR101) over a 1-year period in peanut-allergic children and adolescents.

What does this article add to our knowledge? This follow-on study, which explored long-term PTAH therapy and alternative dosing regimens, demonstrated a potential benefit with continued daily PTAH treatment beyond 1 year.

How does this study impact current management guidelines? This study may help inform selection of oral immunotherapy dosing regimens and treatment duration in peanut-allergic individuals. It also supports the overall favorable benefit-risk profile of long-term oral immunotherapy with PTAH.

BACKGROUND: The randomized, controlled PALISADE trial demonstrated the benefit of daily oral immunotherapy with Peanut (*Arachis Hypogaea*) allergen powder-dnfp (PTAH, formerly AR101) in peanut-allergic children and adolescents.
OBJECTIVE: ARC004, the open-label follow-on study to PALISADE, used 5 dosing cohorts to explore PTAH treatment beyond 1 year and alternative dosing regimens in peanut-allergic individuals.
METHODS: Active arm (PTAH-continuing) PALISADE participants who tolerated 300-mg peanut protein at the exit double-blind placebo-controlled food challenge and placebo arm (PTAH-naive) participants could enter ARC004. PTAH-continuing participants were assigned to receive daily (cohorts 1 and 3A) or non−daily (cohorts 2, 3B, and 3C) dosing regimens; PTAH-naive participants were built up to 300 mg/d PTAH, followed by maintenance dosing. At study completion, participants underwent an exit double-blind placebo-controlled food challenge with doses up to 2000 mg peanut protein. Data were assessed using descriptive statistics.
RESULTS: Overall, 358 (87.5%) eligible participants (4-17 years) entered ARC004 (PTAH-continuing, n = 256; PTAH-naive, n = 102). Among PTAH-continuing participants, exposure-adjusted adverse event rates were 12.94 to 17.54/participant-year and 25.95 to 42.49/participant-year in daily and non−daily dosing cohorts, respectively; most participants (83%) experienced mild or moderate adverse events. Daily dosing

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Conflicts of interest: B. P. Vickery reports advisory board/consultant role with Aimmune Therapeutics, AllerGenis, FARE, and Reacta; site investigator role with Aimmune Therapeutics, DBV, Genentech, and Regeneron; research grants from FARE and the National Institute of Allergy and Infectious Diseases (NIAID). A. Vereda is an employee and stockholder of Aimmune Therapeutics. C. Nilsson reports grants to institution and advisory board fees from Aimmune Therapeutics and speakers fees from MEDA, ALK, Thermo Fisher, and

Abbreviations used
AE- adverse event
DBPCFC- double-blind placebo-controlled food challenge
IDE- initial dose escalation
OIT- oral immunotherapy
*PTAH- Peanut (*Arachis Hypogaea*) allergen powder-dnfp*

cohorts appeared to have higher desensitization rates than non−daily dosing cohorts. Of all PTAH-continuing cohorts, cohort 3A had the longest daily dosing duration and the highest desensitization rates. Changes in immune markers with PTAH continuation demonstrated ongoing immunomodulation. Outcomes in PTAH-naive participants mirrored those of the PALISADE active arm.

CONCLUSIONS: Continued daily PTAH treatment beyond 1 year showed sustained safety and efficacy. Ongoing immunomodulation was observed during the second year of treatment. **(J Allergy Clin Immunol Pract 2021;9:1879-89)**

Key words: *Oral immunotherapy; Peanut allergy; Desensitization; Allergic reactions; Dosing regimens*

INTRODUCTION

Peanut allergy is one of the most common food allergies affecting children and adolescents in the United States and Europe.[1,2] In the United States, peanut allergy is now a treatable condition using oral immunotherapy (OIT), a practice expected to accelerate with the recent approval by the Food and Drug Administration of Palforzia (Peanut [*Arachis Hypogaea*] allergen powder-dnfp [PTAH], formerly AR101).[3] Two phase 3, randomized, placebo-controlled trials testing daily OIT with PTAH in peanut-allergic children (PALISADE [NCT02635776] and ARTEMIS [NCT03201003]) have been completed.[4,5] The phase 3 PALISADE trial enrolled a highly peanut-allergic population from North America and Europe, aged 4 to 55 years, to receive PTAH or placebo for up to 12 months; the primary analysis population consisted of participants aged 4 to 17 years.[5] The PALISADE study demonstrated the benefit of once-daily OIT with PTAH, which resulted in desensitization, defined as an increase in the participants' ability to tolerate increased amounts of peanut protein[5]; these findings were further confirmed in the European phase 3 ARTEMIS trial.[4]

There remains a need for longer-term data on the safety and efficacy of OIT[6,7] in the peanut-allergic population. Based on similar preliminary research related to OIT for other food allergies,[8-10] an investigation into whether nondaily PTAH maintenance regimens can match or improve the clinical benefits of a daily maintenance regimen was warranted. The key objectives of ARC004, the exploratory open-label extension to the PALISADE study, were to evaluate the safety/tolerability of daily and nondaily maintenance regimens, to explore the efficacy of different PTAH regimens with a double-blind placebo-controlled food challenge (DBPCFC) of up to a single 2000-mg dose (cumulative dose, 4034 mg) of peanut protein, and to evaluate the long-term immunologic effects of PTAH.

METHODS

Trial design and participants

The ARC004 open-label trial (NCT02993107) was conducted between December 29, 2016, and May 24, 2019, at 65 study sites across North America, the European Union, and the United Kingdom (complete list of ARC004 investigators and sites in this article's Online Repository at www.jaci-inpractice.org) and included participants with peanut allergy who completed the phase 3 PALISADE trial (Figure 1). Complete inclusion and exclusion criteria for the PALISADE population are described in the primary publication.[5] Participants who completed the PALISADE trial and either were assigned to treatment with PTAH and tolerated the 300-mg dose at the exit DBPCFC or were assigned to the placebo arm in PALISADE could elect to enter the ARC004 trial after providing written informed consent and assent as appropriate (complete list of ARC004 investigators and sites in this article's Online Repository).

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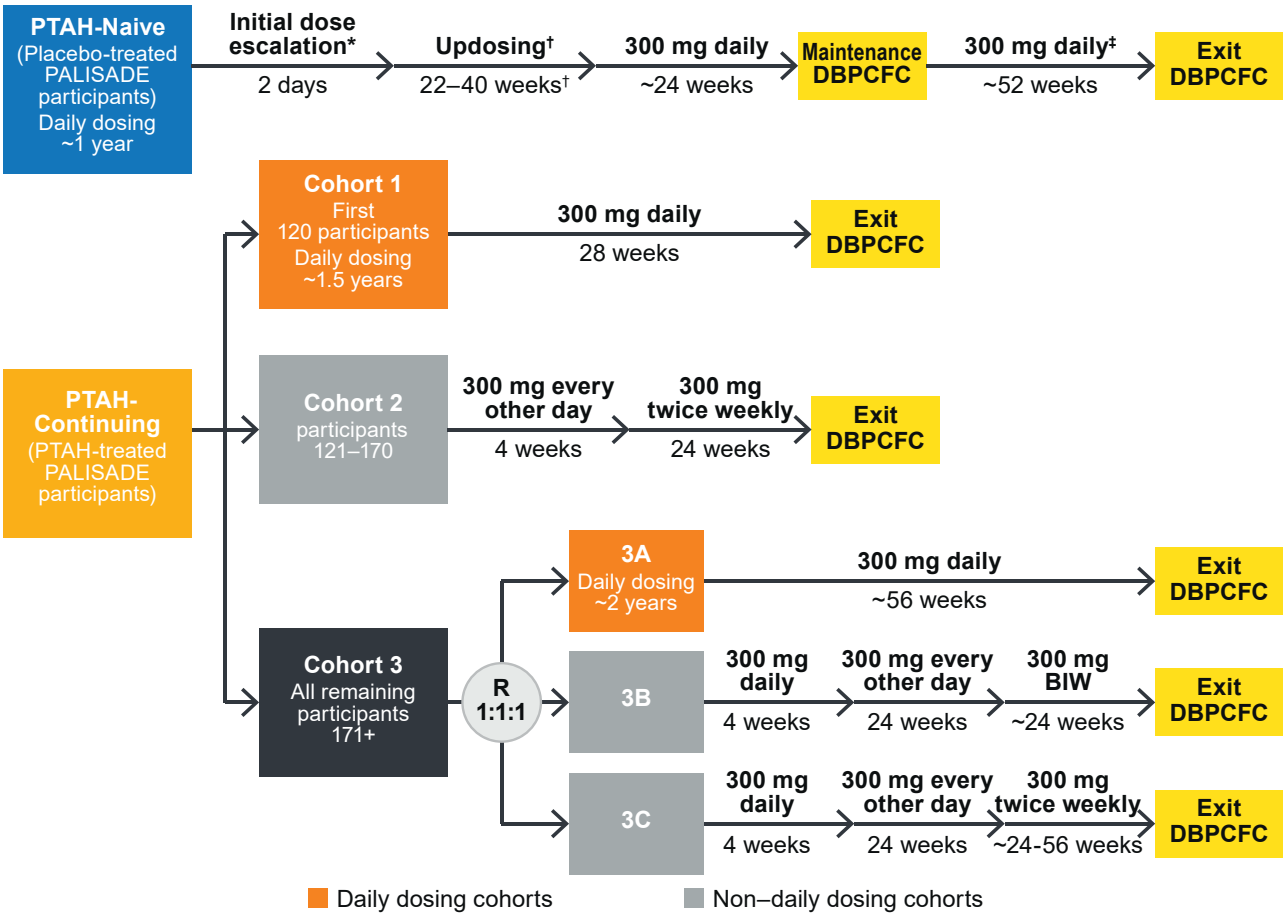

FIGURE 1. ARC004 Trial design. All treatments were administered as tolerated. *Day 1, 0.5- to 3-mg or 6-mg PTAH as tolerated; day 2, confirmation of ability to tolerate 3-mg PTAH. †From 3 mg to 300 mg daily, with dose escalation every 2 weeks. ‡Administration of daily or non–daily dosing regimens was contingent on results; planned regimens were every other day, twice weekly, once weekly, or every other week. Regimens less frequent than twice weekly were not instituted because of small cohort size *and at the recommendation of the Safety Monitoring Committee*. All ARC004 completers had the option of entering the open-label ARC008 study of daily PTAH.

Although some adult (aged 18-55 years) participants (n = 30) from PALISADE also enrolled in ARC004, outcomes reported here are confined to participants aged 4 to 17 years on entry into ARC004. Approvals were obtained from independent ethics committees. All the participants or a parent or guardian provided written informed consent. Minor children provided assent in accordance with local requirements.

Allocation of participants in the ARC004 trial depended on the treatment previously received in the PALISADE trial. Participants in the placebo arm of the PALISADE trial (PTAH-naive group) who entered ARC004 underwent initial dose escalation (IDE) followed by updosing for 22 to 40 weeks, and subsequent maintenance dosing at 300 mg/d for approximately 24 weeks as previously described.[5] After approximately 6 months of maintenance treatment, participants underwent a maintenance DBPCFC to evaluate their ability to tolerate up to 2000 mg (cumulative dose, 4043 mg) of peanut protein.

Participants in the active treatment arm of PALISADE who successfully completed the 300-mg PALISADE exit DBPCFC constituted the PTAH-continuing group; they were enrolled sequentially into 1 of 5 cohorts (Figure 1); randomization was used for cohorts 3A, 3B, and 3C. Both cohorts 1 and 3A represented the daily dosing cohorts and received 300 mg/d PTAH throughout their respective treatment periods (28 weeks and ~56 weeks, respectively). 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 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). Dose modifications (eg, downdosing) were possible to ensure safety (see this article's Online Repository at www.jaci-inpractice.org), and participants who did not tolerate a non–daily dosing schedule could revert to a daily dosing schedule after repeating updosing.

PTAH-naive participants who tolerated greater than or equal to 300 mg in the maintenance DBPCFC could continue to receive PTAH during weeks 28 to 84. All participants in both PTAH-naive and PTAH-continuing groups who completed the trial were eligible for an exit DBPCFC of up to a single highest dose of 2000 mg of peanut protein (cumulative dose, 4043 mg).

Prespecified stopping rules for individual participants and whole cohorts were included in the protocol (see this article's Online

Repository at www.jaci-inpractice.org), with the aim of not losing the desensitization previously acquired in PALISADE.[4] A Safety Monitoring Committee monitored the data on an ongoing basis and was responsible for applying the stopping rules. Participants who completed the ARC004 trial could enter the ARC008 trial (NCT03292484), which was designed to evaluate the long-term safety of once-daily PTAH, and is still ongoing.

Double-blind placebo-controlled food challenges

The DBPCFCs in the ARC004 study were performed using the practical allergy guidelines with modifications to accommodate the 600-mg and 2000-mg dose levels[11] and were conducted in the same manner as described in the PALISADE trial,[5] but with an additional highest dose of 2000-mg peanut protein (doses: 3, 10, 30, 100, 300, 600, 1000, and 2000 mg). Further details regarding the administration of DBPCFCs are provided in this article's Online Repository at www.jaci-inpractice.org.

Assessment of safety and efficacy

Safety and tolerability were assessed by monitoring the incidence of adverse events (AEs), including allergy symptoms, systemic allergic reactions, anaphylaxis, and allergic reactions. The severity of AEs was assessed using the 5-point Common Terminology Criteria for Adverse Events (v.4.03). Hypersensitivity events (allergy symptoms) that occurred throughout the trial were summarized. Allergy symptoms associated with accidental food allergen exposure were also reported.

Assessments of systemic allergic reactions were consistent with the PALISADE study.[5] Anaphylaxis was defined according to National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network criteria.[12] Severity was graded on a 3-point scale according to the European Academy of Allergy and Clinical Immunology guidelines.[13] Specifically, a "systemic allergic reaction" refers to an anaphylactic reaction event of any severity, and "anaphylaxis" was used to distinguish anaphylactic reaction events that were severe. The use of epinephrine as rescue medication was also assessed, and an epinephrine episode was defined as 1 or more doses of epinephrine administered within a 2-hour interval.

During DBPCFCs, symptom severity was rated on a 5-point scale: 1, mild; 2, moderate; 3, severe; 4, life-threatening; and 5, fatal. The desensitization response rate was defined as the proportion of participants who tolerated each challenge dose level of peanut protein in the DBPCFC with no dose-limiting symptoms.

Immune biomarker assessment

Baseline values for total IgE, peanut-specific IgE and IgG_4, and skin prick test assays were defined as the last available measurement before the first dose of PTAH on day 1 of the ARC004 trial for the PTAH-naive group, and as day 1 of the PALISADE trial for participants in the PTAH-continuing cohorts. The rest of the peanut-specific IgE and IgG4 levels were measured using ImmunoCAP (Thermofisher; Uppsala, Sweden).[14]

Statistical analyses

Given the lack of peer-reviewed, published evidence on non−daily dosing regimens, the ARC004 trial was intentionally designed to be exploratory and hypothesis-generating in nature and was not powered to permit statistically meaningful comparisons. Further details regarding the statistical analyses are provided in this article's Online Repository at www.jaci-inpractice.org.

Trial oversight, statement of ethics, and role of sponsor

The ARC004 trial was funded by Aimmune Therapeutics. Approvals from site-specific institutional review boards, ethics committees, research ethics boards, or like authorities were obtained before trial initiation. Further information on trial oversight, ethics, and role of sponsor are provided in this article's Online Repository at www.jaci-inpractice.org.

RESULTS

Participant disposition

Of the 409 participants aged 4 to 17 years who completed the PALISADE trial and were eligible, 358 (87.5%) entered the ARC004 trial (Figure 2), including 102 of 115 (88.7%) completers in the placebo arm and 256 of 294 (87.1%) completers in the active treatment arm. Of the 358 participants in ARC004, 7 withdrew consent before receiving the trial drug and were excluded from the safety population. Overall, 261 of 358 (72.9%) participants completed the trial: 53.9% (55 of 102) of participants in the PTAH-naive group and 80.5% (206 of 256) of participants in the PTAH-continuing group. A total of 80.5% (128 of 143) of participants receiving continued daily PTAH (cohorts 1 and 3A) completed the trial compared with 69% (78 of 113) who received non−daily dosing regimens (cohorts 2, 3B, and 3C). At the time of completion of the ARC004 trial, participants receiving daily dosing in cohort 3A, and all participants in non−daily dosing cohorts (cohorts 2, 3B, and 3C), had received PTAH for 2 years or more from the time of entry into the parent trial (Figure 2).

By the end of the trial, all PTAH-naive participants remained on the daily dosing regimen. At trial completion, PTAH-continuing participants in cohorts 3B and 3C remained in the twice-weekly regimen, and both cohorts had approximately the same length of treatment: 300 mg/d PTAH for 28 weeks, 300 mg every other day for 4 weeks, and 300 mg twice weekly for 24 to 56 weeks or more. A total of 94 PTAH-naive and 160 PTAH-continuing participants who participated in ARC004 entered the ARC008 trial.

Demographic and baseline characteristics

Demographic and baseline characteristics of the safety population (n = 351 participants) at entry into ARC004 are presented in Table I. In the PTAH-continuing population, 64.5% (162 of 251) of participants tolerated the highest dose of peanut protein (1000 mg) administered at ARC004 entry.

Treatment adherence and drug exposure

Treatment adherence was very high across both groups and all cohorts (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). The median percentage of days where a full or partial dose was consumed at home was 96% or more in both PTAH-naive and PTAH-continuing participants. Although treatment adherence was highest in cohort 2 (eg, dosing every other day), variability in adherence was observed in the other non−daily dosing cohorts (Table E1).

The overall median duration of exposure to drug in the PTAH-naive participants was 17.8 months. Median exposure durations in daily dosing cohorts 1 and 3A were 7.2 and 13.0 months, respectively. For non−daily dosing cohorts 2, 3B, and 3C, median durations of exposure were 6.8, 12.7, and 16.5 months, respectively. Complete data on trial drug exposure are

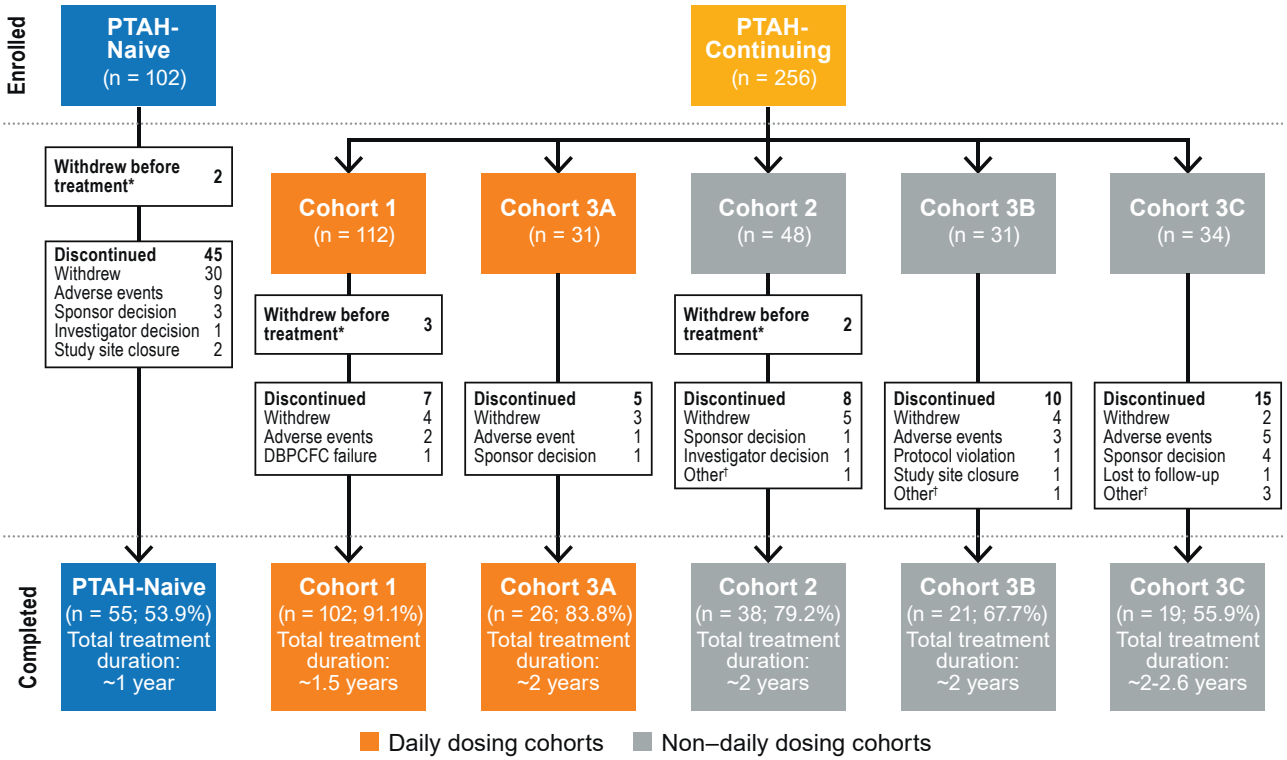

FIGURE 2. Participant (aged 4-17 years) disposition. *Participants were not included in the safety population. †Other reasons for discontinuation were enrollment in long-term safety study (cohort 2, n = 1), recurrent AE (cohort 3B, n = 1), anxiety related to dosing (cohort 3C, n = 1), loss of interest in study participation (cohort 3C, n = 1), and study termination (cohort 3C, n = 1).

presented in Table E2 in this article's Online Repository at www.jaci-inpractice.org.

Desensitization rates at exit DBPCFC

Among PTAH-continuing participants, desensitization rates based on the highest tolerated single dose tested were higher in daily dosing cohorts than in non–daily dosing cohorts (Figure 3). Across all peanut challenge doses, desensitization response rates were highest in cohort 3A, which had the longest duration of daily dosing (56 weeks), and were lowest in cohort 2.

Among PTAH-naive participants, desensitization rates at peanut challenge doses of 1000 mg were 65.3% at maintenance and 72.2% at exit; desensitization rates at peanut challenge doses of 2000 mg were 45.8% at maintenance and 51.4% at exit.

Allergic symptoms at exit and maintenance DBPCFCs

In the PTAH-continuing group, more than 70% of participants in the daily dosing cohorts (cohorts 1 and 3A) had no symptoms at less than or equal to 600- and less than or equal to 1000-mg doses; approximately 69% of participants in cohort 3A had no symptoms at less than or equal to 2000-mg doses (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). In the non–daily dosing cohorts, proportions of participants with no symptoms were approximately 52% to 73% at less than or equal to 600-mg, 40% to 59% at less than or equal to 1000-mg, and 24% to 46% at less than or equal to 2000-mg doses. Epinephrine use for the treatment of allergic symptoms during the exit DBPCFC is presented in Table E3 in this article's Online Repository at www.jaci-inpractice.org.

Safety and tolerability

In the PTAH-continuing group, most patients across all cohorts experienced at least 1 AE; however, exposure-adjusted AE rates were lower in the daily dosing groups than in the non–daily dosing groups (Table II). A total of 18 (6.1%) participants across cohorts 2, 3B, and 3C did not tolerate non–daily dosing and reverted to daily dosing (cohort 2, n = 9 of 46 [19.6%]; cohort 3B, n = 5 of 31 [16.1%]; cohort 3C, n = 4 of 34 [11.8%]). Reasons for reversion to daily dosing included recurring treatment-related gastrointestinal, cutaneous, or respiratory AEs (n = 9), failure to tolerate at least 600-mg peanut protein in the exit DBPCFC (n = 4), anaphylactic reaction (n = 3), or other reason based on the investigator's discretion (n = 2). Most of these 18 patients presented with treatment-related mild to moderate gastrointestinal or respiratory AEs (eg, abdominal pain and discomfort, nausea, oral pruritus, cough, and dyspnea); 3 experienced related moderate systemic allergic reaction while on non–daily dosing. After reverting to daily dosing, treatment-related AEs remained gastrointestinal or respiratory in nature but were less frequent and mostly mild. One participant experienced a moderate systemic allergic reaction both during twice-weekly dosing and after reverting to daily dosing, and subsequently discontinued treatment. The duration of exposure in the 18 participants who had switched back to the daily dosing regimen ranged from 0.2 to 9.2 months.

TABLE I. Demographic and baseline characteristics at ARC004 trial entry (safety population; N = 351)

Characteristic	PTAH-Naive (n = 100) ~52 wk	PTAH-Continuing (n = 251)				
		Daily dosing cohorts		Non–daily dosing cohorts*		
		Cohort 1 (n = 109) ~28 wk	Cohort 3A (n = 31) ~56 wk	Cohort 2 (n = 46) ~28 wk	Cohort 3B* (n = 31) ~56 wk	Cohort 3C* (n = 34) ~56-84 wk
Median age (y) (range)	9.5 (5-17)	11 (5-17)	9 (5-17)	10 (4-17)	9 (5-16)	9 (5-16)
Sex: male, n (%)	65 (65.0)	57 (52.3)	17 (54.8)	25 (54.3)	19 (61.3)	18 (52.9)
No. of systemic allergic reactions due to peanut during lifetime, n (%)						
0	27 (27.0)	36 (33.0)	9 (29.0)	11 (23.9)	11 (35.5)	12 (35.3)
1	32 (32.0)	43 (39.4)	14 (45.2)	20 (43.5)	14 (45.2)	12 (35.3)
2	19 (19.0)	17 (15.6)	6 (19.4)	7 (15.2)	2 (6.5)	2 (5.9)
3	8 (8.0)	8 (7.3)	1 (3.2)	3 (6.5)	3 (9.7)	5 (14.7)
>3	13 (13.0)	5 (4.6)	1 (3.2)	5 (10.9)	1 (3.2)	3 (8.8)
History of asthma, n (%)	47 (47.0)	47 (43.1)	14 (45.2)	28 (60.9)	16 (51.6)	16 (47.1)
Allergic rhinitis, n (%)	80 (80.0)	79 (72.5)	20 (64.5)	33 (71.7)	19 (61.3)	23 (67.6)
Atopic dermatitis, n (%)	56 (56.0)	67 (61.5)	22 (71.0)	32 (69.6)	18 (58.1)	17 (50.0)
Food allergies other than peanut, n (%)	64 (64.0)	67 (61.5)	17 (54.8)	35 (76.1)	16 (51.6)	22 (64.7)
Immunoglobulin and SPT results, median (IQR)						
Total IgE (IU/mL)	484.5 (258-1127)	345.0 (194-783)	371.0 (114-952)	463.0 (239-996)	580.0 (234-1034)	520.5 (204-739)
Peanut-specific IgE (kUA/L)	108.25 (32.9-277.8)	63.5 (20.9-247.5)	45.4 (2.73-220.5)	33.55 (5.82-187.5)	72.0 (10.5-259.0)	90.95 (35.1-301.0)
Peanut-specific IgG_4 (mgA/L)	0.5 (0.3-1.4)	6.1 (2.4-13.4)	7.4 (1.9-20.9)	5.5 (2.2-11.1)	9.8 (2.6-24.1)	9.4 (3.6-29.1)
Peanut-specific IgE/IgG_4 ratio	187.49 (44.55-401.94)	13.26 (2.33-32.50)	6.14 (0.70-21.01)	5.83 (2.37-19.46)	7.13 (2.61-14.86)	7.69 (2.26-33.61)
SPT mean wheal diameter (mm)	10.5 (8.5-13.5)	7.5 (5.5-10.0)	7.0 (4.0-9.5)	6.25 (4.0-9.0)	6.5 (4.5-10.0)	7.0 (5.0-8.5)
Single maximum dose tolerated at trial entry, n (%)						
1 mg	8 (8.0)	0	0	0	0	0
3 mg	17 (17.0)	0	0	0	0	0
10 mg	27 (27.0)	0	0	0	0	0
30 mg	20 (20.0)	0	1 (3.2)†	0	0	0
100 mg	21 (21.0)	0	0	1 (2.2)†	1 (3.2)†	0
300 mg	3 (3.0)	16 (14.7)	1 (3.2)	7 (15.2)	4 (12.9)	2 (5.9)
600 mg	2 (2.0)	25 (22.9)	10 (32.3)	10 (21.7)	4 (12.9)	7 (20.6)
1000 mg	2 (2.0)	68 (62.4)	19 (61.3)	28 (60.9)	22 (71.0)	25 (73.5)

IQR, Interquartile range; *SPT*, skin prick test.
Baseline values were relative to the start of ARC004.
*Participants in cohorts 3B and 3C underwent initial daily dosing for 28 wk.
†These patients did not meet the inclusion/exclusion criteria of the ARC004 study.

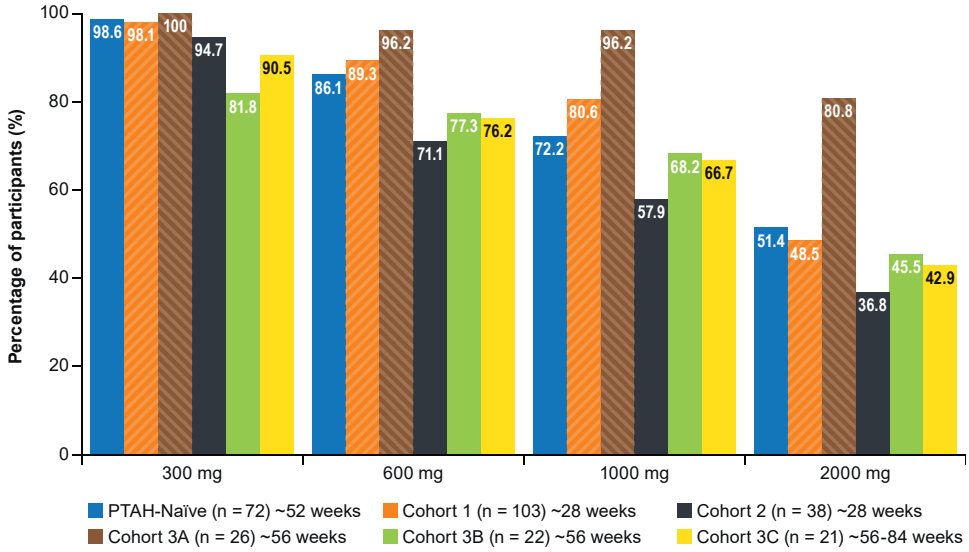

FIGURE 3. Desensitization rates based on the single highest tolerated dose at the exit DBPCFC (completer population; N = 282). Hatch marked bars indicate daily dosing cohorts.

TABLE II. Summary of treatment-emergent AEs (safety population; N = 351)

	PTAH-Naive (N = 100) ~52 wk			PTAH-Continuing (N = 251)				
				Daily dosing cohorts		Non–daily dosing cohorts*		
AE	IDE/updosing (n = 100)	Daily dosing (n = 85)	Total (n = 100)	Cohort 1 (n = 109) ~28 wk	Cohort 3A (n = 31) ~56 wk	Cohort 2 (n = 46) ~28 wk	Cohort 3B* (n = 31) ~56 wk	Cohort 3C* (n = 34) ~56-84 wk
Any AE, n (%)*	94 (94.0)	76 (89.4)	98 (98.0)	90 (82.6)	27 (87.1)	36 (78.3)	28 (90.3)	33 (97.1)
AEs by grade/severity, n (%)								
1: mild	41 (41.0)	45 (52.9)	37 (37.0)	58 (53.2)	15 (48.4)	22 (47.8)	13 (41.9)	12 (35.3)
2: moderate	51 (51.0)	30 (35.3)	58 (58.0)	29 (26.6)	12 (38.7)	14 (30.4)	15 (48.4)	18 (52.9)
3: severe	2 (2.0)	1 (1.2)	3 (3.0)	3 (2.8)	0	0	0	3 (8.8)
Treatment-related AEs, n (%)	81 (81.0)	43 (50.6)	86 (86.0)	47 (43.1)	15 (48.4)	25 (54.3)	14 (45.2)	24 (70.6)
Serious AEs, n (%)	0	0	0	1 (0.9)	0	0	1 (3.2)	1 (2.9)
Serious treatment-related AEs, n (%)	0	0	0	0	0	0	0	0
AEs leading to discontinuation, n (%)	7 (7.0)	2 (2.4)	9 (9.0)	3 (2.8)	1 (3.2)	0	2 (6.5)	1 (2.9)
Allergic reactions, n (%)	83 (83.0)	48 (56.5)	89 (89.0)	53 (48.6)	17 (54.8)	25 (54.3)	21 (67.7)	28 (82.4)
Total exposure (participant-years)	43.76	85.53	129.29	73.74	31.53	25.95	30.08	42.49
Exposure-adjusted AE rates†	54.80	18.13	30.54	12.94	17.54	20.69	13.86	30.10
Exposure-adjusted treatment-related AE rates‡	36.65	12.16	20.45	5.64	4.66	13.41	3.39	20.60

*Participants in cohorts 3B and 3C underwent initial daily dosing for 28 wk.
†Participants with >1 AE were counted only once using the highest severity and closest relationship to study product.
‡Exposure-adjusted event rates were defined as the total number of events divided by the total number of participant-years at risk during the period.

In the PTAH-continuing group, the most commonly occurring AEs and treatment-related AEs were of gastrointestinal and respiratory origin, and occurred more frequently in the non–daily dosing cohorts (see Table E4 in this article's Online Repository at www.jaci-inpractice.org). The incidence of severe AEs was low, occurring in less than 3% of participants treated both daily (3 of 140; 2.1%) and not daily (3 of 111; 2.7% [non–daily portion of treatment]).

Within the daily dosing groups, exposure-adjusted total treatment-related AEs per participant-year improved with time on treatment (Table II). There were 3 serious AEs occurring in 3 participants undergoing daily dosing (1 participant each in cohort 1, 3B, and 3C), all of which were unrelated to study drug (streptococcal infection, abdominal pain, and limb fracture). AEs leading to discontinuation of study treatment occurred in 7 participants in the PTAH-continuing group. Of these AEs,

TABLE III. Incidence of systemic allergic reactions in the PTAH-continuing group (N = 251)

	Daily dosing cohorts		Non−daily dosing cohorts*		
Systemic allergic reaction	Cohort 1 (n = 109) ~28 wk	Cohort 3A (n = 31) ~56 wk	Cohort 2 (n = 46) ~28 wk	Cohort 3B* (n = 31) ~56 wk	Cohort 3C* (n = 34) ~56-84 wk
Participants with at least 1 systemic allergic reaction, n (%)	7 (6.4)	5 (16.1)	0	2 (6.5)	10 (29.4)
Participants with episodes of systemic allergic reaction, n (%)					
1	4 (3.7)	1 (3.2)	0	2 (6.5)	7 (20.6)
2	1 (0.9)	1 (3.2)	0	0	3 (8.8)
3	1 (0.9)	2 (6.5)	0	0	0
>3	1 (0.9)	1 (3.2)	0	0	0
Severity,† n (%)					
Mild	1 (0.9)	2 (6.5)	0	1 (3.2)	3 (8.8)
Moderate	4 (3.7)	3 (9.7)	0	1 (3.2)	4 (11.8)
Severe (including anaphylaxis)	2 (1.8)	0	0	0	3 (8.8)
Participants with episodes requiring epinephrine use, n (%)	7 (6.4)	4 (12.9)	0	2 (6.5)	5 (14.7)
Individual systemic allergic reaction episodes by trigger, n					
Trial product	7	12	0	2	10
Other food allergen	5	1	0	0	2
Non−food allergen	1	1	0	0	1

*Participants in cohorts 3B and 3C underwent initial daily dosing for 28 wk.
†Participants with more than 1 systemic allergic reaction were counted only once using the highest severity.

throat irritation, systemic allergic reaction, hypersensitivity, abdominal pain, throat irritation, urticaria, and flushing occurred during daily dosing in cohorts 1 and 3A (all n = 1); abdominal pain, cough, and dyspnea occurred during twice-weekly dosing in cohorts 3B and 3C (all n = 1). The most frequently occurring AEs and exposure-adjusted AEs considered to be allergic reactions are presented in Tables E4 and E5, respectively, in this article's Online Repository at www.jaci-inpractice.org.

Safety outcomes in the PTAH-naive group (Table II and Tables E4 and E5) were similar to those observed during active treatment in the PALISADE trial.[5] Almost all (98%) participants in the PTAH-naive group experienced AEs; 86% experienced treatment-related AEs. Most AEs in the PTAH-naive group occurred during the IDE and updosing periods. Nine participants discontinued treatment because of AEs (IDE/updosing, n = 7; daily dosing, n = 2). Eosinophilic esophagitis (confirmed by endoscopy) was reported in 2 PTAH-naive participants (1 during updosing and 1 during maintenance) and led to treatment discontinuation. One eosinophilic esophagitis event that occurred during updosing (12-mg PTAH, day 50) was severe and considered by the investigator to be unrelated to treatment. The eosinophilic esophagitis event during maintenance (300-mg PTAH, day 293) was moderate and considered to be related to PTAH. Symptoms resolved in both participants after discontinuation of PTAH.

Systemic allergic reactions

The proportion of participants in the PTAH-continuing group who experienced a systemic allergic reaction ranged from 0% to 29.4% across daily and non−daily dosing cohorts (Table III). Among participants in the daily dosing cohorts (cohorts 1 and 3A), 12 participants experienced systemic allergic reactions, most (10 of 12) of which were mild or moderate in severity. Nine participants in non−daily dosing cohorts (cohorts 3B [n = 2] and 3C [n = 7]) experienced only mild or moderate systemic allergic reactions. No systemic allergic reactions occurred in cohort 2. The profile of systemic allergic reactions in the PTAH-naive group was generally consistent with that observed during active treatment in the PALISADE trial. A total of 17.0% of participants (17 of 100) experienced systemic allergic reactions and all were of mild or moderate severity (see Table E6 in this article's Online Repository at www.jaci-inpractice.org); most systemic allergic reactions (72.7%) occurred 2 hours or less after PTAH dosing.

Treatment-related anaphylaxis (ie, severe systemic allergic reaction) occurred during daily dosing periods in 2 participants in cohort 1 and in 3 participants in cohort 3C; all 5 participants who experienced anaphylaxis were female (aged 5-15 years) and all but 1 had a history of systemic allergic reaction at baseline. None of the 5 participants required prolonged hospitalization (observational visit only) or more than 1 epinephrine use. One of the 2 participants in cohort 1 who experienced anaphylaxis had a cofactor of intercurrent illness, but no predisposing cofactor was reported for the second participant. Of the 3 participants in cohort 3C who experienced anaphylaxis during daily dosing, 2 had predisposing cofactors of intercurrent illness, in combination with either fasting (n = 1) or fatigue (n = 1); the third participant had cofactors that included exercise and allergic rhinitis (see Table E7 in this article's Online Repository at www.jaci-inpractice.org).

Accidental exposure to food allergens

Accidental exposures to any food allergens occurred across all cohorts (see Table E8 in this article's Online Repository at

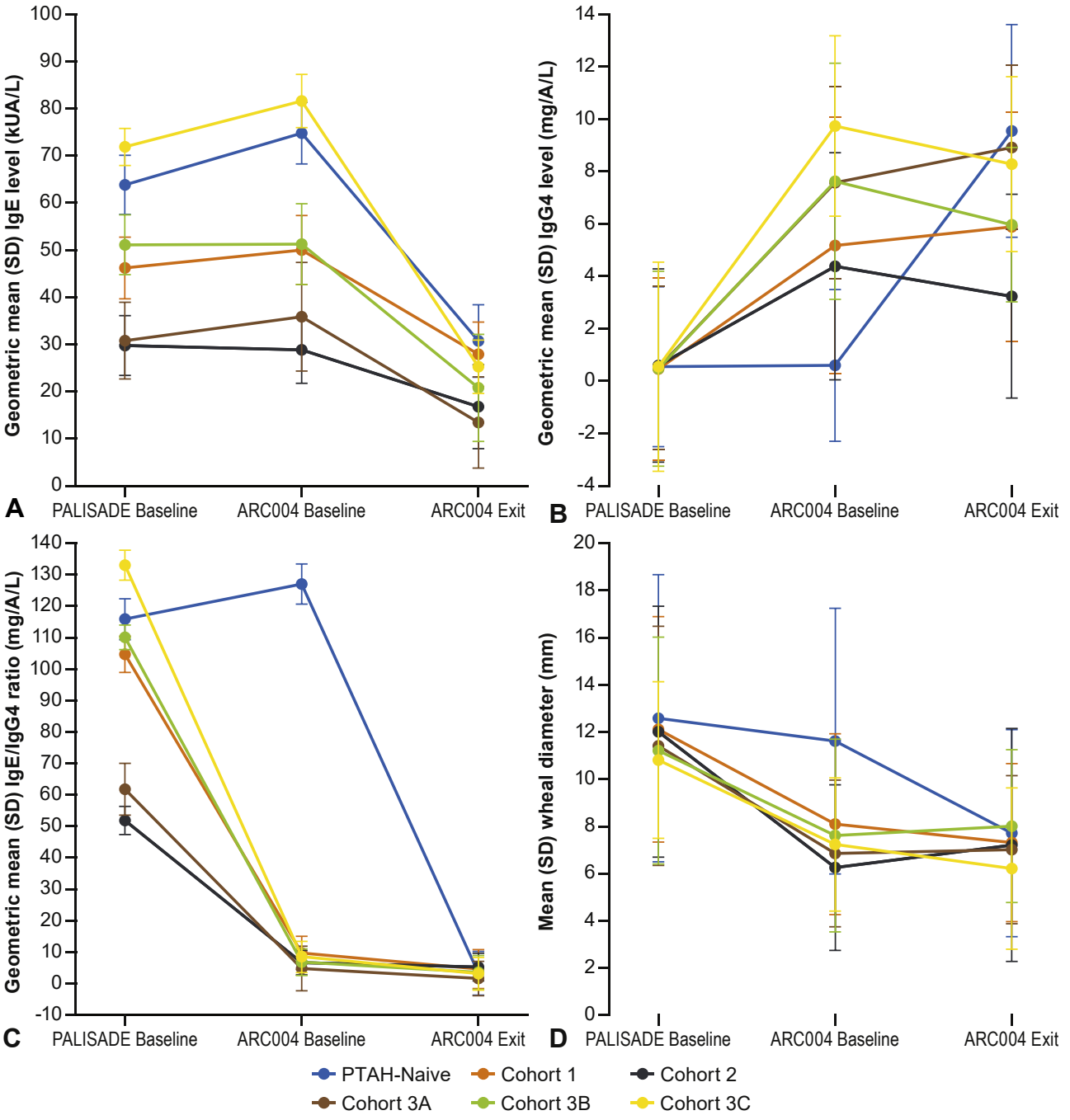

FIGURE 4. Peanut-specific IgE and IgG_4 levels and SPT wheal diameter: baseline vs trial exit. Geometric mean values for (**A**) peanut-specific IgE, (**B**) IgG_4, and (**C**) IgE/IgG_4 ratio at PALISADE baseline, ARC004 baseline, and ARC004 study exit. (**D**) The SPT mean wheal diameter at PALISADE baseline, ARC004 baseline, and ARC004 study exit. *SPT*, Skin prick test. PALISADE baseline values for peanut-specific IgE and IgG_4 and mean SPT wheal diameter were defined as the last available measurement before the first dose of the trial product on day 1 of the ARC004 trial for the PTAH-naive group and as day 1 of the PALISADE trial for participants in the PTAH-continuing cohorts.

www.jaci-inpractice.org); none were associated with serious symptoms. Most participants experienced no more than 1 accidental exposure. At study entry, peanut-related exposures were reported in approximately greater than or equal to 47% of participants across all PTAH-continuing cohorts. Generally, the proportions of accidental exposures requiring treatment were greater in daily dosing cohorts (cohorts 1 and 3A) than in non–daily dosing cohorts (cohorts 2, 3B, and 3C), but the highest rate of 13.3% was seen in the non–daily dosing cohort 3C (Table E8). Among PTAH-continuing cohorts, the number

of events was small and thus no specific trend in the incidence of accidental exposures was observed across daily and non−daily dosing cohorts or daily or non−daily dosing periods within individual cohorts.

In PTAH-naive participants, more participants experienced accidental exposures during IDE/updosing (16%) than during maintenance (∼12%); most participants experienced no more than 1 accidental exposure (Table E8). Approximately one-third of all accidental exposures were peanut related. Although most exposures required treatment, epinephrine use was greater during IDE/updosing than during maintenance periods.

Use of epinephrine as rescue medication

In the PTAH-continuing group (n = 251), 15 participants had 1 use of epinephrine and 7 participants had more than 1 use of epinephrine. Use of epinephrine occurred most frequently in cohort 3C (23.5%) and mainly occurred during twice-weekly dosing in this cohort. Across all cohorts, most epinephrine episodes were associated with mild or moderate AEs. Two epinephrine episodes each during daily dosing in cohorts 1 and 3C were associated with severe AEs. No epinephrine episode in PTAH-continuing participants was associated with a serious AE. Overall, 24 of 37 (64.9%) epinephrine episodes were associated with treatment-related AEs. Most (91.9%) epinephrine use occurred at locations in community settings outside the trial site.

Overall, 20 participants in the PTAH-naive group (n = 100) had at least 1 epinephrine episode. Almost all epinephrine episodes were associated with mild or moderate AEs, and none were considered serious. Twenty-four of 30 (80%) epinephrine episodes were associated with treatment-related AEs. Most epinephrine use (63.3%) occurred at locations outside the trial site.

Change in peanut-specific IgE and IgG4 levels and skin prick test wheal diameter

Change from baseline in immunoglobulin values (ie, peanut-specific IgE and IgG_4 levels) were consistent with continued immunomodulation (Figure 4, *A-C*) from the time of entry into PALISADE (ie, PALISADE baseline) to the ARC004 study exit. At the ARC004 study exit, IgE levels had decreased from the time of PALISADE entry in both PTAH-naive and PTAH-continuing groups. IgG_4 levels, which had increased in all PTAH-continuing cohorts from PALISADE entry to ARC004 entry, continued to increase to the time of ARC004 study exit in daily dosing cohorts 1 and 3A. Mean skin prick test wheal diameter in participants continuing PTAH decreased to a similar extent across all PTAH-continuing cohorts from the time of PALISADE entry to ARC004 study exit (Figure 4, *D*).

DISCUSSION

The approval of PTAH OIT for children and adolescents with peanut allergy is reshaping the treatment paradigm for this population. A high proportion of participants (87.5%) from the PALISADE trial entered the ARC004 study with a high rate of retention to study completion. The ARC004 trial demonstrated that, in children and adolescents, continued daily treatment with PTAH beyond 1 year is safe and is associated with continued and improved efficacy. Immunomodulation continued to mature during the second year of treatment. During the second year of PTAH treatment, daily dosing had a better safety and efficacy profile than non−daily dosing, with lower rates of total exposure-adjusted AEs and fewer severe systemic allergic reactions that mainly occurred (during daily dosing periods in cohorts 1 and 3C) in participants with modifiable cofactors. Overall, these findings suggest that the benefit-risk profile of daily dosing administered during the first 2 years of treatment was better than that of less frequent (nondaily) dosing.

Completion rates were higher in PTAH-continuing participants compared with PTAH-naive participants, which may have stemmed from trial fatigue or the disappointment that participants assigned to receive placebo felt after experiencing no improvement in peanut tolerability at PALISADE completion. For PTAH-naive participants who completed ARC004, clinical outcomes were generally consistent with those reported in the active arm of the PALISADE trial.[5] A high proportion (254 of 351 [72.4%]) of participants treated in ARC004 entered the follow-on ARC008 study (NCT03292484).

Before the phase 3 PALISADE and ARTEMIS trials, data related to OIT for peanut allergy were mainly derived from small-scale uncontrolled studies that appeared limited in various ways.[4,5] Recently published meta-analysis of peanut OIT (12 studies examined by Chu et al[15] and 27 studies examined by Grzeskowiak et al[16]) concluded that despite increasing desensitization, OIT increases the likelihood of allergic reactions.[15] However, the duration of follow-up in all but 1 of the studies was less than 1 year and none had explored the effect of dosing frequency.[15,16] In contrast, participants who received OIT with PTAH in the PALISADE trial and entered ARC004 had received more than 2 years of treatment in some cases. Of note in the daily dosing cohorts, desensitization rates across all peanut challenge doses up to 1000 mg at the ARC004 exit DBPCFC (80.8%-100%) were higher than those observed in the active treatment arm exit DBPCFC of the PALISADE trial (76.6%-50.3%)[5]; moreover, 80.8% of participants in cohort 3A, which had the longest duration of daily dosing, tolerated a single 2000-mg challenge (cumulatively 4043 mg or equivalent to ∼14 peanut kernels) during DBPCFC. This was a meaningful improvement from median tolerated dose of 10 mg (∼one-tenth of peanut kernel) at the PALISADE baseline. In ARC004, there was a trend toward lower rates of exposure-adjusted treatment-related AEs among PTAH-continuing participants who received daily dosing (cohorts 1 and 3A) than among those who received non−daily dosing (cohorts 2, 3B, and 3C). Thus, continued administration of daily PTAH over an additional approximately 6-month to approximately 1-year period in ARC004 appeared to mitigate AE risk, while still effectively maintaining desensitization.

Generalization of results from ARC004 to the wider peanut-allergic population may be limited because analyses were restricted to participants aged 4 to 17 years who had sensitivity to less than or equal to 100-mg peanut protein at the time of enrollment into the PALISADE trial, and those with poorly controlled asthma or chronic gastrointestinal disorders at screening were excluded. As an open-label extension of the PALISADE trial, the aim of the ARC004 trial was to collect data on the longer-term effects of PTAH OIT on the maturation of the immunomodulatory processes and the efficacy and safety of daily and non−daily dosing regimens during the first 2 years of treatment, with the aim of providing further guidance on the administration of peanut OIT in children and adolescents. Limitations of this study are the open-label trial design, which resulted in the study being underpowered to detect significant differences between groups or cohorts. Furthermore, all

participants were sequentially assigned to treatment, which could have introduced bias, and cohort sizes were small.

CONCLUSIONS

Longer-term daily dosing of peanut OIT with PTAH resulted in improved safety and efficacy. After approximately 2 years of continued daily treatment with PTAH, 80% of participants who completed ARC004 were desensitized to 2000-mg peanut protein (cumulatively 4043-mg peanut protein or equivalent to ~14 peanut kernels). Immunologic changes suggest ongoing immunomodulation during the first 2 years of treatment. Longer-term open-label daily dosing with PTAH appeared to have a better overall benefit-risk profile than non—daily dosing, with further benefit observed with 2 years of daily dosing relative to 1 year of daily dosing.[5] Evaluation and confirmation of the benefits of long-term daily dosing beyond 2 years with PTAH is required.

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ONLINE REPOSITORY

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INCLUSION AND EXCLUSION CRITERIA

Participants could enroll in the ARC004 study if they completed the PALISADE study, which consisted of participants in the active treatment arm who tolerated 300-mg peanut protein at the exit DBPCFC and participants in the placebo arm who completed the exit DBPCFC. All participants entering ARC004 were required to provide written informed consent. Female participants of child-bearing potential were required to use effective birth control.

Exclusion criteria were early discontinuation from PALISADE, failure to tolerate 443-mg cumulative peanut protein dose with mild or no symptoms at the PALISADE exit DBPCFC, meeting any longitudinally applicable criteria for the PALISADE trial (outlined below), or any other condition that in the investigator's opinion precludes participation for safety reasons.

Longitudinally applicable exclusion criteria

1. History of cardiovascular disease including uncontrolled or inadequately controlled hypertension
2. History of chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that is at significant risk of becoming unstable or requiring a change in the chronic therapeutic regimen
3. History of eosinophilic esophagitis or other eosinophilic gastrointestinal disease
4. Concurrent participation in any other interventional study
5. Participants in the "build-up" phase of immunotherapy to another allergen (ie, participants who have not reached maintenance dosing)
6. Severe asthma as defined by the 2007 National Heart, Lung, and Blood Institute criteria
7. Mild or moderate asthma that is uncontrolled or difficult to control as defined by
   a. FEV_1 less than 80% of predicted value, or ratio of FEV_1 to forced vital capacity less than 75% of predicted value, with or without controller medications (only for those 6 years or older and able to do spirometry) or
   b. Inhaled corticosteroid dosing of more than 500 g daily fluticasone (or equivalent inhaled corticosteroids based on the National Heart, Lung, and Blood Institute dosing chart)
8. History of intravenous, intramuscular, or steroid medications administered in the following manner:
   a. History of daily oral steroid administration for >1 month
   b. Two-burst course of oral, intramuscular, or intravenous steroids, defined as more than or equal to 1 mg/kg of prednisone or prednisone equivalent of more than or equal to 1-week duration, in the past year
9. Inability to discontinue antihistamines for 5 half-lives before the initial day of dose escalation, skin prick test, or DBPCFC
10. Lack of an available palatable vehicle food to which the participant is not allergic
11. Use of any therapeutic antibody (eg, omalizumab, mepolizumab, and reslizumab), any investigational peanut OIT

other than PTAH, or any other immunomodulatory therapy excluding corticosteroids within the previous 6 months
12. Use of beta blockers (oral), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers
13. Pregnancy or lactation
14. Having the same place of residence as another study participant
15. Participation in another clinical trial within 30 days or 5 half-lives of the investigational product, whichever is longer, before enrollment in PALISADE
16. Development of dose-limiting symptoms in reaction to the placebo part of the PALISADE screening DBPCFC
17. History of mast cell disorder, including mastocytosis, urticaria pigmentosa, and hereditary or idiopathic angioedema
18. Allergy to oat
19. Hypersensitivity to epinephrine or any of the excipients in the product

Statistical Analyses

Given the lack of peer-reviewed, published evidence on non−daily dosing regimens, the ARC004 trial was intentionally designed to be exploratory and hypothesis-generating in nature and was not powered to permit statistically meaningful comparisons. Accrual of 80% of the total PALISADE population into the ARC004 study would provide an 80% probability of observing at least 1 AE, with a background rate of 4 AEs per 1000 participants. There was no prospective power calculation for efficacy in ARC004.

Primary analyses were conducted in participants, aged 4 to 17 years at entry into ARC004, who received at least 1 dose of PTAH and constituted the safety population. The completer population was defined as all participants in the safety population who had an evaluable peanut DBPCFC.

All data were summarized using descriptive statistics within the treatment group and the cohort. Analyses of systemic allergic reactions included the number of systemic allergic reactions, attribution of the systemic allergic reactions (ie, trial product, other food allergen, or other), number of participants experiencing systemic allergic reactions, and the number of systemic allergic reaction episodes. Evaluations of epinephrine use (excluding use during DBPCFCs) included the number and proportion of participants with any epinephrine episode and the number of epinephrine episodes per participant (1, 2, 3, or >3). The number of participants with any accidental food allergen exposure, number of accidental exposures per participant, and total number of food allergen exposures were summarized.

Summary statistics were implemented for analyses of derived skin prick test mean wheal diameter as well as changes in wheal diameter from baseline. Geometric means and SDs were determined for peanut-specific IgE, IgG_4, and the IgE/IgG_4 ratio.

Trial Oversight, Statement of Ethics, and Role of Sponsor

The ARC004 trial was funded by Aimmune Therapeutics. Approvals from site-specific institutional review boards, ethics committees, research ethics boards, or like authorities were obtained before trial initiation. Prospective participants and/or their parents or guardians were informed that their participation in the trial was voluntary and that they could withdraw from the trial at any time for any reason. All participants or their parents or guardians completed an informed consent as well as an age-appropriate assent form as per local guidelines and the provisions for biospecimen collection and handling. Aimmune Therapeutics monitored safety and efficacy throughout the trial.

The trial design was codeveloped with the company's independent Scientific Advisory Board. Together with the principal investigators, the trial sponsor was involved in data collection, data analysis, data interpretation, and the writing of this report. The first (B.V.) and senior authors (D.C.A.) of this article were given access to all relevant data in the study. The corresponding author (D.C.A.) had full access to the data and had final responsibility for the decision to submit for publication.

CRITERIA FOR DOSE MODIFICATION

In the event of questionable tolerability, administration of the study product under medical supervision at the study site was recommended. For repeated mild symptoms occurring during dosing at home, the dose may be split into 2 doses taken 8 to 12 hours apart for up to 2 weeks. Alternatively, dosing was temporarily withheld for up to 2 weeks or was reduced by 1 or 2 levels and maintained at the reduced dose for at least 2 weeks or was maintained at the same dose level for 1 to 2 weeks before attempting dose reescalation. Dose modifications in the event of a dose that was not tolerated are as follows: For mild symptoms, a 1- to 2-level dose reduction followed by maintenance of the reduced dose for at least 2 weeks was recommended and the study product was to be discontinued if not tolerated after 2 dose reductions. For moderate symptoms, a 1- to 2-level dose reduction was required until the study product was tolerated with no more than mild symptoms. Severe symptoms required a 2-level dose reduction for at least 2 to 4 weeks; the study product was to be discontinued if moderate or severe symptoms occurred at the reduced dose. Symptoms requiring treatment with 2 doses of epinephrine required a 2-level dose reduction and maintenance of the reduced dose for 6 to 8 weeks; the study product was discontinued if moderate or severe symptoms occurred at the reduced dose.

Criteria for temporary dose reductions for intercurrent AEs during once-daily dosing included the following: for dose reductions over 4 consecutive days, the next dose at the previous dose level could be administered at home or at the study site, and the dose level continued for the 2-week dosing interval. For dose reductions over 5 to 7 consecutive days, dosing at the reduced or previous dose level was to be administered at the study site, and the dose level continued for at least 2 weeks before dose escalation. For dose reductions over 8 to 14 consecutive days, the next dose at 1 level above the reduced dose was to be administered at the study site. If the escalation to the next dose level was successful, the dose level would continue for at least 2 weeks before dose escalation.

STOPPING RULES

Individual stopping rules

Participants were permitted to stop the study at any time by withdrawing consent if they experienced subjectively intolerable AEs or dosing symptoms, or for any other reason. All participants discontinuing the study early and permanently discontinuing PTAH were to return to the clinical research center for an early discontinuation visit no later than 14 days after the last PTAH exposure.

When receiving daily dosing (including updosing and maintenance for PTAH-naive participants, and daily extended maintenance for both PTAH-naive and PTAH-continuing groups, as applicable), 7 or more consecutive days of missed daily dosing because of noncompliance constituted an individual stopping rule. During updosing, PTAH-naive participants were required to halt and then restart updosing with a reduced dose if more than 4 days of dosing had been missed. Missing 3 or more consecutive days on 3 occasions while on daily dosing during any period was an individual stopping rule, as was missing 15 or more consecutive days of daily dosing for any reason.

Any participant receiving nondaily dosing who had 1 related serious AE, 1 related AE graded as severe, 2 related AEs occurring on separate occasions, both graded moderate, or 3 consecutive doses judged "not tolerated" was considered as a treatment failure and discontinued from ARC004 for safety reasons. These participants were eligible to enroll in ARC008 and receive PTAH daily in the repeat updosing period. If ARC008 was not available, participants were to begin daily dosing and have visits in the repeat updosing period in ARC004. Once the target dose of 300 mg daily was reached and maintained for 2 weeks, participants were able to continue this dose regimen until ARC008 was available. Failure to accomplish updosing of study product after 3 attempts or failure to identify a tolerated dose of study product after 3 attempts at dose reduction resulted in the cessation of dosing and discontinuation from the study as an escalation failure nonresponder. Administration of 3 or more doses of epinephrine for treatment of any dose-related allergic reaction in any participant during any period was considered a stopping rule.

Cohort stopping rules

ARC004 consecutively enrolled eligible participants into different cohorts, each of which produced evidence of the feasibility and safety of adjusting extended maintenance dosing from a daily to nondaily schedule. Information that became available as each cohort proceeded through the study was evaluated before determining whether the next cohort could advance to a longer interval between doses. No participant was exposed to a longer interval between doses if evidence from the previous cohort suggested that doing so would more likely than not cause participants to either experience more frequent or more severe AEs, or lose desensitization that was gained/maintained, had they remained on more frequent dosing. Because participants in cohorts 3B and 3C had 28 additional weeks of daily maintenance, they were allowed to proceed to every other day and twice-weekly dosing independent of cohort 2's experience according to the judgment of the Safety Monitoring Committee.

For each cohort, all participants discontinuing early because of AEs (ie, dropouts) were considered treatment failures. Likewise, participants who were deemed to have lost desensitization during the ARC004 exit DBPCFC, when compared with either the ARC003 exit DBPCFC (PTAH-continuing) or the ARC004 postmaintenance DBPCFC (PTAH-naive), were considered treatment failures (eg, failed completers), based on the following criteria:

1. Participants tolerating 443 mg at the previous DBPCFC had to tolerate greater than or equal to 443-mg peanut protein at the ARC004 exit DBPCFC, or be considered a treatment failure
2. Participants tolerating 1043-mg peanut protein at the previous DBPCFC had to tolerate greater than or equal to 443 mg at the ARC004 exit DBPCFC, or be considered a treatment failure
3. Participants tolerating 2043-mg (or greater, for PTAH-naive participants) peanut protein at the previous DBPCFC had to tolerate greater than or equal to 1043-mg peanut protein at the ARC004 exit DBPCFC, or be considered a treatment failure

The treatment failure rate in each cohort was monitored on an ongoing basis by the Safety Monitoring Committee, and calculated according to the following formula:

Treatment failure rate = [(dropouts) + (failed completers)]/planned size* for the cohort.

*Assumptions = Up to approximately 500 ARC003 completers (having received active drug or placebo in ARC003 at a 3:1 ratio) are projected for recruitment into ARC004. This assumes a loss of 15% of the randomized ARC003 population due to attrition, AEs, and so forth. Thus, the planned sizes for the ARC004 cohorts are as follows, though the actual number may vary because of recruitment:

- Cohort 1 = 120, prespecified
- Cohort 2 = 50, prespecified
- Cohort 3 = 175, distributed equally across cohorts 3A, 3B, and 3C
- Group 1 = 130 (25% of ARC003 enrollment, accounting for 5% dropout)

Whenever the treatment failure rate was greater than 50%, this stopping rule was met and further prolongation of the dosing interval in any subsequent cohort would cease. As an additional safety precaution, if individual stopping rules (eg, due to AEs) were invoked in 10 of the first 20 participants to enroll in any cohort, further enrollment in that cohort would cease. Finally, the Safety Monitoring Committee retained the authority to stop further enrollment into a cohort at any time for any reason. If any of these conditions transpired, all remaining participants, including ongoing participants in the terminated cohort, and future participants would receive 300-mg PTAH at the longest interval tolerated by a previous cohort.

ADMINISTRATION OF DBPCFCS

The DBPCFC entailed administration of increasing amounts of peanut protein or placebo (oat flour) mixed with a vehicle food at 20- to 30-minute intervals. The peanut and placebo DBPCFCs were conducted on separate days and assigned in random order. Participants did not take their PTAH dose on the same day as the DBPCFC. The exit DBPCFC was not performed for participants who did not tolerate non−daily dosing or for participants who switched to once-daily dosing after missing a non−daily dose for more than 3 days. Before the DBPCFC, exacerbation of asthma (as determined by active wheezing or peak expiratory flow <80% of predicted flow rate) was assessed. Discontinuation of antihistamines or other medications that could interfere with assessment of an allergic reaction was required for 5 half-lives of the medication before the DBPCFC.

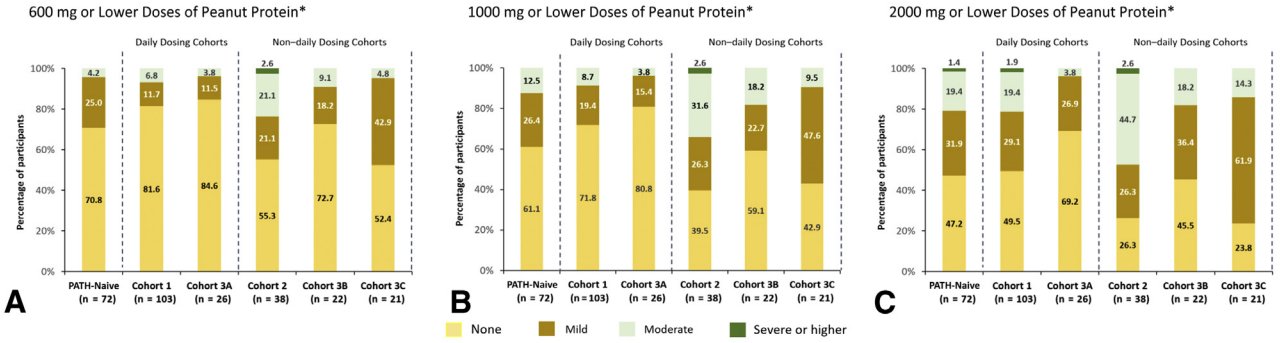

FIGURE E1. Maximum symptom severity at DBPCFC (completer population; N = 282) at peanut challenge doses of 600 mg or lower (**A**), 1000 mg or lower (**B**), and 2000 mg or lower (**C**). *The sum of the columns may be 99.9% or 100.1% due to rounding.

TABLE E1. Treatment compliance with planned dosing at home (safety population; N = 351)

			PTAH-Continuing (n = 251)									
					Non–daily dosing cohorts							
	PTAH-Naive (n = 100) ~52 wk		Daily dosing cohorts		Cohort 2 (n = 46) ~28 wk		Cohort 3B (n = 31) ~56 wk			Cohort 3C (n = 34) ~56-84 wk		
Compliance parameter, median (IQR)	IDE/updosing (n = 100)	Daily dosing (n = 85)	Cohort 1 (n = 109) ~28 wk	Cohort 3A (n = 31) ~56 wk	Every other day (n = 46)	Twice weekly (n = 44)	Daily (n = 31)	Every other day (n = 27)	Twice weekly (n = 26)	Daily (n=34)	Every other day (n = 31)	Twice weekly (n = 30)
No. of planned dosing days at home	143.0 (132-163)	382.0 (209-471)	214.0 (199-294)	389.0 (382-399)	14.0 (13-16)	49.0 (46-54)	191.5 (186-195)	13.0 (12-16)	47.0 (43-52)	194.0 (190-196)	14.5 (12-17)	87.5 (73-103)
Percentage of planned dosing days where a full or partial dose was consumed	98.70 (96.40-99.48)	98.24 (95.73-99.58)	97.37 (94.01-99.50)	98.72 (94.94-99.48)	100 (94.28-100)	100 (98.81-100)	97.78 (92.31-99.50)	100 (100-100)	100 (98.04-100)	96.83 (91.51-98.97)	100 (91.67-100)	100 (94.12-100)
Percentage of planned dosing days where a full dose was consumed	97.70 (94.04-99.30)	97.96 (95.34-99.58)	97.23 (93.26-99.48)	98.15 (94.68-99.23)	100 (93.33-100)	100 (98.04-100)	97.78 (92.31-99.46)	100 (100-100)	100 (95.74-100)	95.77 (90.95-98.97)	100 (91.67-100)	100 (92.16-100)
Percentage of planned dosing days where a dose was missed	1.30 (0.52-3.60)	1.76 (0.42-4.27)	2.63 (0.50-5.99)	1.28 (0.52-5.06)	0 (0-5.72)	0 (0-1.19)	2.22 (0.50-7.69)	0 (0-0)	0 (0-1.96)	3.17 (1.03-8.49)	0 (0-8.33)	0 (0-5.88)

IQR, Interquartile range.

TABLE E2. Treatment exposure (safety population; N = 351)

			PTAH-Continuing (n = 251)									
					Non–daily dosing cohorts							
	PTAH-Naive (n = 100) ~52 wk		Daily dosing cohorts		Cohort 2 (n = 46) ~28 wk		Cohort 3B (n = 31) ~56 wk			Cohort 3C (n = 34) ~56-84 wk		
Exposure parameter	IDE/updosing (n = 100)	Daily dosing (n = 85)	Cohort 1 (n = 109) ~28 wk	Cohort 3A (n = 31) ~56 wk	Every other day (n = 46)	Twice weekly (n = 44)	Daily (n = 31)	Every other day (n = 27)	Twice weekly (n = 26)	Daily (n = 34)	Every other day (n = 31)	Twice weekly (n = 30)
Median duration of exposure (mo) (IQR)	5.13 (4.70-5.84)	12.76 (7.11-15.69)	7.24 (6.61-9.84)	12.99 (12.83-13.26)	0.99 (0.89-1.09)	5.79 (5.43-6.64)	6.41 (6.25-6.48)	0.92 (0.86-1.12)	5.56 (5.10-6.02)	6.41 (6.32-6.58)	0.95 (0.86-1.12)	9.72 (8.55-12.01)
Duration of exposure by category (mo), n (%)												
0-3	7 (7.0)		1 (0.9)	1 (3.2)	3 (6.5)			1 (3.2)			1 (2.9)	
4-6	6 (6.0)		5 (4.6)	2 (6.5)	5 (10.9)			2 (6.5)			1 (2.9)	
7-9	7 (7.0)		65 (59.6)	0	31 (67.4)			3 (9.7)			5 (14.7)	
10-12	8 (8.0)		33 (30.3)	1 (3.2)	6 (13.0)			2 (6.5)			2 (5.9)	
13-15	10 (10.0)		4 (3.7)	26 (83.9)	1 (2.2)			20 (64.5)			1 (2.9)	
16-18	14 (14.0)		0	1 (3.2)	0			2 (6.5)			11 (32.4)	
19-21	30 (30.0)		1 (0.9)	0	0			1 (3.2)			13 (38.2)	
22-24	13 (13.0)		0	0	0			0			0	
>24	5 (5.0)		0	0	0			0			0	

IQR, Interquartile range.

TABLE E3. Epinephrine use as rescue medication at the exit DBPCFC (completer population; N = 282)

		PTAH-Continuing (n = 210)				
		Daily dosing cohorts		Non–daily dosing cohorts		
Any epinephrine use as rescue medication at exit DBPCFC, n (%)	PTAH-Naive ~52 wk (n = 72)	Cohort 1 (n = 103) ~28 wk	Cohort 3A (n = 26) ~56 wk	Cohort 2 (n = 38) ~28 wk	Cohort 3B (n = 22) ~56 wk	Cohort 3C (n = 21) ~56-84 wk
Placebo challenge						
Yes	0	0	0	0	0	0
No	72 (100)	102 (99)	26 (100)	38 (100)	22 (100)	21 (100)
Peanut challenge						
Yes	9 (12.5)	24 (23.3)	1 (3.8)	12 (31.6)	1 (4.5)	4 (19.9)
No	63 (87.5)	79 (76.7)	25 (96.2)	26 (68.4)	21 (95.5)	17 (81.0)

TABLE E4. Incidence of AEs occurring in ≥5% of participants (safety population; N = 351)*

	PTAH-Naive (n = 100) ~52 wk			PTAH-Continuing (n = 251)									
				Daily dosing cohorts		Non–daily dosing cohorts							Overall
						Cohort 2 (n = 46) ~28 wk		Cohort 3B (n = 31) ~56 wk			Cohort 3C (n = 34) ~56-84 wk			
AEs, n (%)	IDE/ updosing (n = 100)	Daily dosing (n = 85)	Total (n = 100)	Cohort 1 (n = 109) ~28 wk	Cohort 3A (n = 31) ~56 wk	Every other day (n = 46)	Twice weekly (n = 44)	Daily (n = 31)	Every other day (n = 27)	Twice weekly (n = 26)	Daily (n = 34)	Every other day (n = 31)	Twice weekly (n = 30)	Daily dosing (n = 205)
Cough	39 (39.0)	19 (22.4)	44 (44.0)	16 (14.7)	8 (25.8)	4 (8.7)	6 (13.6)	7 (22.6)	4 (14.8)	6 (23.1)	13 (38.2)	2 (6.5)	7 (23.3)	44 (21.5)
Pyrexia	17 (17.0)	14 (16.5)	24 (24.0)	20 (18.3)	8 (25.8)	2 (4.3)	2 (4.5)	6 (19.4)	0	1 (3.8)	10 (29.4)	1 (3.2)	6 (20.0)	44 (21.5)
Vomiting	34 (34.0)	13 (15.3)	42 (42.0)	18 (16.5)	6 (19.4)	1 (2.2)	5 (11.4)	7 (22.6)	0	2 (7.7)	6 (17.6)	1 (3.2)	5 (16.7)	37 (18.0)
Urticaria	27 (27.0)	16 (18.8)	37 (37.0)	16 (14.7)	7 (22.6)	2 (4.3)	4 (9.1)	4 (12.9)	0	3 (11.5)	9 (26.5)	1 (3.2)	2 (6.7)	36 (17.6)
Headache	19 (19.0)	14 (16.5)	27 (27.0)	12 (11.0)	8 (25.8)	5 (10.9)	8 (18.2)	5 (16.1)	1 (3.7)	2 (7.7)	11 (32.4)	1 (3.2)	6 (20.0)	36 (17.6)
Upper respiratory tract infection	15 (15.0)	12 (14.1)	23 (23.0)	20 (18.3)	3 (9.7)	1 (2.2)	5 (11.4)	4 (12.9)	0	2 (7.7)	5 (14.7)	0	4 (13.3)	32 (15.6)
Abdominal pain	37 (37.0)	10 (11.8)	38 (38.0)	11 (10.1)	5 (16.1)	1 (2.2)	6 (13.6)	3 (9.7)	0	5 (19.2)	12 (35.3)	2 (6.5)	10 (33.3)	31 (15.1)
Throat irritation	28 (28.0)	12 (14.1)	32 (32.0)	15 (13.8)	5 (16.1)	7 (15.2)	8 (18.2)	3 (9.7)	0	2 (7.7)	5 (14.7)	1 (3.2)	8 (26.7)	28 (13.7)
Oropharyngeal pain	18 (18.0)	12 (14.1)	23 (23.0)	7 (6.4)	7 (22.6)	2 (4.3)	2 (4.5)	6 (19.4)	0	2 (7.7)	4 (11.8)	2 (6.5)	4 (13.3)	24 (11.7)
Nasopharyngitis	11 (11.0)	11 (12.9)	16 (16.0)	5 (4.6)	5 (16.1)	0	5 (11.4)	4 (12.9)	1 (3.7)	1 (3.8)	8 (23.5)	0	2 (6.7)	22 (10.7)
Rhinorrhea	24 (24.0)	8 (9.4)	28 (28.0)	7 (6.4)	3 (9.7)	2 (4.3)	1 (2.3)	4 (12.9)	2 (7.4)	2 (7.7)	6 (17.6)	1 (3.2)	4 (13.3)	20 (9.8)
Nausea	28 (28.0)	14 (16.5)	33 (33.0)	9 (8.3)	5 (16.1)	2 (4.3)	8 (18.2)	3 (9.7)	2 (7.4)	1 (3.8)	1 (2.9)	0	4 (13.3)	18 (8.8)
Nasal congestion	18 (18.0)	6 (7.1)	22 (22.0)	8 (7.3)	2 (6.5)	2 (4.3)	4 (9.1)	3 (9.7)	1 (3.7)	3 (11.5)	5 (14.7)	0	2 (6.7)	18 (8.8)
Viral infection	6 (6.0)	5 (5.9)	10 (10.0)	9 (8.3)	5 (16.1)	0	1 (2.3)	1 (3.2)	0	0	2 (5.9)	1 (3.2)	3 (10.0)	17 (8.3)
Upper abdominal pain	28 (28.0)	11 (12.9)	31 (31.0)	9 (8.3)	5 (16.1)	4 (8.7)	4 (9.1)	2 (6.5)	0	4 (15.4)	1 (2.9)	0	4 (13.3)	17 (8.3)
Systemic allergic reaction	8 (8.0)	11 (12.9)	17 (17.0)	7 (6.4)	5 (16.1)	0	0	1 (3.2)	0	1 (3.8)	3 (8.8)	1 (3.2)	7 (23.3)	16 (7.8)
Sneezing	16 (16.0)	5 (5.9)	18 (18.0)	8 (7.3)	3 (9.7)	0	4 (9.1)	2 (6.5)	1 (3.7)	4 (15.4)	2 (5.9)	2 (6.5)	3 (10.0)	15 (7.3)
Oral pruritus	16 (16.0)	4 (4.7)	17 (17.0)	6 (5.5)	4 (12.9)	1 (2.2)	5 (11.4)	2 (6.5)	0	2 (7.7)	2 (5.9)	1 (3.2)	6 (20.0)	14 (6.8)
Influenza	2 (2.0)	5 (5.9)	7 (7.0)	7 (6.4)	1 (3.2)	0	1 (2.3)	5 (16.1)	0	0	1 (2.9)	0	2 (6.7)	14 (6.8)
Diarrhea	8 (8.0)	3 (3.5)	10 (10.0)	5 (4.6)	4 (12.9)	1 (2.2)	1 (2.3)	3 (9.7)	0	1 (3.8)	2 (5.9)	0	0	14 (6.8)
Pruritus	15 (15.0)	10 (11.8)	19 (19.0)	7 (6.4)	1 (3.2)	3 (6.5)	5 (11.4)	2 (6.5)	1 (3.7)	5 (19.2)	3 (8.8)	3 (9.7)	2 (6.7)	13 (6.3)
Rash	10 (10.0)	5 (5.9)	14 (14.0)	6 (5.5)	1 (3.2)	1 (2.2)	0	2 (6.5)	0	1 (3.8)	2 (5.9)	0	3 (10.0)	11 (5.4)
Asthma	3 (3.0)	1 (1.2)	4 (4.0)	3 (2.8)	0	1 (2.2)	4 (9.1)	4 (12.9)	0	1 (3.8)	4 (11.8)	0	2 (6.7)	11 (5.4)

*Summary includes all events occurring in ≥5% of participants in the PTAH-continuing overall daily dosing cohort.

TABLE E5. Exposure-adjusted AE rates for the most frequent (≥5% of participants) treatment-emergent AEs (safety population; N = 351)*

	PTAH-Naive (n = 100) ~52 wk			PTAH-Continuing (n = 251)			
				Daily dosing cohorts		Non–daily dosing cohorts*	
						Cohort 2 (n = 46) ~28 wk PYE = 25.95	
No. of AEs (events per PY)	IDE/updosing (n = 100) PYE = 43.76	Daily dosing (n = 85) PYE = 85.53	Total (n = 100) PYE = 129.29	Cohort 1 (n = 109) ~28 wk PYE = 73.74	Cohort 3A (n = 31) ~56 wk PYE = 31.53	Every other day (n = 46) PYE = 3.95	Twice weekly (n = 44) PYE = 22.0
Cough	97 (2.22)	50 (0.58)	147 (1.14)	29 (0.39)	57 (1.81)	5 (1.26)	10 (0.45)
Pyrexia	26 (0.59)	25 (0.29)	51 (0.39)	27 (0.37)	19 (0.60)	3 (0.76)	2 (0.09)
Vomiting	102 (2.33)	14 (0.16)	116 (0.90)	32 (0.43)	8 (0.25)	2 (0.51)	8 (0.36)
Urticaria	52 (1.19)	44 (0.51)	96 (0.74)	32 (0.43)	34 (1.08)	2 (0.51)	10 (0.45)
Headache	41 (0.94)	28 (0.33)	69 (0.53)	22 (0.30)	19 (0.60)	8 (2.02)	14 (0.64)
Upper respiratory tract infection	30 (0.69)	19 (0.22)	49 (0.38)	27 (0.37)	7 (0.22)	1 (0.25)	6 (0.27)
Abdominal pain	232 (5.30)	83 (0.97)	315 (2.44)	22 (0.30)	43 (1.36)	2 (0.51)	11 (0.50)
Throat irritation	431 (9.85)	322 (3.76)	753 (5.82)	38 (0.52)	14 (0.44)	53 (13.41)	24 (1.09)
Oropharyngeal pain	57 (1.30)	25 (0.29)	82 (0.63)	9 (0.12)	28 (0.89)	3 (0.76)	5 (0.23)
	5 (0.32)	1 (0.46)	1 (0.08)	11 (0.63)	0	7 (0.31)	30 (0.22)
7 (0.32)							
Rhinorrhea	41 (0.94)	24 (0.28)	65 (0.50)	23 (0.31)	15 (0.48)	3 (0.76)	16 (0.73)
Nausea	185 (4.23)	56 (0.65)	241 (1.86)	15 (0.20)	5 (0.16)	3 (0.76)	11 (0.50)
Nasal congestion	51 (1.17)	10 (0.12)	61 (0.47)	13 (0.18)	37 (1.17)	3 (0.76)	5 (0.23)
Viral infection	8 (0.18)	5 (0.06)	13 (0.10)	12 (0.16)	7 (0.22)	0	1 (0.05)
Upper abdominal pain	162 (3.70)	61 (0.71)	223 (1.72)	136 (1.84)	28 (0.89)	12 (3.04)	63 (2.86)
Systemic allergic reaction	9 (0.21)	13 (0.15)	22 (0.17)	13 (0.18)	14 (0.44)	0	0
Sneezing	44 (1.01)	10 (0.12)	54 (0.42)	24 (0.33)	7 (0.22)	0	5 (0.23)
Oral pruritus	105 (2.40)	249 (2.91)	354 (2.74)	232 (3.15)	10 (0.32)	8 (2.02)	32 (1.45)
Influenza	2 (0.05)	6 (0.07)	8 (0.06)	7 (0.09)	1 (0.03)	0	1 (0.05)
Diarrhea	64 (1.46)	3 (0.04)	67 (0.52)	11 (0.15)	15 (0.48)	3 (0.76)	1 (0.05)
Pruritus	27 (0.62)	20 (0.23)	47 (0.36)	11 (0.15)	2 (0.06)	3 (0.76)	7 (0.32)
Rash	10 (0.23)	6 (0.07)	16 (0.12)	6 (0.08)	1 (0.03)	1 (0.25)	0
Asthma	3 (0.07)	2 (0.02)	5 (0.04)	3 (0.04)	0	2 (0.51)	10 (0.45)

TABLE E5. *(Continued)*

PTAH-Continuing (n = 251)						
Non–daily dosing cohorts*						
Cohort 3B* (n = 31) ~56 wk PYE = 30.08			Cohort 3C* (n = 34) ~56-84 wk PYE = 42.49			Overall
Daily (n = 31) PYE = 15.82	Every other day (n = 27) PYE = 2.18	Twice weekly (n = 26) PYE = 12.08	Daily (n = 34) PYE = 17.58	Every other day (n = 31) PYE = 2.47	Twice weekly (n = 30) PYE = 22.43	Daily dosing (n = 205) PYE = 138.67
16 (1.01)	4 (1.83)	20 (1.66)	29 (1.65)	2 (0.81)	16 (0.71)	131 (0.94)
13 (0.82)	0	1 (0.08)	14 (0.80)	1 (0.40)	9 (0.40)	73 (0.53)
19 (1.20)	0	2 (0.17)	16 (0.91)	1 (0.40)	8 (0.36)	75 (0.54)
5 (0.32)	0	4 (0.33)	14 (0.80)	1 (0.40)	4 (0.18)	85 (0.61)
5 (0.32)	3 (1.37)	4 (0.33)	31 (1.76)	4 (1.62)	16 (0.71)	77 (0.56)
9 (0.57)	0	2 (0.17)	13 (0.74)	0	4 (0.18)	56 (0.40)
5 (0.32)	0	10 (0.83)	44 (2.50)	2 (0.81)	49 (2.18)	114 (0.82)
4 (0.25)	0	2 (0.17)	184 (10.46)	14 (5.66)	91 (4.06)	240 (1.73)
9 (0.57)	0	2 (0.17)	5 (0.28)	2 (0.81)	5 (0.22)	51 (0.37)
5 (0.32)	1 (0.46)	1 (0.08)	11 (0.63)	0	7 (0.31)	30 (0.22)
6 (0.38)	2 (0.92)	2 (0.17)	11 (0.63)	1 (0.40)	10 (0.45)	55 (0.40)
6 (0.38)	2 (0.92)	1 (0.08)	1 (0.06)	0	11 (0.49)	27 (0.19)
10 (0.63)	1 (0.46)	4 (0.33)	10 (0.57)	0	4 (0.18)	70 (0.50)
1 (0.06)	0	0	3 (0.17)	1 (0.40)	7 (0.31)	23 (0.17)
3 (0.19)	0	7 (0.58)	2 (0.11)	0	6 (0.27)	169 (1.22)
1 (0.06)	0	1 (0.08)	3 (0.17)	1 (0.40)	9 (0.40)	31 (0.22)
2 (0.13)	2 (0.92)	10 (0.83)	4 (0.23)	3 (1.21)	4 (0.18)	37 (0.27)
3 (0.19)	0	6 (0.50)	2 (0.11)	3 (1.21)	11 (0.49)	247 (1.78)
5 (0.32)	0	0	1 (0.06)	0	2 (0.09)	14 (0.10)
8 (0.51)	0	1 (0.08)	3 (0.17)	0	0	37 (0.27)
2 (0.13)	1 (0.46)	5 (0.41)	3 (0.17)	3 (1.21)	6 (0.27)	18 (0.13)
2 (0.13)	0	1 (0.08)	3 (0.17)	0	3 (0.13)	12 (0.09)
6 (0.38)	0	1 (0.08)	6 (0.34)	0	2 (0.09)	15 (0.11)

PY, Participant-year; *PYE*, participant-year event.
‡Events were included and sorted consistent with those selected at the per-participant level in Table E4.

TABLE E6. Incidence of systemic allergic reactions in PTAH-naive participants

	PTAH-Naive (n = 100) ~52 wk		
Parameter	**IDE/updosing (n = 100)**	**Daily dosing (n = 85)**	**Total (n = 100)**
Any systemic allergic reaction, n (%)	8 (8.0)	11 (12.9)	17 (17.0)
No. of systemic allergic reactions			
1	7 (7.0)	9 (10.6)	13 (13.0)
2	1 (1.0)	2 (2.4)	3 (3.0)
3	0	0	1 (1.0)
>3	0	0	0
Systemic allergic reactions by maximum severity, n (%)			
Mild	4 (4.0)	6 (7.1)	10 (10.0)
Moderate	4 (4.0)	5 (5.9)	7 (7.0)
Severe (anaphylaxis)	0	0	0
Epinephrine use for systemic allergic reaction events, n (%)	6 (6.0)	8 (9.4)	12 (12.0)
Systemic allergic reactions by trigger			
Study product	4	11	15
Food allergen	4	0	4
Non−food allergen	1	2	3
Systemic allergic reaction−associated symptoms in ≥5% of participants			
Urticaria	3 (3.0)	10 (11.8)	12 (12.0)
Pruritus	3 (3.0)	4 (4.7)	6 (6.0)
Wheezing	2 (2.0)	4 (4.7)	6 (6.0)
Cough	4 (4.0)	4 (4.7)	6 (6.0)
Dyspnea	4 (4.0)	5 (5.9)	8 (8.0)

TABLE E7. Anaphylaxis events by participant during daily dosing in PTAH-continuing participants

Participant no.	Day after start of treatment*	Dosing period	Time after dose (h)	Trigger	Epinephrine use (yes/no)	Discontinuation (yes/no)	Predisposing cofactors
Cohort 1							
1	30	Daily dosing	0.8	PTAH	Yes	No	Intercurrent illness
2	72	Daily dosing	4.0	PTAH	Yes	Yes	None identified
Cohort 3C							
1	72	Daily dosing	0.17	PTAH	No	No	Intercurrent illness, fasting
2	57	Daily dosing	1.43	PTAH	Yes	No	Exercise, allergic rhinitis
3	138	Daily dosing	0.08	PTAH	Yes	No	Intercurrent illness, fatigue

*Defined as the day after the start of treatment with PTAH in the follow-on study.

TABLE E8. Accidental food allergen exposure (safety population; N = 351)

	PTAH-Naive (n = 100) ~52 wk			PTAH-Continuing (n = 251)									
				Daily dosing cohorts		Non–daily dosing cohorts*							
						Cohort 2 (n = 46) ~28 wk		Cohort 3B* (n = 31) ~56 wk			Cohort 3C* (n = 34) ~56-84 wk		
Food allergen exposure parameter	IDE/ updosing (n = 100)	Daily dosing (n = 85)	Total (n = 100)	Cohort 1 (n = 109) ~28 wk	Cohort 3A (n = 31) ~56 wk	Every other day (n = 46)	Twice weekly (n = 44)	Daily (n = 31)	Every other day (n = 27)	Twice weekly (n = 26)	Daily (n = 34)	Every other day (n = 31)	Twice weekly (n = 30)
Any food allergen exposure, n (%)	16 (16.0)	10 (11.8)	23 (23.0)	15 (13.8)	7 (22.6)	1 (2.2)	4 (9.1)	4 (12.9)	0	2 (7.7)	3 (8.8)	1 (3.2)	5 (16.7)
1 exposure	11 (11.0)	9 (10.6)	15 (15.0)	13 (11.9)	5 (16.1)	1 (2.2)	3 (6.8)	4 (12.9)	0	2 (7.7)	3 (8.8)	1 (3.2)	4 (13.3)
2 exposures	5 (5.0)	1 (1.2)	7 (7.0)	2 (1.8)	1 (3.2)	0	2 (2.3)	0	0	0	0	0	1 (3.3)
3 exposures	0	0	1 (1.0)	0	1 (3.2)	0	0	0	0	0	0	0	0
Peanut-related food allergen exposure, n (%)	5 (5.0)	3 (3.5)	8 (8.0)	7 (6.4)	6 (19.4)	1 (2.2)	4 (9.1)	0	0	1 (3.8)	1 (2.9)	0	3 (10.0)
1 exposure	5 (5.0)	3 (3.5)	8 (8.0)	6 (5.5)	5 (16.1)	1 (2.2)	4 (9.1)	0	0	1 (3.8)	1 (2.9)	0	3 (10.0)
2 exposures	0	0	0	1 (0.9)	0	0	0	0	0	0	0	0	0
3 exposures	0	0	0	0	1 (3.2)	0	0	0	0	0	0	0	0
Non–peanut-related food allergen exposure, n (%)	13 (13.0)	8 (9.4)	19 (19.0)	8 (7.3)	2 (6.5)	0	1 (2.3)	4 (12.9)	0	1 (3.8)	2 (5.9)	1 (3.2)	3 (10.0)
1 exposure	10 (10.0)	8 (9.4)	14 (14.0)	7 (6.4)	2 (6.5)	0	1 (2.3)	4 (12.9)	0	1 (3.8)	2 (5.9)	1 (3.2)	3 (10.0)
2 exposures	3 (3.0)	0	5 (5.0)	1 (0.9)	0	0	0	0	0	0	0	0	0
Food allergen exposure requiring treatment, n (%)	15 (15.0)	7 (8.2)	20 (20.0)	11 (10.1)	3 (9.7)	1 (2.2)	3 (6.8)	4 (12.9)	0	1 (3.8)	2 (5.9)	1 (3.2)	4 (13.3)
Epinephrine use	4 (4.0)	1 (1.2)	4 (4.0)	4 (3.7)	1 (3.2)	0	1 (2.3)	0	0	0	1 (2.9)	0	4 (13.3)

QD, Once daily.
*Participants in cohorts 3B and 3C underwent initial QD dosing for 28 wk.