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Continuous and daily oral immunotherapy for peanut allergy: results from a 2-year open-label follow-on study

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DISCLOSURES

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Andrea Vereda is an employee and stockholder of Aimmune Therapeutics.

Caroline Nilsson reports grants to institution and advisory board fees from Aimmune Therapeutics and speakers fees from MEDA, ALK, Thermo Fisher, GSK.

George du Toit reports research grants to institution and advisory board fees from Aimmune Therapeutics.

Wayne G Shreffler reports membership on Scientific Advisory Board, Aimmune Therapeutics, and consultancies for DBV Technologies and Sanofi.

A Wesley Burks has received research support, advisory board fees, and lecture honoraria/consultation fees from Aimmune Therapeutics.

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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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.

Kirsten Beyer reports advisory board/consulting fees from Aimmune Therapeutics, ALK, Bausch & Lomb, Bencard, Danone, DBV, Hycor, Infectopharm, Mabyon, 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 is an employee and stockholder of Aimmune Therapeutics. He has patents pending for the following: US 16/542,198; PCT/US2019/046706; US 16/721,805; PCT/US2019/067634.

HIGHLIGHTS

1. 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.

2. 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.

3. 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.

KEY WORDS: oral immunotherapy, peanut allergy, desensitization, allergic reactions, dosing regimens

ABBREVIATIONS

AE, adverse event

CTCAE, Common Terminology Criteria for Adverse Events

DBPCFC, double-blind placebo-controlled food challenge

EoE, eosinophilic esophagitis

FDA, Food and Drug Administration

IDE, initial dose escalation

Ig, immunoglobulin

IQR, interquartile range

OIT, oral immunotherapy

PTAH, PeanuT (*Arachis Hypogaea*) allergen powder-dnfp

SD, standard deviation

SPT, skin prick test

U.S., United States

ABSTRACT

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 five 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 (DBPCFC) and placebo arm (PTAH-naïve) 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-naïve participants were built up to 300-mg/day PTAH, followed by maintenance dosing. At study completion, participants underwent an exit DBPCFC 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-naïve, n=102). Among PTAH-continuing participants, exposure-adjusted adverse event (AE) rates were 12.94-17.54/participant-year (PY) and 25.95-42.49/PY in daily and non-daily dosing cohorts, respectively; most participants (83%) experienced mild or moderate AEs. Daily dosing 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-naïve participants mirrored those of the PALISADE active arm.

Conclusion: Continued daily PTAH treatment beyond 1 year showed sustained safety and efficacy. Ongoing immunomodulation was observed during the second year of treatment.

INTRODUCTION

Peanut allergy is one of the most common food allergies affecting children and adolescents in the United States (U.S.) and Europe.^{1,2} In the U.S., 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 (FDA) 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], 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 4-17 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 protein⁵; 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 non-daily 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 non-daily maintenance regimens, to explore the efficacy of different PTAH regimens with a 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 **Online Repository**) 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 the **Online Repository**). Although some adult (aged 18-55 years) participants (n=30) from PALISADE also enrolled in ARC004, outcomes reported here are confined to participants aged 4-17 years upon entry into ARC004.

Allocation of participants in the ARC004 trial depended upon the treatment previously received in the PALISADE trial. Participants in the placebo arm of the PALISADE trial (PTAH-naïve group) who entered ARC004 underwent initial dose escalation (IDE) followed by updosing for 22-40 weeks, and subsequent maintenance dosing at 300 mg/day 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 one of five 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/day 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 (e.g., down dosing) were possible to ensure safety (**Online Repository**), and participants who did not tolerate a non-daily dosing schedule could revert to a daily dosing schedule after repeating up dosing.

PTAH-naïve participants who tolerated ≥ 300 mg in the maintenance DBPCFC could continue to receive PTAH during Weeks 28-84. All participants in both PTAH-naïve 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).

Pre-specified stopping rules for individual participants and whole cohorts were included in the protocol (**Online Repository**), 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 PRACTALL guidelines with modifications to accommodate the 600-mg and 2000-mg dose levels¹¹ 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 the **Online Repository**.

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 (CTCAE; 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 one 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 immunoglobulin (Ig) E, peanut-specific IgE and IgG4, and skin prick test (SPT) assays were defined as the last available measurement before the first dose of PTAH on Day 1 of the ARC004 trial for the PTAH-naïve group, and as Day 1 of the PALISADE trial for participants in the PTAH-continuing cohorts. The rest of the peanut-specific IgE and Ig4 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 the **Online Repository**.

235

236 *Trial oversight, statement of ethics and role of sponsor*

237 The ARC004 trial was funded by Aimmune Therapeutics. Approvals from site-specific
238 institutional review boards, ethics committees, research ethics boards, or like authorities, were
239 obtained prior to trial initiation. Further information on trial oversight, ethics and role of sponsor are
240 provided in the **Online Repository**.

RESULTS

Participant disposition

Of the 409 participants aged 4-17 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, seven 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% (n=55/102) of participants in the PTAH-naïve group and 80.5% (n=206/256) of participants in the PTAH-continuing group. A total of 80.5% (n=128/143) of participants receiving continued daily PTAH (Cohorts 1 and 3A) completed the trial compared with 69% (n=78/113) 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 ≥ 2 years of PTAH from the time of entry into the parent trial (**Figure 2**).

By the end of the trial, all PTAH-naïve 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/day PTAH for 28 weeks, 300 mg every other day for 4 weeks, and 300 mg twice weekly for ≥ 24 -56 weeks. A total of 94 PTAH-naïve 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 shown (**Table 1**). In the PTAH-continuing population, 64.5% (n=162/251) 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 (**Table E1**). The median percentage of days where a full or partial dose was consumed at home was $\geq 96\%$ in both PTAH-naïve and PTAH-continuing participants. While treatment adherence was highest in Cohort 2 (e.g., 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-naïve 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 presented in the **Table E2**.

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-naïve 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 ≤ 600 - and ≤ 1000 -mg doses; approximately 69% of participants in Cohort 3A had no symptoms at ≤ 2000 -mg doses (**Figure E1**). In the non-daily dosing cohorts, proportions of participants with no symptoms were approximately 52-73% at ≤ 600 -mg, 40-59% at ≤ 1000 -mg, and 24-46% at ≤ 2000 -mg doses. Epinephrine use for the treatment of allergic symptoms during the exit DBPCFC is presented in **Table E3**.

Safety and tolerability

In the PTAH-continuing group, most patients across all cohorts experienced at least one AE; however, exposure-adjusted AE rates were lower in the daily dosing groups than the non-daily dosing groups (**Table 2**). 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=9/46; [19.6%]; Cohort 3B, n=5/31 [16.1%]; Cohort 3C, n=4/34 [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 (e.g., abdominal pain and discomfort, nausea, oral pruritus, cough, and dyspnea); three 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.

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 (**Table E4**). The incidence of severe AEs was low, occurring in <3% of participants treated both daily (3/140; 2.1%) and not daily (n=3/111; 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 2**). There were three serious AEs occurring in three participants undergoing daily dosing (one participant each in Cohort 1, 3B, and 3C), all of which were unrelated to study drug (streptococcal infection, abdominal pain, and limb fracture). Adverse events leading to discontinuation of study treatment occurred in seven participants in the PTAH-continuing group. Of these AEs, 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.

Safety outcomes in the PTAH-naïve group (**Table 2** and **Tables E4-E5**) were similar to those observed during active treatment in the PALISADE trial.⁵ Almost all (98%) participants in the PTAH-naïve group experienced AEs; 86% experienced treatment-related AEs. Most AEs in the PTAH-naïve group occurred during the IDE and updosing periods. Nine participants discontinued treatment due to AEs (IDE/updosing, n=7; daily dosing, n=2). Eosinophilic esophagitis (EoE; confirmed by endoscopy) was reported in two PTAH-naïve participants (one during updosing and one during maintenance) and led to treatment discontinuation. One EoE event that occurred during updosing (12-mg PTAH, Day 50) was severe and considered by the investigator to be unrelated to treatment. The EoE 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 3**). Among participants in the daily dosing cohorts (Cohorts 1 and 3A), 12 participants experienced systemic allergic reactions, most (n=10/12) 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-naïve group was generally consistent with that observed during active treatment in the PALISADE trial. A total of 17.0% of participants (n=17/100) experienced systemic allergic reactions and all were of mild or moderate severity (**Table E6**); most systemic allergic reactions (72.7%) occurred ≤ 2 hours after PTAH dosing.

Treatment-related anaphylaxis (i.e., severe systemic allergic reaction) occurred during daily dosing periods in two participants in Cohort 1 and in three participants in Cohort 3C; all five participants who experienced anaphylaxis were female (aged 5-15 years) and all but one had a history of systemic

allergic reaction at baseline. None of the five participants required prolonged hospitalization (observational visit only) or more than one epinephrine use. One of the two participants in Cohort 1 who experienced anaphylaxis had a cofactor of intercurrent illness, but no predisposing co-factor was reported for the second participant. Of the three participants in Cohort 3C who experienced anaphylaxis during daily dosing, two 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 (**Table E7**).

Accidental exposure to food allergens

Accidental exposures to any food allergens occurred across all cohorts (**Table E8**); none were associated with serious symptoms. Most participants experienced no more than one accidental exposure. Peanut-related exposures were reported in approximately $\geq 47\%$ 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-naïve participants, more participants experienced accidental exposures during IDE/updosing (16%) than during maintenance (~12%); most participants experienced no more than one accidental exposure (**Table E8**). Approximately one-third of all accidental exposures were peanut related. While 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 one use of epinephrine and seven participants had >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-naïve group (n=100) had at least one 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 SPT wheal diameter

Change from baseline in immunoglobulin values (i.e., peanut-specific IgE and IgG4 levels) were consistent with continued immunomodulation (**Figure 4 A-C**) from the time of entry into PALISADE (i.e., 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-naïve and PTAH-continuing groups. IgG4 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 SPT 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 4D**).

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 co-factors. 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 (non-daily) dosing.

Completion rates were higher in PTAH-continuing participants compared to PTAH-naïve 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-naïve participants who completed ARC004, clinical outcomes were generally consistent with those reported in the active arm of the PALISADE trial.⁵ A high proportion (254/351; 72.4%) of participants treated in ARC004 entered the follow-on ARC008 study (NCT03292484).

Prior to 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 and colleagues¹⁵ and 27 studies examined by Grzeskowiak and colleagues¹⁶) concluded that despite increasing desensitization, OIT increases the likelihood of allergic reactions.¹⁵ However, the duration of follow-up in all but one 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 (~1/10th 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 ~6-month to ~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 4-17 years who had sensitivity 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.

In conclusion, 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

448 observed with 2 years of daily dosing relative to 1 year of daily dosing.⁵ Evaluation and confirmation of
449 the benefits of long-term daily dosing beyond 2 years with PTAH is required.

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CONTRIBUTIONS

Brian P Vickery was a primary investigator and contributed the design of the study protocol running the trial, and treating participants; analysis and interpretation of data; drafting the manuscript and revising it critically; and approving the version to be published. He agrees to be accountable for all aspects of the work.

Andrea Vereda contributed to the design of the study protocol; analysis and interpretation of data; reviewing the manuscript and revising it critically; and approving the version to be published. She agrees to be accountable for all aspects of the work.

Caroline Nilsson was a primary investigator and contributed to running the trial, treating participants, and collection of data; reviewing the manuscript and revising it critically; and approving the version to be published. She agrees to be accountable for all aspects of the work.

George du Toit was a primary investigator and contributed the design of the study protocol, running the trial, and treating participants; analysis and interpretation of data; drafting the manuscript and revising it critically; and approving the version to be published. He agrees to be accountable for all aspects of the work.

Wayne G Shreffler was a primary investigator and contributed to running the trial, treating participants, and the collection, analysis, and interpretation of data; drafting the manuscript and revising it critically; and approving the version to be published. He agrees to be accountable for all aspects of the work.

A Wesley Burks was a primary investigator and contributed to running the trial, treating participants, and the collection, analysis, and interpretation of data; drafting the manuscript and revising it critically; and approving the version to be published. He agrees to be accountable for all aspects of the work.

Stacie M Jones was a primary investigator and contributed to running the trial, treating participants, and collection of data; reviewing the manuscript and revising it critically; and approving the version to be published. She agrees to be accountable for all aspects of the work.

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Robert Ryan contributed to the analysis and interpretation of data; reviewing the manuscript and revising it critically; and approving the version to be published. He agrees to be accountable for all aspects of the work.

Daniel C Adelman contributed to the design of the study protocol and statistical analysis plan; analysis and interpretation of data; drafting the manuscript and revising it critically; and approving the version to be published. He agrees to be accountable for all aspects of the work.

ETHICS COMMITTEE APPROVAL

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.

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Aimmune Therapeutics designed and sponsored the trial. Professional assistance with editing, formatting, and coordinating author reviews was paid for by the sponsor and provided by OPEN Health Medical Communications. There were no agreements between the sponsor and the authors or their institutions that treated the trial data as confidential information of the sponsor.

DATA SHARING

All relevant data are within the manuscript and its online repository files. De-identified participant data (including data dictionaries) will not be shared, Peanut (*Arachis hypogaea*) allergen powder-dnfp (PALFORZIA), the first oral biological immunotherapy, is approved by the US Food and Drug Administration on and is currently being considered by other regulatory authorities for marketing authorization. Any clarification requests can be made to the corresponding author.

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TABLES

Table 1. Demographic and Baseline Characteristics at ARC004 Trial Entry (Safety Population; N=351)

Characteristic	PTAH Naïve (n=100) ~52 Weeks	PTAH Continuing (n=251)				
		Daily Dosing Cohorts		Non-Daily Dosing Cohorts*		
		Cohort 1 (n=109) ~28 Weeks	Cohort 3A (n=31) ~56 Weeks	Cohort 2 (n=46) ~28 Weeks	Cohort 3B* (n=31) ~56 Weeks	Cohort 3C* (n=34) ~56-84 Weeks
Median age, years (range)	9.5 (5-17)	11 (5-17)	9 (5-17)	10 (4-17)	9 (5-16)	9 (5-16)
Male, n (%)	65 (65.0)	57 (52.3)	17 (54.8)	25 (54.3)	19 (61.3)	18 (52.9)
Number 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 IgG4 (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/IgG4 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)

Note: Baseline values were relative to the start of ARC004.

*Participants in Cohorts 3B and 3C underwent initial daily dosing for 28 weeks.

[†]These patients did not meet the inclusion/exclusion criteria of the ARC004 study.

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; Ig, immunoglobulin; IQR, interquartile range; PTAH, PeanuI (*Arachis Hypogaea*) allergen powder-dnfp; SPT, skin prick test.

Table 2. Summary of Treatment-Emergent Adverse Events (Safety Population; N=351)

	PTAH-Naïve (N=100) ~52 Weeks			PTAH-Continuing (N=251)				
	IDE/Updosing (n=100)	Daily Dosing (n=85)	Total (n=100)	Daily Dosing Cohorts		Non-Daily Dosing Cohorts *		
				Cohort 1 (n=109) ~28 Weeks	Cohort 3A (n=31) ~56 Weeks	Cohort 2 (n=46) ~28 Weeks	Cohort 3B* (n=31) ~56 Weeks	Cohort 3C* (n=34) ~56-84 Weeks
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 weeks.

**Participants with >1 adverse event 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.

Abbreviations: AE, adverse event; IDE, initial dose escalation; PTAH, PeanuT (*Arachis Hypogaea*) allergen powder-dnfp.

Table 3. Incidence of Systemic Allergic Reactions in the PTAH-Continuing Group (N=251)

	Daily Dosing Cohorts		Non-Daily Dosing Cohorts*		
	Cohort 1 (n=109) ~28 Weeks	Cohort 3A (n=31) ~56 Weeks	Cohort 2 (n=46) ~28 Weeks	Cohort 3B* (n=31) ~56 Weeks	Cohort 3C* (n=34) ~56-84 Weeks
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 weeks.

**Participants with more than one systemic allergic reaction were counted only once using the highest severity.

Abbreviation: PTAH, PeanuT (*Arachis Hypogaea*) allergen powder-dnfp.

FIGURE LEGENDS

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 due to 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.

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; PTAH, Peanut (*Arachis Hypogaea*) allergen powder-dnfp.

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 adverse event (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).

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; PTAH, Peanut (*Arachis Hypogaea*) allergen powder-dnfp.

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.

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; PTAH, PeanuT (Arachis Hypogaea) allergen powder-dnfp.

Figure 4. Peanut-Specific IgE and IgG4 Levels and SPT Wheal Diameter: Baseline vs Trial Exit

Geometric mean values for peanut-specific IgE (A), IgG4 (B), and IgE/IgG4 ratio (C) at PALISADE baseline, ARC004 baseline, and ARC004 study exit are shown. Panel (D) shows the SPT mean wheal diameter at PALISADE baseline, ARC004 baseline, and ARC004 study exit.

PALISADE baseline values for peanut-specific IgE and IgG4, 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-naïve group and as Day 1 of the PALISADE trial for participants in the PTAH-continuing cohorts.

Abbreviations: Ig, immunoglobulin; PTAH, PeanuT (Arachis Hypogaea) allergen powder-dnfp; SD, standard deviation; SPT, skin prick test

ONLINE REPOSITORY TABLES

Table E1. Treatment Compliance With Planned Dosing at Home (Safety Population; N=351)

Compliance Parameter, Median (IQR)	PTAH Naïve (n=100) ~52 Weeks		PTAH Continuing (n=251)									
	IDE/Updosing (n=100)	Daily Dosing (n=85)	Daily Dosing Cohorts		Non-Daily Dosing Cohorts							
			Cohort 1 (n=109) ~28 Weeks	Cohort 3A (n=31) ~56 Weeks	Cohort 2 (n=46) ~28 Weeks		Cohort 3B (n=31) ~56 Weeks			Cohort 3C (n=34) ~56-84 Weeks		
					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)
Number 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)

Abbreviations: IDE, initial dose escalation; IQR, interquartile range; PTAH, PeanuT (*Arachis Hypogaea*) allergen powder-dnfp.

Table E2. Treatment Exposure (Safety Population; N=351)

Exposure Parameter	PTAH Naïve (n=100) ~52 Weeks		PTAH Continuing (n=251)									
			Daily Dosing Cohorts		Non-Daily Dosing Cohorts							
	IDE/Updosing (n=100)	Daily Dosing (n=85)	Cohort 1 (n=109) ~28 Weeks	Cohort 3A (n=31) ~56 Weeks	Cohort 2 (n=46) ~28 Weeks		Cohort 3B (n=31) ~56 Weeks			Cohort 3C (n=34) ~56-84 Weeks		
					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, months (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, n (%)												
0-3 months	7 (7.0)		1 (0.9)	1 (3.2)	3 (6.5)		1 (3.2)			1 (2.9)		
4-6 months	6 (6.0)		5 (4.6)	2 (6.5)	5 (10.9)		2 (6.5)			1 (2.9)		
7-9 months	7 (7.0)		65 (59.6)	0	31 (67.4)		3 (9.7)			5 (14.7)		
10-12 months	8 (8.0)		33 (30.3)	1 (3.2)	6 (13.0)		2 (6.5)			2 (5.9)		
13-15 months	10 (10.0)		4 (3.7)	26 (83.9)	1 (2.2)		20 (64.5)			1 (2.9)		
16-18 months	14 (14.0)		0	1 (3.2)	0		2 (6.5)			11 (32.4)		
19-21 months	30 (30.0)		1 (0.9)	0	0		1 (3.2)			13 (38.2)		
22-24 months	13 (13.0)		0	0	0		0			0		
>24 months	5 (5.0)		0	0	0		0			0		

Abbreviations: IDE, initial dose escalation; IQR, interquartile range; PTAH, PeanuT (*Arachis Hypogaea*) allergen powder-dnfp.

Table E3. Epinephrine Use as Rescue Medication at the Exit DBPCFC (Completer Population; N=282)

Any Epinephrine Use as Rescue Medication at Exit DBPCFC, n (%)	PTAH Naïve ~52 Weeks (n=72)	PTAH Continuing (n=210)				
		Daily Dosing Cohorts		Non-Daily Dosing Cohorts		
		Cohort 1 (n=103)	Cohort 3A (n=26)	Cohort 2 (n=38)	Cohort 3B (n=22)	Cohort 3C (n=21)
		~28 Weeks	~56 Weeks	~28 Weeks	~56 Weeks	~56-84 Weeks
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)

Abbreviations: DCPCFC, double-blind placebo-controlled food challenge; PTAH, Peanut (*Arachis Hypogaea*) allergen powder-dnfp.

Table E4. Incidence of Adverse Events Occurring in ≥5% of Participants (Safety Population; N=351)*

Adverse Events, n (%)	PTAH Naïve (n=100) ~52 Weeks			PTAH Continuing (n=251)										
	IDE/Updosing (n=100)	Daily Dosing (n=85)	Total (n=100)	Daily Dosing Cohorts		Non-Daily Dosing Cohorts								Overall
				Cohort 1 (n=109) ~28 Weeks	Cohort 3A (n=31) ~56 Weeks	Cohort 2 (n=46) ~28 Weeks		Cohort 3B (n=31) ~56 Weeks			Cohort 3C (n=34) ~56-84 Weeks			Daily dosing (n=205)
						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)	
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.

Abbreviations: IDE, initial dose escalation; PTAH, PeanuT (*Arachis Hypogaea*) allergen powder-dnfp.

Table E5. Exposure-Adjusted Adverse Event Rates for the Most Frequent (≥5% of Participants) Treatment-Emergent Adverse Events (Safety Population; N=351)*

Number of Adverse Events, (Events per PY)	PTAH Naïve (n=100) ~52 Weeks			PTAH Continuing (n=251)										
	IDE/ Updosing (n=100) PYE=43.76	Daily Dosing (n=85) PYE=85.53	Total (n=100) PYE=129.29	Daily Dosing Cohorts		Non-Daily Dosing Cohorts*								Overall
				Cohort 1 (n=109) ~28 Weeks PYE=73.74	Cohort 3A (n=31) ~56 Weeks PYE=31.53	Cohort 2 (n=46) ~28 Weeks PYE=25.95		Cohort 3B* (n=31) ~56 Weeks PYE=30.08			Cohort 3C* (n=34) ~56-84 Weeks PYE=42.49			Daily dosing (n=205) PYE=138.67
						Every Other Day (n=46) PYE=3.95	Twice Weekly (n=44) PYE=22.0	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	
Cough	97 (2.22)	50 (0.58)	147 (1.14)	29 (0.39)	57 (1.81)	5 (1.26)	10 (0.45)	16 (1.01)	4 (1.83)	20 (1.66)	29 (1.65)	2 (0.81)	16 (0.71)	131 (0.94)
Pyrexia	26 (0.59)	25 (0.29)	51 (0.39)	27 (0.37)	19 (0.60)	3 (0.76)	2 (0.09)	13 (0.82)	0	1 (0.08)	14 (0.80)	1 (0.40)	9 (0.40)	73 (0.53)
Vomiting	102 (2.33)	14 (0.16)	116 (0.90)	32 (0.43)	8 (0.25)	2 (0.51)	8 (0.36)	19 (1.20)	0	2 (0.17)	16 (0.91)	1 (0.40)	8 (0.36)	75 (0.54)
Urticaria	52 (1.19)	44 (0.51)	96 (0.74)	32 (0.43)	34 (1.08)	2 (0.51)	10 (0.45)	5 (0.32)	0	4 (0.33)	14 (0.80)	1 (0.40)	4 (0.18)	85 (0.61)
Headache	41 (0.94)	28 (0.33)	69 (0.53)	22 (0.30)	19 (0.60)	8 (2.02)	14 (0.64)	5 (0.32)	3 (1.37)	4 (0.33)	31 (1.76)	4 (1.62)	16 (0.71)	77 (0.56)
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)	9 (0.57)	0	2 (0.17)	13 (0.74)	0	4 (0.18)	56 (0.40)
Abdominal pain	232 (5.30)	83 (0.97)	315 (2.44)	22 (0.30)	43 (1.36)	2 (0.51)	11 (0.50)	5 (0.32)	0	10 (0.83)	44 (2.50)	2 (0.81)	49 (2.18)	114 (0.82)
Throat irritation	431 (9.85)	322 (3.76)	753 (5.82)	38 (0.52)	14 (0.44)	53 (13.41)	24 (1.09)	4 (0.25)	0	2 (0.17)	184 (10.46)	14 (5.66)	91 (4.06)	240 (1.73)
Oropharyngeal pain	57 (1.30)	25 (0.29)	82 (0.63)	9 (0.12)	28 (0.89)	3 (0.76)	5 (0.23)	9 (0.57)	0	2 (0.17)	5 (0.28)	2 (0.81)	5 (0.22)	51 (0.37)
Nasopharyngitis	15 (0.34)	16 (0.19)	31 (0.24)	9 (0.12)	5 (0.16)	0	7 (0.32)	5 (0.32)	1 (0.46)	1 (0.08)	11 (0.63)	0	7 (0.31)	30 (0.22)
Rhinorrhea	41 (0.94)	24 (0.28)	65 (0.50)	23 (0.31)	15 (0.48)	3 (0.76)	16 (0.73)	6 (0.38)	2 (0.92)	2 (0.17)	11 (0.63)	1 (0.40)	10 (0.45)	55 (0.40)
Nausea	185 (4.23)	56 (0.65)	241 (1.86)	15 (0.20)	5 (0.16)	3 (0.76)	11 (0.50)	6 (0.38)	2 (0.92)	1 (0.08)	1 (0.06)	0	11 (0.49)	27 (0.19)
Nasal congestion	51 (1.17)	10 (0.12)	61 (0.47)	13 (0.18)	37 (1.17)	3 (0.76)	5 (0.23)	10 (0.63)	1 (0.46)	4 (0.33)	10 (0.57)	0	4 (0.18)	70 (0.50)
Viral infection	8 (0.18)	5 (0.06)	13 (0.10)	12 (0.16)	7 (0.22)	0	1 (0.05)	1 (0.06)	0	0	3 (0.17)	1 (0.40)	7 (0.31)	23 (0.17)
Upper abdominal pain	162 (3.70)	61 (0.71)	223 (1.72)	136 (1.84)	28 (0.89)	12 (3.04)	63 (2.86)	3 (0.19)	0	7 (0.58)	2 (0.11)	0	6 (0.27)	169 (1.22)
Systemic allergic reaction	9 (0.21)	13 (0.15)	22 (0.17)	13 (0.18)	14 (0.44)	0	0	1 (0.06)	0	1 (0.08)	3 (0.17)	1 (0.40)	9 (0.40)	31 (0.22)
Sneezing	44 (1.01)	10 (0.12)	54 (0.42)	24 (0.33)	7 (0.22)	0	5 (0.23)	2 (0.13)	2 (0.92)	10 (0.83)	4 (0.23)	3 (1.21)	4 (0.18)	37 (0.27)
Oral pruritus	105 (2.40)	249 (2.91)	354 (2.74)	232 (3.15)	10 (0.32)	8 (2.02)	32 (1.45)	3 (0.19)	0	6 (0.50)	2 (0.11)	3 (1.21)	11 (0.49)	247 (1.78)
Influenza	2 (0.05)	6 (0.07)	8 (0.06)	7 (0.09)	1 (0.03)	0	1 (0.05)	5 (0.32)	0	0	1 (0.06)	0	2 (0.09)	14 (0.10)
Diarrhea	64 (1.46)	3 (0.04)	67 (0.52)	11 (0.15)	15 (0.48)	3 (0.76)	1 (0.05)	8 (0.51)	0	1 (0.08)	3 (0.17)	0	0	37 (0.27)
Pruritus	27 (0.62)	20 (0.23)	47 (0.36)	11 (0.15)	2 (0.06)	3 (0.76)	7 (0.32)	2 (0.13)	1 (0.46)	5 (0.41)	3 (0.17)	3 (1.21)	6 (0.27)	18 (0.13)
Rash	10 (0.23)	6 (0.07)	16 (0.12)	6 (0.08)	1 (0.03)	1 (0.25)	0	2 (0.13)	0	1 (0.08)	3 (0.17)	0	3 (0.13)	12 (0.09)
Asthma	3 (0.07)	2 (0.02)	5 (0.04)	3 (0.04)	0	2 (0.51)	10 (0.45)	6 (0.38)	0	1 (0.08)	6 (0.34)	0	2 (0.09)	15 (0.11)

*Events were included and sorted consistent with those selected at the per-participant level in Table S4.
Abbreviations: IDE, initial dose escalation; PTAH, *Arachis Hypogaea* allergen powder-dnfp; PY, participant–year; PYE, participant–year event.

Table E6. Incidence of Systemic Allergic Reactions in PTAH-Naïve Participants

	PTAH Naïve (n=100)		
	Journal Pre-proof		
	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)
Number 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)

Abbreviations: IDE, initial dose escalation; PTAH, PeanuT (*A*rachis *H*ypogaea) allergen powder-dnfp.

Table E7. Anaphylaxis Events by Participant During Daily Dosing in PTAH-Continuing Participants

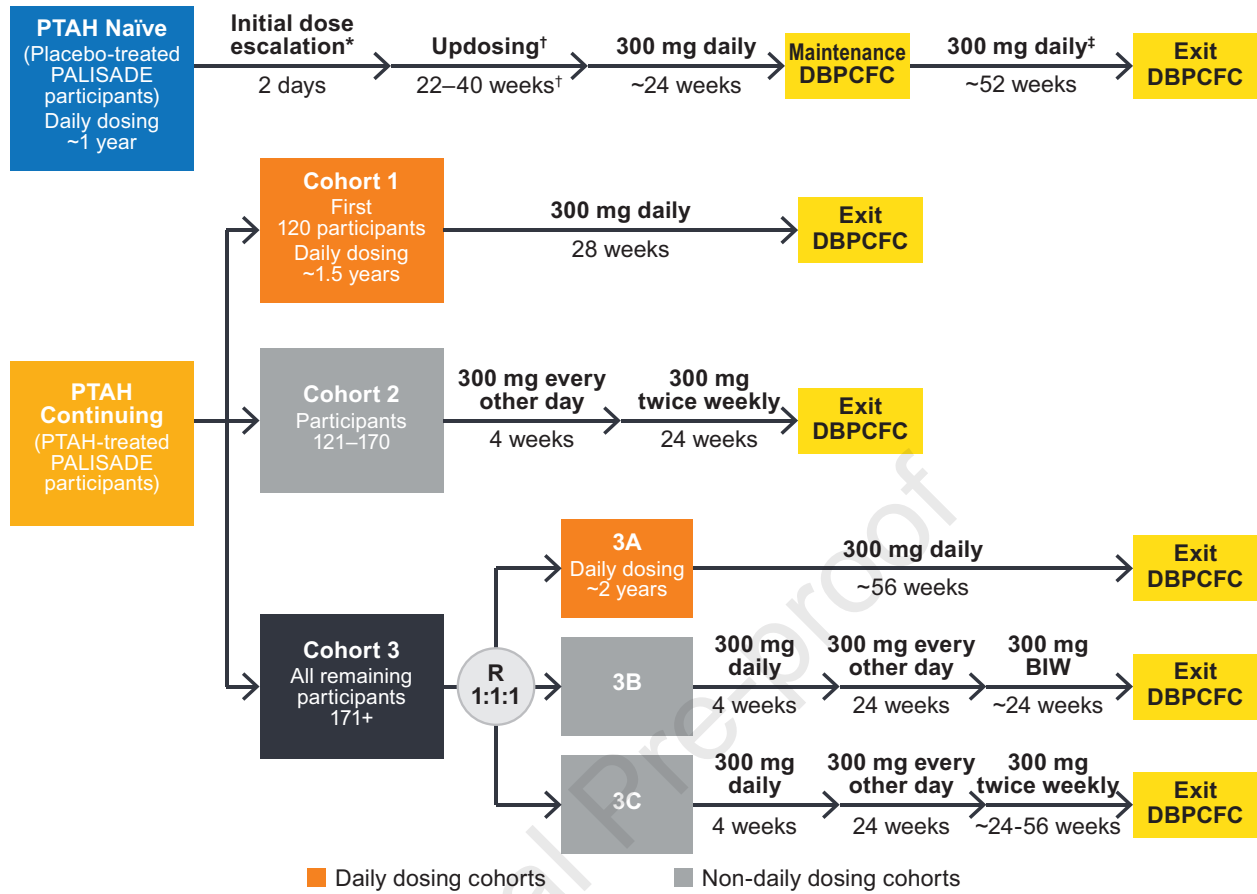
Participant no.	Day After Start of Treatment*	Dosing Period	Time After Dose (Hours)	Trigger	Epinephrine Use (Yes/No)	Discontinuation (Yes/No)	Predisposing Co-factors
Cohort 1							
1	30	Daily dosing	0.8	PTAH	Yes	No	Intercurrent illness
2	72	Daily dosing	4.0	PTAH	Yes	Yes	None identified
Cohort 3C							
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

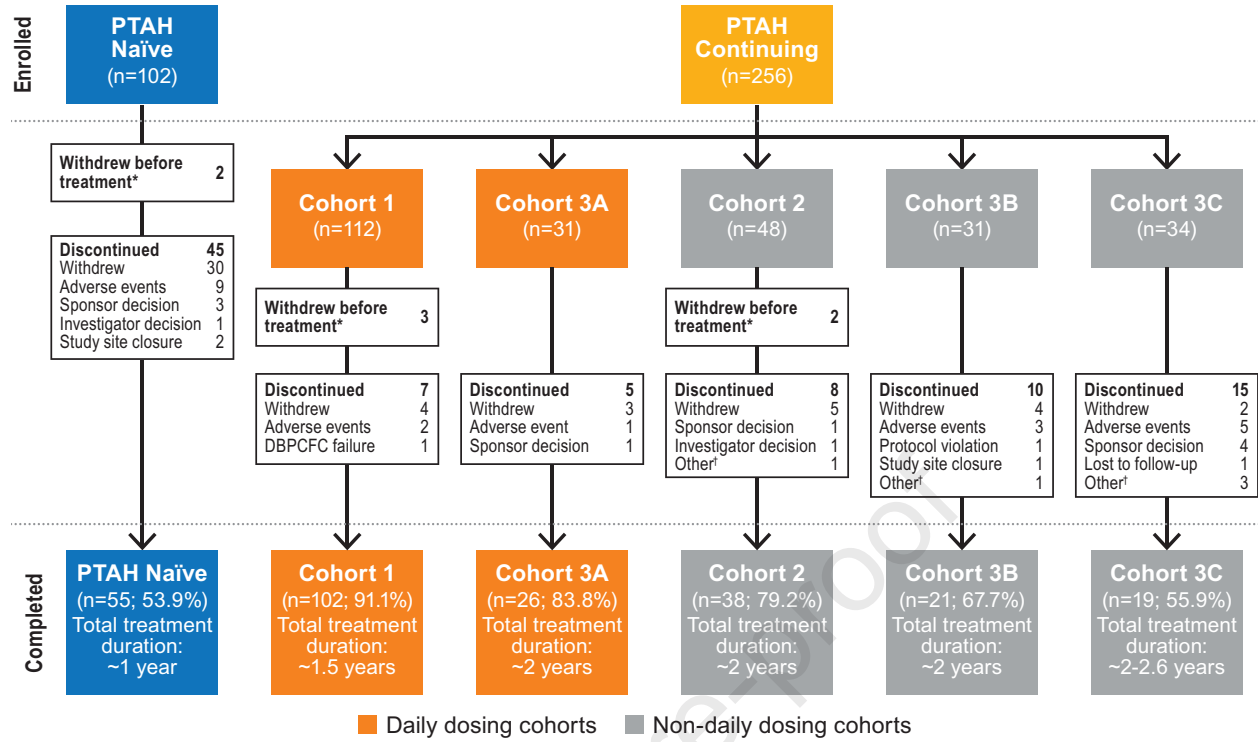
*Defined as the day after the start of treatment with PTAH in the follow-on study.
Abbreviations: no, number; PTAH, PeanuT (*A*rachis *H*ypogaea) allergen powder-dnfp.

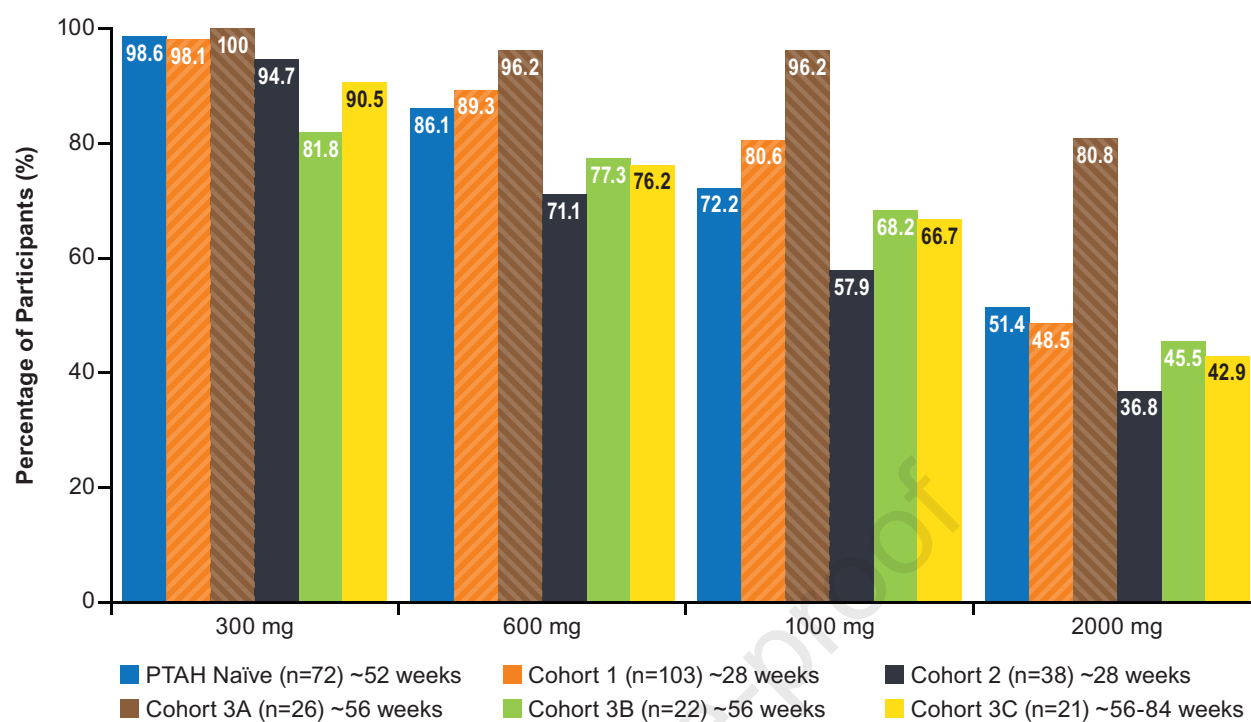
Table E8. Accidental Food Allergen Exposure (Safety Population; N=351)

Food Allergen Exposure Parameter	PTAH Naïve (n=100) ~52 Weeks			PTAH Continuing (n=251)									
	IDE/ Updosing (n=100)	Daily Dosing (n=85)	Total (n=100)	Daily Dosing Cohorts		Non-Daily Dosing Cohorts*							
				Cohort 1 (n=109) ~28 Weeks	Cohort 3A (n=31) ~56 Weeks	Cohort 2 (n=46) ~28 Weeks		Cohort 3B* (n=31) ~56 Weeks			Cohort 3C* (n=34) ~56-84 Weeks		
						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)

*Participants in Cohorts 3B and 3C underwent initial QD dosing for 28 weeks.
Abbreviations: IDE, initial dose escalation; PTAH, PeanuT (*Arachis Hypogaea*) allergen powder-dnfp; QD, once daily.







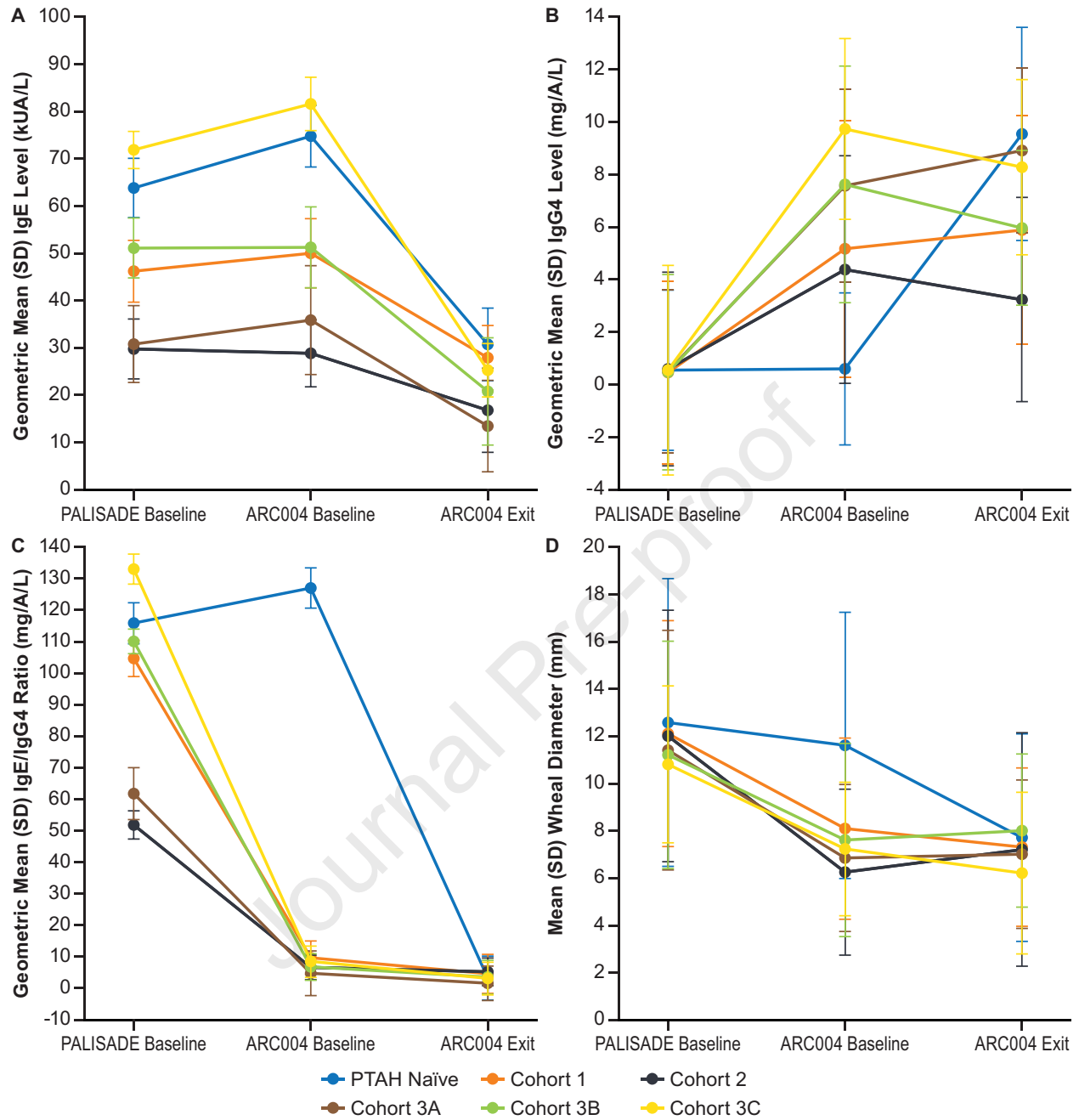
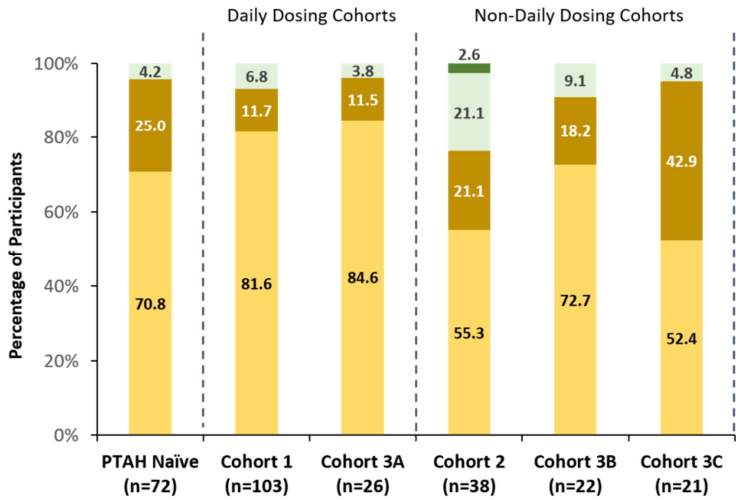
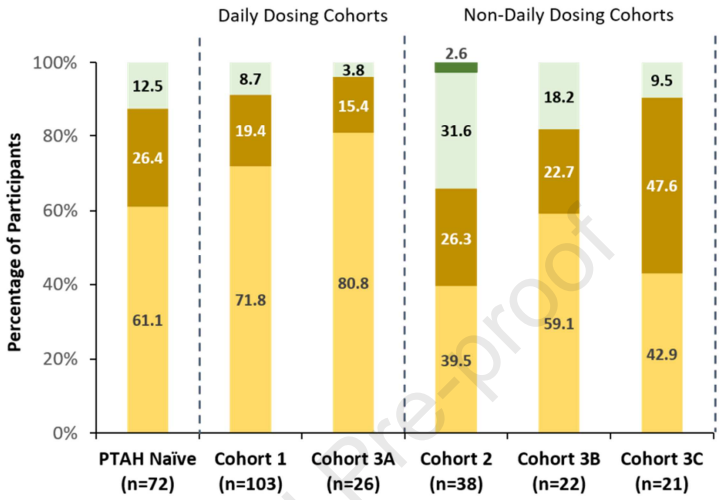


Figure E1.

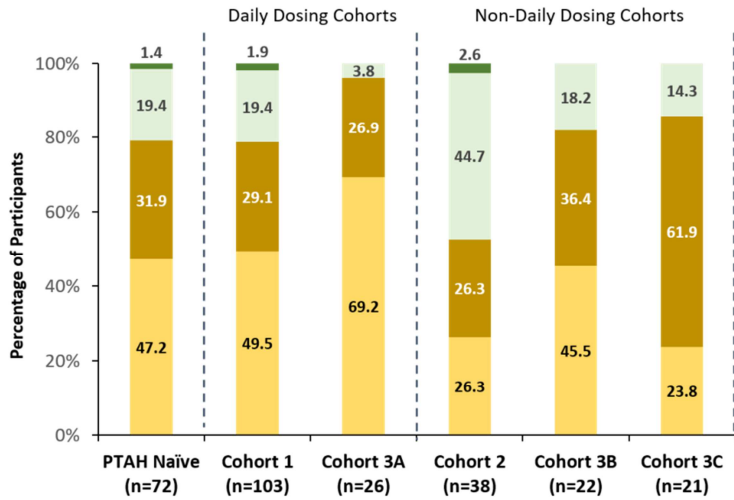
A. 600 mg or Lower Doses of Peanut Protein*



B. 1000 mg or Lower Doses of Peanut Protein*



C. 2000 mg or Lower Doses of Peanut Protein*



*The sum of the columns may be 99.9% or 100.1% due to rounding.

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; PTAH, PeanuT (*A*rachis *H*ypogaea) allergen powder-dnfp.