

Original Article

Efficacy and Safety of AR101 in Oral Immunotherapy for Peanut Allergy: Results of ARC001, a Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Trial

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What is already known about this topic? Two randomized controlled trials have used differing methods to demonstrate desensitization after peanut oral immunotherapy (OIT).

What does this article add to our knowledge? This is the first randomized, placebo-controlled phase 2 peanut OIT study with entry and exit double-blind, placebo-controlled food challenges using a current good manufacturing practice (cGMP) manufactured characterized biologic drug product demonstrating clinical and immunomodulatory changes indicating desensitization.

How does this study impact current management guidelines? This study provides proof-of-concept demonstrating the effectiveness of a standardized OIT product and protocol in a multicenter trial. Three large phase 3 trials of AR101 are ongoing and will provide high-quality evidence likely to influence practice.

BACKGROUND: Peanut oral immunotherapy, using a variety of approaches, has been previously shown to induce desensitization in peanut-allergic subjects, but no products have been approved for clinical use by regulatory agencies.

OBJECTIVE: We performed the first phase 2 multicentered study to assess the safety and efficacy of AR101, a novel oral biologic drug product.

METHODS: A randomized, double-blind, placebo-controlled trial was conducted at 8 US centers. Eligible subjects were 4 to 26 years old, sensitized to peanut, and had dose-limiting symptoms to ≤ 143 mg of peanut protein in a screening double-blind, placebo-controlled food challenge (DBPCFC). Subjects were randomized 1:1 to daily AR101 or placebo and gradually up-dosed from 0.5 to 300 mg/day. The primary endpoint was

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Abbreviations used

AE- Adverse event
 CI- Confidence interval
 DBPCFC- Double-blind, placebo-controlled food challenge
 EoE- Eosinophilic esophagitis
 FDA- United States Food and Drug Administration
 GI- Gastrointestinal
 IQR- Interquartile range
 ITT- Intent-to-treat
 MTD- Maximum tolerated dose
 OIT- Oral immunotherapy
 ps-IgE- Peanut-specific IgE
 SAE- Serious adverse event
 SD- Standard deviation
 SPT- Skin prick test
 TEAE- Treatment-emergent AE

the proportion of subjects in each arm able to tolerate ≥ 443 mg (cumulative peanut protein) at exit DBPCFC with no or mild symptoms.

RESULTS: Fifty-five subjects (29 AR101, 26 placebo) were enrolled. In the intention-to-treat analysis, 23 of 29 (79%) and 18 of 29 (62%) AR101 subjects tolerated ≥ 443 mg and 1043 mg at exit DBPCFC, respectively, versus 5 of 26 (19%) and 0 of 26 (0%) placebo subjects (both $P < .0001$). Compared with placebo, AR101 significantly reduced symptom severity during exit DBPCFCs and modulated peanut-specific cellular and humoral immune responses. Gastrointestinal (GI) symptoms were the most common treatment-related adverse events (AEs) in both groups, with 6 AR101 subjects (21%) withdrawing, 4 of those due primarily to recurrent GI AEs.

CONCLUSIONS: In this study, AR101 demonstrated an acceptable safety profile and demonstrated clinical activity as a potential immunomodulatory treatment option in peanut-allergic children over the age of 4, adolescents, and young adults. © 2017 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2017;■:■-■)

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Food allergy is a potentially life-threatening condition that affects approximately 5% to 10% of people throughout the developed world,¹⁻⁴ but as yet no specific treatment has been approved by the United States Food and Drug Administration (FDA) or European Medicines Agency. The current standard of care is limited to diagnosis, avoidance of the allergenic food, and treatment of allergic reactions from accidental ingestion with autoinjectable epinephrine.⁵⁻⁷

Peanut is among the most prevalent of the food allergies, affecting approximately 1 in 70 children and 1 in 160 adults in the United States.⁸ Peanut allergy typically begins in early childhood, but unlike many food allergies, it persists into adulthood in 80% of affected individuals.⁹⁻¹¹ Reactions to peanut can be triggered by milligram exposures,¹² are frequently severe, and account for most food allergy-related deaths.¹³ Because peanut can be frequently encountered in a wide variety of foods, as many as 50% of peanut-allergic individuals were found to have had an accidental ingestion over a 2-year period.^{14,15} There remains a clear unmet need for a treatment to help protect peanut-allergic individuals in case of accidental exposure.

Over the past decade, numerous reports on oral immunotherapy (OIT) for IgE-mediated allergies to foods have been published.¹⁶⁻²³ OIT involves exposing allergic individuals to gradually escalating doses of an allergen to render effector cells less reactive, thereby inducing desensitization. Goals for OIT-induced desensitization include reduced reactivity to an extent that can provide reliable protection against a potentially severe or life-threatening reaction after an accidental exposure.

The first randomized controlled trial to demonstrate the efficacy of OIT for peanut allergy was reported in 2011 by a US group,¹⁶ and a second followed in the UK in 2014¹⁷; however, the former did not perform food challenges at entry and the latter did not include a placebo control group. Although these and other OIT studies¹⁸⁻²³ have shown OIT to be a promising treatment approach in peanut allergy, it has not yet been recommended for routine clinical practice.^{5,6} Because most OIT studies have been small and limited by various flaws that limit

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the impact of their findings, a state of clinical equipoise still exists regarding the safety and efficacy of OIT, and it currently remains experimental.²⁴ In addition to these safety and efficacy concerns, a major barrier to the general acceptance of OIT for the treatment of peanut allergy is the absence of a product approved for this purpose by regulatory agencies.²⁵⁻²⁷ The regulatory path requires a product to be thoroughly characterized, manufactured reproducibly to well-defined standards, used according to clinically tested procedures, and shown to have a favorable risk-benefit profile; studies conducted in accordance with these requirements will help to generate high-quality data that are now critically needed in large numbers of participants. Thus, adequately powered, multicenter, randomized controlled phase 2 and 3 trials using uniform methods and standardized products will provide key evidence for the scientific community, regulators, patients, caregivers, payers, and other stakeholders to further evaluate the safety and effectiveness of food immunotherapy products. The ARC001 study, the first multicenter, randomized, placebo-controlled, phase 2 peanut OIT trial to include double-blind, placebo-controlled food challenges (DBPCFCs) at both screening and exit, was undertaken to assess the efficacy and safety of AR101, a novel oral biologic drug product containing a characterized peanut protein profile, in reducing clinical reactivity to peanut in peanut-allergic children and young adults.

METHODS

Study participant selection, screening, and randomization

The trial was appropriately registered (ClinicalTrials.gov Identifier: NCT01987817) and conducted in accordance with the principles of the Declaration of Helsinki and the ethics committees at each investigative site. Eligible subjects were aged 4 to 26 years with a clinical history of peanut allergy and either serum peanut-specific IgE (ps-IgE) ≥ 0.35 kU_A/L or peanut skin prick test (SPT) wheal diameter ≥ 3 mm larger than the negative control within the preceding 12 months, or both. Subjects were excluded for a history of frequent or repeated, severe or life-threatening anaphylaxis, eosinophilic gastrointestinal (GI) disease, or severe or uncontrolled asthma (see full inclusion/exclusion criteria in Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Eligible participants experienced dose-limiting allergic symptoms at or before reaching the 100 mg single dose (143 mg cumulative) of peanut protein during a screening DBPCFC, confirming that they could tolerate no more than 43 mg of cumulative peanut protein at study entry. The screening DBPCFC, performed in accordance with the PRACTALL consensus report,²⁸ consisted of a peanut (flour) challenge and a placebo (oat flour) challenge done on separate days and assigned in random order. Eligible subjects were randomized in a 1:1 ratio to either AR101 or placebo, according to a central randomization schedule of randomly permuted blocks that was prepared by an independent unblinded statistician and accessed by the investigational sites via an automated system.

Study oversight

Study protocol and consent forms were approved by the investigational sites' institutional review boards. The study was conducted under an FDA-reviewed investigational new drug application. Written informed consent was obtained from adult patients and from the parent/guardian for minor subjects (ie, <18 years). Written assent was obtained from children according to local standards. An independent

data monitoring committee assessed safety data periodically throughout the trial. Investigative sites ensured that all subjects had an in-date epinephrine autoinjector and were trained in its use.

Study products (AR101 and placebo)

The active ingredient in AR101 consists of defatted lightly roasted peanut flour characterized by a number of tests including high-performance liquid chromatography, enzyme-linked immunosorbent assay, and assay for protein content. This characterization includes a determination of the relative potency of the Ara h 1, Ara h 2, and Ara h 6 antigens and content uniformity for product release. Additional protein determinations, which include these antigens as well as Ara h 3 and Ara h 8, have been conducted to demonstrate that they are consistently present in the lot of peanut material used. The defatting process supports storage conditions, enables a more robust pharmaceutical processing, and may remove some of the peanut flavor.

AR101, a powder, was administered in graduated doses (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org) from capsules containing 0.5, 1, 10, 20, or 100 mg of peanut protein, formulated with bulking and flow agents. Matching placebo capsules contained oat flour and excipients. Study product was consumed after opening the capsules and mixing its content into an age-appropriate, nonallergenic, vehicle food (eg, applesauce, pudding). Participants otherwise abstained from peanut exposure.

Study endpoints and assessments

The primary endpoint of ARC001 was the response rate, defined as the proportion of subjects who were able to successfully consume a single dose of ≥ 300 mg (443 mg cumulative) of peanut protein with no dose-limiting symptoms, as defined by PRACTALL guidelines,²⁸ at exit DBPCFC. The exit DBPCFC tested doses of 3, 10, 30, 100, 300, and 600 mg given consecutively, as tolerated, 20 to 30 minutes apart without repeating a dose. There were 2 key secondary endpoints, the maximum dose achieved with no or minimal symptoms (ie, symptoms that did not prohibit escalation to the next dose as defined by PRACTALL guidelines) at exit DBPCFC, and the change in the maximum tolerated dose (MTD) from screening to exit DBPCFC.²⁸ The probability estimates for MTD were based on the discrete hazards model with terms for treatment and MTD at baseline in the log10 scale. Following Chinchilli, the extreme value hazard function (the discrete-time analog of the Cox proportional hazards function) was used and the model fit with logistic regression using the complementary log-log link function.²⁸ Probability estimates were adjusted for the MTD at baseline and calculated at the median of the MTD at baseline. For subjects who did not undergo exit DBPCFC, values for the MTD at the exit challenge were imputed using the MTD of peanut protein tolerated in their screening DBPCFC. Other secondary endpoints included change from baseline in ps-IgE and peanut-specific IgG₄ (ps-IgG₄) serum levels (Immulate, Siemens Healthcare, Erlangen, Germany), and in peanut SPT wheal diameter. Wheal size was calculated as the average of the longest diameter and the midpoint perpendicular diameter using a standard, 1:20 dilution of peanut extract. Wilcoxon sign-rank was used to calculate *P* values for changes from baseline, and Wilcoxon rank-sum was used to calculate *P* values for AR101 compared with the placebo group.

The primary efficacy analysis was a comparison of the response rate between treatment groups (AR101 vs placebo) in the intent-to-treat (ITT) population of all subjects randomized and dosed with study product, assessed by 2-sided Fisher's exact test. Some results

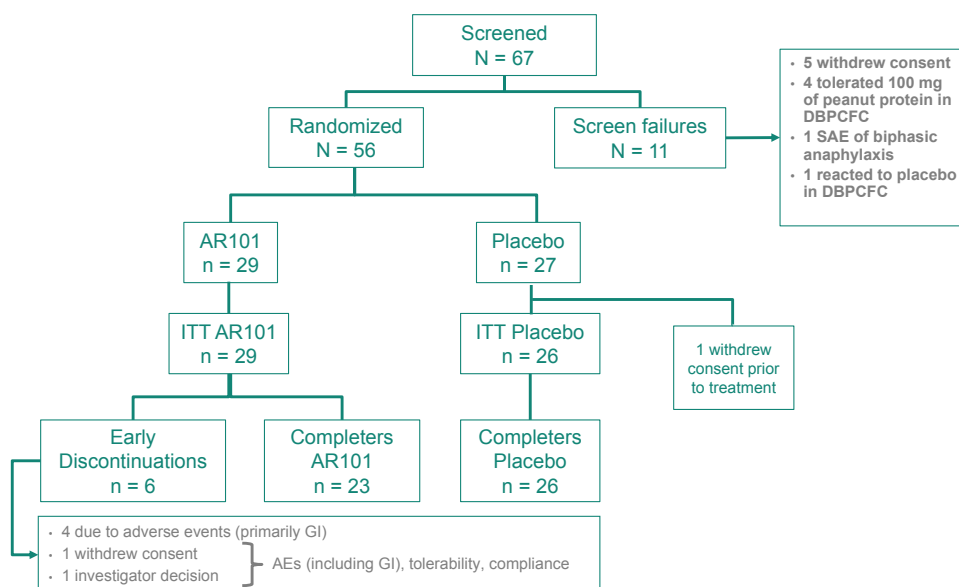


FIGURE 1. ARC001 enrollment and disposition. *AE*, Adverse event; *DBPCFC*, double-blind, placebo-controlled food challenge; *GI*, gastrointestinal; *ITT*, intent-to-treat; *SAE*, serious adverse event.

are also presented on the completer population, that is, subjects who underwent exit DBPCFC. The key secondary endpoints were each tested in the ITT population at the 0.05 level, in hierarchical order, provided the preceding test was significant. Assessment of the safety of peanut OIT was based on comparison of adverse event (AE) rates between the AR101 and placebo groups.

Oral immunotherapy dosing regimen

In brief, study product dosing began with incremental escalation from 0.5 to a maximum of 6 mg in a single day, with confirmation of the ability to tolerate 3 or 6 mg over the next 1 to 2 days (Initial Escalation phase), followed by biweekly up-dosing to a final dose of 300 mg/day (Up-dosing phase) over 20 to 34 weeks (Figure E1). The protocol permitted adjustments to the biweekly up-dosing schedule as needed, for example, temporary dose reduction if a dose level was not tolerated. Severity of dose-related allergic symptoms was determined per investigator judgment, using the definitions in the PRACTALL report on DBPCFC as a general guide.²⁸ Subjects were cautioned against activities likely to increase reactivity (eg, exercising or taking hot showers or baths within 4 hours after dosing). Temporary dose reductions were allowed while subjects were suffering from symptoms of an upper respiratory infection or influenza, or during menses. Investigators were allowed to hold doses per their discretion for any reported AE. For convenience, a reference for assessing symptom severity, consistent with both the PRACTALL guidelines and the Consortium of Food Allergy Research's specific grading system for allergic reactions, was included in the protocol (Table E2, available in this article's Online Repository at www.jaci-inpractice.org).²⁹ Subjects unable to reach the 300 mg/day dose by study week 34 were considered escalation failures. Subjects who tolerated 300 mg/day for 2 consecutive weeks were eligible for Exit DBPCFC (completer population).

Sample size

A sample size of 50 subjects randomized equally to 2 arms was calculated to provide at least 80% power to detect a treatment group difference of approximately 41% for the primary efficacy analysis.

Based on the available literature, a 20% withdrawal rate and 25% placebo-response rate among completers were assumed. Subjects already in the screening process when the 50th subject was randomized were allowed to proceed and be randomized if all entry criteria were met.

RESULTS

Study participants

Of 67 subjects screened, 11 were ineligible for enrollment: 5 withdrew consent, 1 reacted to placebo in the screening DBPCFC, 1 experienced a serious adverse event (SAE) from the DBPCFC, and 4 tolerated the top DBPCFC dose of 143 mg of peanut protein (Figure 1). The remaining 56 subjects had dose-limiting symptoms at or before a cumulative dose of 143 mg of peanut protein, and were randomized to either AR101 or placebo. One subject, randomized to placebo, withdrew consent before receiving any study product, yielding 55 subjects in the ITT population, 29 in the AR101 arm, and 26 in the placebo arm. During the screening DBPCFC, 9 (16%), 24 (44%), and 22 (40%) of the subjects in the ITT population tolerated the 3, 13, and 43 mg nominal dose level of cumulative peanut protein, respectively. Demographic data and baseline characteristics are presented in Table 1.

Efficacy of AR101 versus placebo

Twenty-three AR101 subjects (79%) completed the study in a median of 22 weeks (interquartile range [IQR] 21-26) and mean of 24 weeks (standard deviation [SD] 3.75), and 26 placebo subjects (100%) completed the study in a median of 22 weeks (IQR 21-24) and mean of 22 weeks (SD 2.0). No subjects discontinued the study during the Initial Escalation phase.

The 6 AR101 subjects who discontinued treatment before the exit DBPCFC were considered nonresponders. Of the 26 placebo subjects who completed the study, 5 tolerated 443 mg cumulative of peanut protein at exit DBPCFC. Hence, in the ITT population, 23 of 29 AR101 subjects (79%) were treatment responders, as compared with 5 of 26 placebo subjects (19%)

TABLE 1. Subject demographic and baseline characteristics at screening

Demographic/Characteristic	Placebo	Active (AR101)
ITT population, n	26	29
Age, median (min, max)	8 y (4-14)	7 y (4-21)
Sex, n (%)	16 male (62%) 10 female (38%)	20 male (69%) 9 female (31%)
Race/ethnicity, n (%)		
American Indian/Alaska Native	1 (4%)	0
Asian	1 (4%)	1 (3%)
Black African Heritage	2 (8%)	1 (3%)
Hawaiian/Pacific Islander	0	0
White	20 (77%)	26 (90%)
Other	2 (8%)	1 (3%)
Positive lifetime history of anaphylaxis to peanut, n (%)	15 (56%)	15 (52%)
Allergy to a food other than peanut, n (%)	20 (74%)	24 (83%)
Other allergic conditions, n (%)		
None	4 (15%)	2 (7%)
Asthma	11 (41%)	12 (41%)
Atopic dermatitis/eczema	11 (41%)	19 (66%)
Allergic rhinitis/hay fever	18 (67%)	18 (62%)
Other (eg, other food allergy, drug allergy)	4 (15%)	7 (24%)
Peanut-specific IgE, median (min, max)	100.0 kU _A /L (3.5 to ≥100*)	64.3 kU _A /L (0.8 to ≥100*)
Peanut SPT wheal diameter, median (min, max)	13 mm (5-26)	14 mm (5-30)
MTD†, cumulative, median (min, max)	28 mg (3-43)	13 mg (3-43)

DBPCFC, Double-blind, placebo-controlled food challenge; ITT, intent-to-treat; MTD, maximum tolerated dose; SPT, skin prick test.

*16 placebo and 12 AR101 subjects had screening values at the upper limit of quantification of 100 kU_A/L (Immulate).

†Maximum tolerated dose during screening DBPCFC.

($P < .0001$) (Figure 2, A). In the completer population (Figure 2, B), 23 of 23 AR101 subjects (100%) were treatment responders, as compared with 5 of 26 placebo subjects (19%) ($P < .0001$). The highest possible single dose of peanut protein administered during the exit DBPCFC was 600 mg, for a cumulative total of 1043 mg. Eighteen AR101 subjects (62% in the ITT population and 78% in the completer population) were able to successfully consume this amount of peanut protein, compared with none in the placebo group ($P < .0001$).

For the key secondary endpoint of the maximum dose achieved with no or mild symptoms at exit DBPCFC, the probability of tolerating each challenge dose or higher was increased with AR101 treatment as compared with placebo in the ITT population (Figure 3; discrete hazards model adjusted for baseline MTD). The probability of tolerating 443 mg cumulative of peanut protein or higher was 0.82 for AR101 and 0.14 for placebo, and the probability of tolerating 1043 mg cumulative of peanut protein or higher was 0.59 for AR101 and 0.01 for placebo. The corresponding hazard ratio of the probability of reacting to a challenge dose in AR101 subjects to placebo

subjects, given no reaction to a lower dose, was 0.10 (95% confidence interval [CI]: 0.04, 0.25; $P < .0001$), indicating that the risk of failing the exit DBPCFC for AR101 subjects was one-tenth that of placebo subjects. For the key secondary endpoint of change from baseline in MTD, a larger increase in MTD was observed for subjects assigned to AR101 versus placebo (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). Based on geometric mean estimates of the ratio of Exit DBPCFC MTD to baseline, there was a 18.38-fold increase for AR101 as compared with a 2.14-fold increase for placebo in the ITT population, which increases to 39.28-fold versus 2.14-fold in the completer population (both $P < .0001$ for AR101 vs placebo).

The severity of allergic symptoms occurring at each dose in the exit DBPCFC was also assessed, yielding a profile of symptom severity as a function of challenge dose (Figure 4). The percentage of subjects experiencing one or more allergic symptoms graded as mild, moderate, or severe was lower in the AR101 than in the placebo group at every dose of peanut protein. Of the 23 AR101 subjects passing the exit DBPCFC at 443 mg cumulative of peanut protein, 20 (87%) had no symptoms and 3 (13%) had only mild symptoms (Figure 4, B). No AR101 subjects experienced severe symptoms during the exit DBPCFC, and moderate symptoms were not encountered until the highest dose (1043 mg cumulative dose) (Figure 4, B and D). By contrast, 10 placebo subjects (38%) experienced severe symptoms at some point in the DBPCFC, 2 (9%) occurring at the 43 mg cumulative dose; and at least 1 placebo subject experienced moderate or severe symptoms at each dose (Figure 4, A and C). At the 1043 mg cumulative challenge dose, 61% of AR101 and no placebo subjects were symptom free (Figure 4, A and B).

We performed an exploratory analysis of epinephrine as a rescue medication during DBPCFC as an additional indicator of severity of allergic reaction. Of the 63 subjects who underwent screening DBPCFC, 9 (14%) received a single injection of epinephrine: 4 were randomized to AR101, 4 to placebo, and 1 was not enrolled. At exit DBPCFC, 11 of 26 placebo subjects (42%) were administered epinephrine, 3 of whom required 2 injections, whereas 2 of 23 AR101 subjects (9%) received a single injection of epinephrine, both at the final 600 mg challenge dose. Two placebo subjects reacted at the 30 mg dose level (1 requiring 2 doses of epinephrine); one reacted at the 100 mg dose level and four each at the 300 (2 requiring 2 doses of epinephrine) and 600 mg levels.

Effect of AR101 on immunologic responses to peanut

The mean change in maximal peanut SPT wheal diameter from screening to study exit was -7.0 mm (95% CI: -9.9 , -4.1) in the AR101 and -1.8 mm (95% CI: -4.8 , 1.1) in the placebo group ($P = .0132$; Figure 5, A). The geometric mean serum ps-IgG₄ level increased from 0.734 to 3.609 mcg/mL in the AR101 group, with a relative change from baseline of 5.068 (95% CI: 3.640, 7.055), compared with levels of 0.510 and 0.540 mcg/mL and a relative increase of 1.066 (95% CI: 0.905, 1.255) in the placebo group ($P < .0001$; Figure 5, B). Similarly, small increases in ps-IgE from screening to exit were noted in both groups and the difference was not statistically significant. The observed 4-fold decrease in the serum ps-IgE/IgG₄ in the AR101 relative to the placebo resulted entirely from the AR101 group's rise in ps-IgG₄ (Figure 5, C).

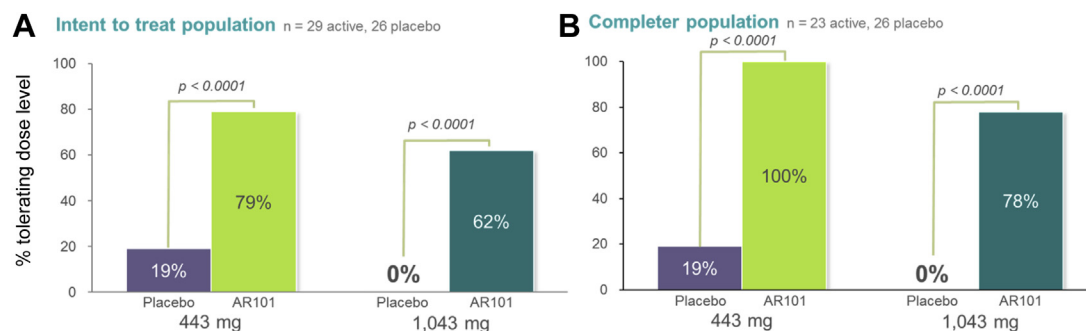


FIGURE 2. Clinical response to AR101. The percentage of subjects receiving AR101 or placebo who were able to successfully tolerate the indicated dose at the exit DBPCFC is listed on the y-axis for the primary endpoint (443 mg cumulative of peanut protein or the 300 mg dose level) and the top challenge dose tested (1043 mg cumulative of peanut protein or the 600 mg dose level). **A**, Results for the ITT population, where all subjects withdrawing before the exit DBPCFC are considered treatment failures. **B**, Results for the completer population who undertook the exit DBPCFC. *DBPCFC*, Double-blind, placebo-controlled food challenge; *ITT*, intent-to-treat.

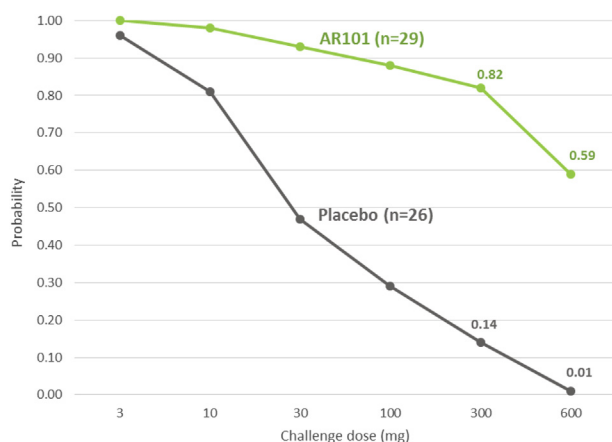


FIGURE 3. Probability of tolerating each exit DBPCFC dose or higher. Plots of the probability of subjects in the ITT population tolerating each challenge dose or higher at the exit DBPCFC (y-axis) as a function of challenge dose administered (x-axis). Green line: AR101 group; gray line: placebo group. *DBPCFC*, Double-blind, placebo-controlled food challenge; *ITT*, intent-to-treat.

Safety

Twenty-eight of 29 AR101 subjects (96.6%) and 22 of 26 placebo subjects (84.6%) experienced at least 1 AE during the course of treatment. In total, there were 413 treatment-emergent AEs in the AR101 group (a rate of 35.9 TEAEs per year of exposure), and 135 TEAEs in the placebo group (12.1 TEAEs/year). AEs assessed as being (possibly, probably, or definitely) related to study product occurred in 27 AR101 subjects (93%) and 12 placebo subjects (46%) (Table E4, available in this article's Online Repository at www.jaci-inpractice.org). In the AR101 group, 96% of treatment-related AEs were graded as mild and 4% as moderate, with moderate AEs including urticaria, pruritus, vomiting, abdominal pain, gastritis, and anaphylaxis. In addition, 1 subject experienced wheezing after accidentally inhaling some of the study product during the preparation of a dose. In the placebo group, 94% were graded as mild and 6% as moderate. Moderate AEs in this group included urticaria, angioedema, nausea, and abdominal pain. No AEs in either group were graded as severe.

The most common treatment-related AEs comprised GI symptoms in both the AR101 (66%) and placebo (27%) groups (Table E5, available in this article's Online Repository at www.jaci-inpractice.org). GI symptoms related to AR101 ranged in severity from mild oral pruritus to moderate vomiting and/or abdominal pain, with > 95% of these symptoms being graded mild in severity. Six AR101 subjects (21%), all of whom had baseline ps-IgE levels of >100 kU_A/L, withdrew from treatment prematurely (Table E6, available in this article's Online Repository at www.jaci-inpractice.org). Four of these cases were deemed by the site investigator to be due directly to recurrent GI AEs. In 2 additional subjects, GI and other allergic symptoms, as well as anxiety and medication compliance, contributed to the family's and investigator's decision, respectively, to withdraw the subject. In 5 of these 6 cases, onset of GI symptoms occurred early in the course of OIT, within the first month, at the 3 to 12 mg dose levels. In the sixth, symptoms of irritability began on study day 3, at the 6 mg level, but vomiting did not occur until study day 45, at the 40 mg level. In one case, endoscopic biopsy was performed and revealed the presence of eosinophilic esophagitis. In all cases, GI symptoms resolved within 3 weeks of discontinuing OIT. There was one treatment-related SAE of moderate severity anaphylaxis that occurred in a subject playing basketball 16 hours after dose, which was treated with epinephrine at home and resolved under observation in the emergency department. Because the subject had been experiencing mild but recurrent GI symptoms, the SAE was judged by the investigator to be possibly related to study product.

DISCUSSION

Previous studies using commercial peanut products have suggested that OIT is a suitable approach to treating peanut allergy.¹⁶⁻²³ However, limitations of former studies included the lack of a placebo arm, the lack of performing an entry or exit gold-standard DBPCFC to determine the peanut sensitivity of the subject before or after OIT, or both. This early-stage work has led to the first clinical trial of AR101, an oral biologic drug product that is manufactured to current good manufacturing practice (cGMP) specifications and developed for this purpose. AR101 is encapsulated in a range of doses and release tested for consistent major allergen content and freedom from microbial

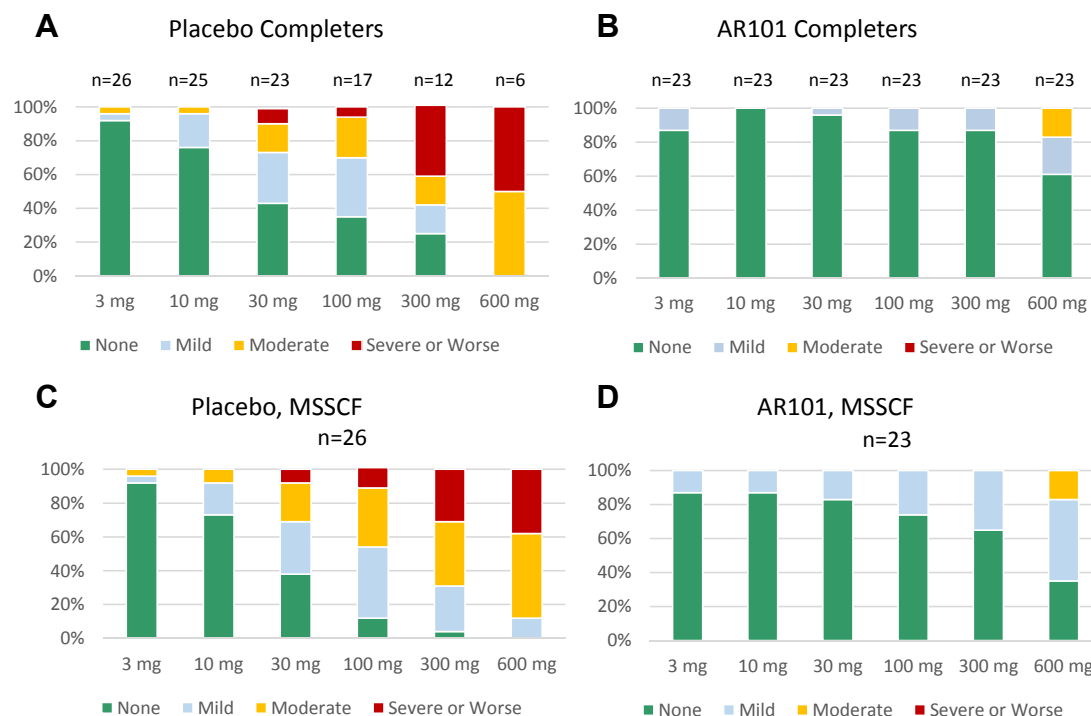


FIGURE 4. Symptom severity at each exit DBPCFC dose level. The proportion of subjects from the placebo group (A) and AR101 group (B) in the completer population (without imputation) experiencing the indicated severity of allergic reactions at each dose of peanut protein of the exit DBPCFC. Note that in the placebo group the number of subjects undergoing testing at a specific challenge dose decreases as the challenge dose level increases. This is because subjects who fail to tolerate a given challenge dose with no or only mild symptoms were prohibited from advancing to the next challenge dose level. Panels (C) and (D) show the results for all placebo and AR101 subjects, respectively, who entered the exit DBPCFC with the maximum symptom severity carried forward (MSSCF). In the MSSCF representation, the grade of the most severe symptom elicited at any administered challenge dose was used as the imputation value for any subsequent dose that was either not given or resulted in a less severe symptom score. As values for subjects no longer eligible to progress in the DBPCFC were imputed, the number of subjects at each challenge dose level remains constant. *DBPCFC*, Double-blind, placebo-controlled food challenge.

contamination and other allergens. We report here the results from the build-up and early maintenance phases of the first peanut OIT trial of AR101, one that included both a randomized placebo control group and entry and exit DBPCFCs.

In this phase 2 trial, AR101 met its primary endpoint, demonstrating desensitization to a level of peanut protein that exceeds the amount of peanut typically triggering a reaction with accidental ingestion. Specifically, during the exit DBPCFC, 79% of the ITT population tolerated a single dose of 300 mg (443 mg cumulative) of peanut protein with no or mild symptoms in the AR101 group, compared with 19% in the placebo group. Additionally, all AR101 subjects who completed the protocol tolerated 443 mg, the cumulative equivalent of approximately one and a half peanuts (J. Baumert and S. Taylor, Food Allergy Research and Resource Program, personal communication, September 23, 2016), and 78% tolerated a 600 mg single highest dose (1043 mg total), the cumulative equivalent of approximately 4 peanuts, with no or mild symptoms. Comparing the MTD of peanut protein attained at the exit DBPCFC with the screening DBPCFC, AR101 induced an 18-fold increase in the amount of peanut protein tolerated. In addition, AR101 modified peanut-specific immune responses by suppressing SPT reactivity and enhancing IgG4 production, effects consistent

with those previously reported in other studies. Overall, AR101's safety profile was consistent with other OIT studies, and the dose-related AEs in the 21% unable to tolerate AR101 quickly reversed on discontinuation.

The present study demonstrated that 22 weeks of AR101 treatment significantly raised the threshold at which allergic reactions to peanut were elicited, compared with placebo. The maximum severity of symptoms during exit DBPCFC in the AR101 group was also decreased relative to the placebo group, across the range of challenge doses tested. These data suggest, but do not prove, that AR101 could potentially reduce the severity of allergic reactions. The decreased use of epinephrine during exit DBPCFC in the AR101 relative to the placebo group further supports this idea. However, although DBPCFCs are the accepted gold-standard experimental model of food allergen exposure, they occur under tightly controlled conditions with graduated dosing and should not be interpreted to replicate accidental exposures. Whether relevant clinical protection from accidents can be inferred from an absolute amount of threshold reactivity, and/or the post-treatment change, is an unsettled subject that will likely require very large and meticulously performed future "real-world" surveillance studies because our understanding of thresholds over time is limited, tolerated

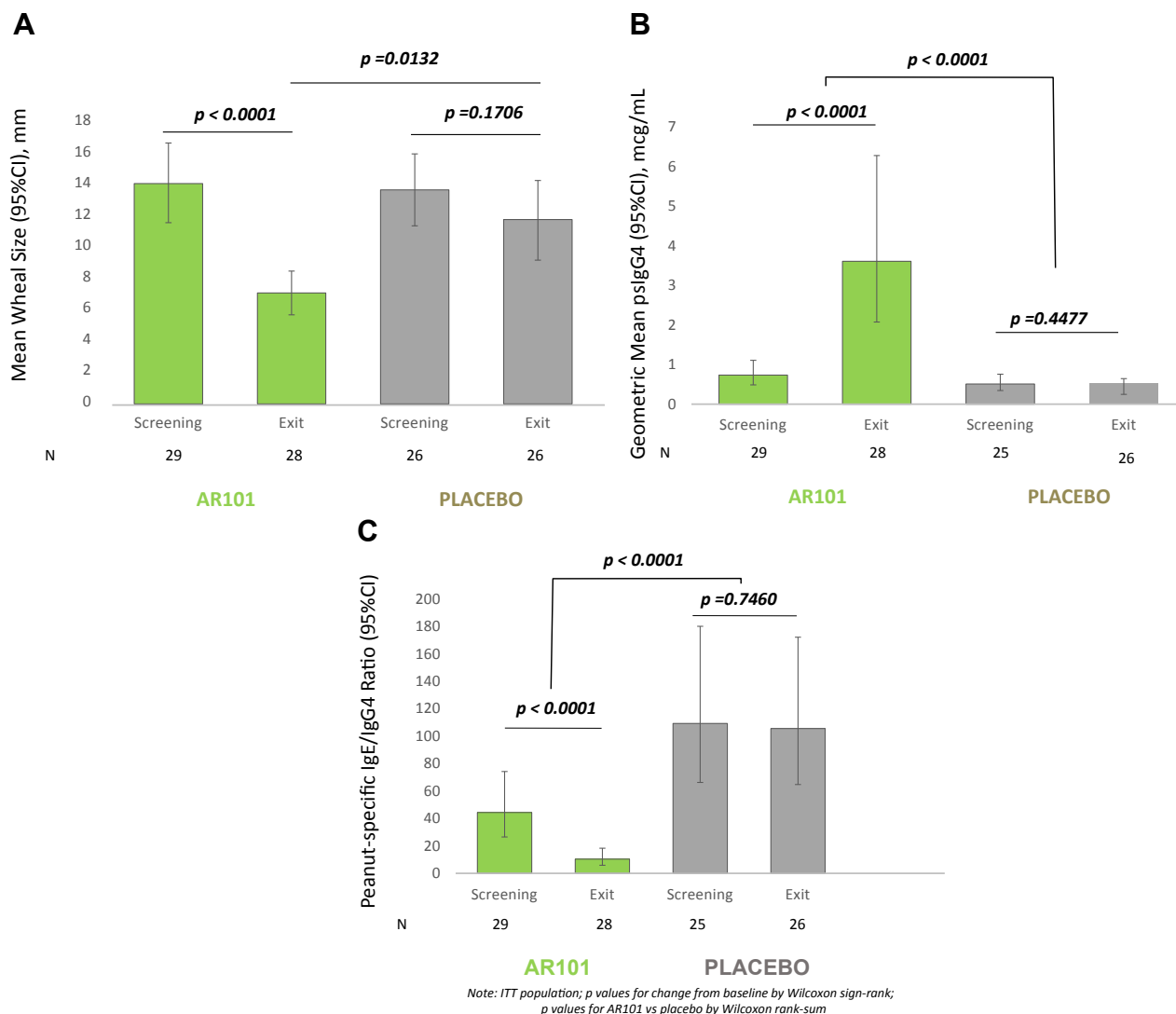


FIGURE 5. Immunomodulatory changes during therapy. SPT mean wheal diameter (**A**), peanut-specific IgG4 geometric mean (**B**), and peanut-specific IgE/IgG4 ratio (**C**) at screening and exit visits in the treatment and placebo ITT populations. *CI*, Confidence interval; *ITT*, intent-to-treat.

exposures may be clinically silent, and life-threatening events are rare. Nonetheless, experimentally observed desensitization is important because in most cases of accidental ingestion, symptoms are elicited before the allergic individual is aware of allergen ingestion.³⁰ In addition, low eliciting dose thresholds (ie, around 100 mg, or less than half of a peanut) are common in peanut-allergic patients¹² and often reported in real life.^{15,31} However, accidental ingestions of larger amounts (ie, in a fully ingested contaminated meal) can and do occur,³¹ and may represent a higher risk for mortality.³² In addition, evidence from observational and interventional studies suggests that an individual's eliciting threshold can vary over time because of the presence of augmenting cofactors that are often unavoidable (eg, fever, menses), and others that are poorly understood.³³⁻³⁷ Thus an ideal form of therapy for peanut allergy would provide a substantial margin of efficacy, similar to the effect size demonstrated here and in previous academic trials of peanut OIT.^{16-19,23}

Interestingly, we observed a 19% desensitization response rate in the placebo group, which is consistent with natural variation in threshold levels, has been observed in other studies, and emphasizes the need for rigorous controls, even when evaluating treatments for persistent conditions like peanut allergy.

Nearly 80% of AR101 subjects completed the study, with dose-limiting GI AEs in 4 subjects, tolerability concerns with 1 participant, and compliance issues in 1 participant (Figure 1). Consistent with the known mechanisms of OIT, transient allergic symptoms occurred in nearly all AR101 subjects, but 96% were mild. These reactions were not dose-limiting and did not require medical intervention. No AEs were graded as severe. Overall, side effects were similar to those reported from previous peanut OIT trials, with GI symptoms predominating.^{17-20,34,38,39} Recurrent GI side effects were also the most common reason for premature discontinuation, similar to reports from previous peanut OIT trials.⁴⁰ Onset was generally early in the course of treatment, and

symptoms often were not closely associated with the time of dosing. In all cases of early discontinuation, the screening ps-IgE level was >100 kU_A/L, and symptoms resolved within 3 weeks of discontinuing AR101; conversely, there were no treatment-related withdrawals in subjects who had a prestudy ps-IgE of ≤ 100 kU_A/L. The association between high ps-IgE and withdrawal was a *post hoc* finding that is consistent with previously published reports of OIT treatment failure.^{21,41} Though intriguing, this observation should be considered preliminary. The relationship between fully quantified ps-IgE and safety outcomes will be further examined as a prespecified endpoint in the phase 3 studies. In one case, a diagnosis of eosinophilic esophagitis (EoE) was confirmed by biopsy. There is a strong relationship between food allergy and EoE, and a recent review documented 20 cases of EoE emerging during the course of OIT trials, estimating the overall prevalence of EoE among participants undergoing OIT at 3% to 4%.⁴² It is currently unclear whether OIT causes EoE or allows preexisting subclinical EoE to become symptomatic, though withdrawal of the OIT typically results in remission.⁴³ Given the association between food allergy and EoE, a high index of suspicion for EoE should be maintained whenever chronic recurrent GI symptoms occur during OIT.

No subjects reported accidental peanut ingestion. One AR101 subject (described above) received a single epinephrine injection for moderate anaphylaxis at home after receiving his dose, possibly related to treatment. Nevertheless, its occurrence emphasizes the need for patients and the parents of pediatric patients undergoing OIT to be educated in the early recognition and prompt treatment of anaphylaxis.

This study had limitations, several of which were deliberately imposed and intended to promote safety, consistent with phase 2 development. These included constraint of the study's total sample size, restrictions on the age of subjects at enrollment, and exclusion of subjects with a history of life-threatening anaphylaxis and severe and/or poorly controlled asthma. We also excluded less sensitive individuals whose reaction thresholds were ≥ 143 mg of peanut protein at the screening DBPCFC. Thus, we cannot generalize the findings from ARC001 to these peanut-allergic populations, but future phase 3 and 4 studies will be able to provide informative data. It is also important to note that we are reporting data only from the build-up and early maintenance phases of this phase 2 trial, and analysis of subjects on maintenance dosing for longer periods of time and in larger populations (eg, in 3 ongoing phase 3 studies of AR101) will be required to make more definitive conclusions regarding safety and efficacy. Finally, it will be important to establish the impact of AR101 on food allergy-related quality of life in phase 3, as it was not measured in ARC001.

In summary, ARC001 was the first phase 2 peanut OIT study to use sufficiently rigorous design features, and it provided preliminary but high-quality evidence that AR101 has immunomodulatory activity that can significantly reduce clinical reactivity to peanut after build-up to 300 mg of peanut protein and 2 weeks of maintenance therapy on this dose. On average, after approximately 6 months of treatment with AR101, subjects experienced, in the context of the DBPCFC, an 18-fold increase in the amount of peanut protein successfully tolerated, as well as a significant blunting in the severity of allergic symptoms. Larger and longer placebo-controlled studies are required to better characterize the safety and effectiveness of AR101 in broader

populations. As a standardized and highly characterized pharmaceutical, AR101 has the potential to provide an overall safe and effective means to desensitize peanut-allergic children older than 4 years, adolescents, and young adults in an appropriately supervised clinical setting, a hypothesis that is currently being further tested in an ongoing phase 3 program.

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REFERENCES

- Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011;128:e9-17.
- Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy* 2014;69:992-1007.
- Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol* 2011;127:668-676.e1-2.
- Savage J, Johns CB. Food allergy: epidemiology and natural history. *Immunol Allergy Clin North Am* 2015;35:45-59.
- Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. *J Allergy Clin Immunol* 2010;126:1105-18.
- Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol* 2014;134:1016-1025.e43.
- Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bind-slev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014;69:1008-25.
- Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol* 2010;125:1322-6.
- Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. *J Allergy Clin Immunol* 2001;107:367-74.
- Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. The natural progression of peanut allergy: Resolution and the possibility of recurrence. *J Allergy Clin Immunol* 2003;112:183-9.
- Ho MH, Wong WH, Heine RG, Hosking CS, Hill DJ, Allen KJ. Early clinical predictors of remission of peanut allergy in children. *J Allergy Clin Immunol* 2008;121:731-6.
- Allen KJ, Remington BC, Baumert JL, Crevel RW, Houben GF, Brooke-Taylor S, et al. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. *J Allergy Clin Immunol* 2014;133:156-64.
- Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;107:191-3.
- Rimbaud L, Heraud F, La Vieille S, Leblanc J, Crepet A. Quantitative risk assessment relating to the inadvertent presence of peanut allergens in various food products. *Int Food Risk Anal J* 2013;3:1-11.
- Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock SA. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. *J Pediatr* 2000;137:749-55.
- Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol* 2011;127:654-60.
- Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet* 2014;383:1297-304.

18. Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol* 2009;124:292-300.e1-97.
19. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschoner J, de Oliveira LC, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol* 2010;126:83-91.e1.
20. Yu GP, Weldon B, Neale-May S, Nadeau KC. The safety of peanut oral immunotherapy in peanut-allergic subjects in a single-center trial. *Int Arch Allergy Immunol* 2012;159:179-82.
21. Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol* 2014;133:468-75.
22. Tang ML, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, et al. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. *J Allergy Clin Immunol* 2015;135:737-744.e8.
23. Bird JA, Feldman M, Arneson A, Dougherty I, Brown LS, Burk CM, et al. Modified peanut oral immunotherapy protocol safely and effectively induces desensitization. *J Allergy Clin Immunol Pract* 2015;3:433-435.e1-3.
24. Yee CS, Rachid R. The heterogeneity of oral immunotherapy clinical trials: implications and future directions. *Curr Allergy Asthma Rep* 2016;16:25.
25. Sampson HA. Peanut oral immunotherapy: is it ready for clinical practice? *J Allergy Clin Immunol Pract* 2013;1:15-21.
26. Wood RA, Sampson HA. Oral immunotherapy for the treatment of peanut allergy: is it ready for prime time? *J Allergy Clin Immunol Pract* 2014;2:97-8.
27. Greenhawt MJ, Vickery BP. Allergist-reported trends in the practice of food allergen oral immunotherapy. *J Allergy Clin Immunol Pract* 2015;3:33-8.
28. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol* 2012;130:1260-74.
29. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med* 2012;367:233-43.
30. Nguyen-Luu NU, Ben-Shoshan M, Alizadehfar R, Joseph L, Harada L, Allen M, et al. Inadvertent exposures in children with peanut allergy. *Pediatr Allergy Immunol* 2012;23:133-9.
31. Deschildre A, Elegbede CF, Just J, Bruyere O, Van der Brempt X, Papadopoulos A, et al. Peanut-allergic patients in the MIRABEL survey: characteristics, allergists' dietary advice and lessons from real life. *Clin Exp Allergy* 2016;46:610-20.
32. Turner PJ, Baumert JL, Beyer K, Boyle RJ, Chan CH, Clark AT, et al. Can we identify patients at risk of life-threatening allergic reactions to food? *Allergy* 2016;71:1241-55.
33. Glaumann S, Nopp A, Johansson SG, Borres MP, Nilsson C. Oral peanut challenge identifies an allergy but the peanut allergen threshold sensitivity is not reproducible. *PLoS One* 2013;8:e53465.
34. Varshney P, Steele PH, Vickery BP, Bird JA, Thyagarajan A, Scurlock AM, et al. Adverse reactions during peanut oral immunotherapy home dosing. *J Allergy Clin Immunol* 2009;124:1351-2.
35. Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, Steele PH, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. *J Allergy Clin Immunol* 2009;124:286-91. 291.e1-6.
36. Smith PK, Hourihane JO, Lieberman P. Risk multipliers for severe food anaphylaxis. *World Allergy Organ J* 2015;8:30.
37. Hourihane JO, Grimshaw KE, Lewis SA, Briggs RA, Trewhin JB, King RM, et al. Does severity of low-dose, double-blind, placebo-controlled food challenges reflect severity of allergic reactions to peanut in the community? *Clin Exp Allergy* 2005;35:1227-33.
38. Clark AT, Islam S, King Y, Deighton J, Anagnostou K, Ewan PW. Successful oral tolerance induction in severe peanut allergy. *Allergy* 2009;64:1218-20.
39. Anagnostou K, Clark A, King Y, Islam S, Deighton J, Ewan P. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. *Clin Exp Allergy* 2011;41:1273-81.
40. Virkud YV, Burks AW, Steele PH, Edwards LJ, Berglund JP, Jones SM, et al. Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. *J Allergy Clin Immunol* 2017;139:882-888.e5.
41. Keet CA, Frischmeyer-Guerrero PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. *J Allergy Clin Immunol* 2012;129:448-55. 455.e1-5.
42. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2014;113:624-9.
43. Semancik E, Sayej WN. Oral immunotherapy for peanut allergy induces eosinophilic esophagitis: three pediatric case reports. *Pediatr Allergy Immunol* 2016;27:539-41.

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TABLE E1. Inclusion and exclusion criteria

Inclusion criteria

Subjects who meet all of the following criteria are eligible for enrollment as study subjects:

1. Age 4 through 26 y
2. Clinical history of allergy to peanuts or peanut-containing foods
3. Serum IgE to peanut of ≥ 0.35 kUA/L (determined by the UniCAP™ automated immunoassay system within the past 12 mo) and/or an SPT to peanut >3 mm compared with control
4. Experience dose-limiting symptoms at or before the 100 mg (143 mg cumulative) dose of peanut protein (measured as 200 mg of peanut flour) on screening DBPCFC conducted in accordance with PRACTALL guidelines
5. Written informed consent from parent/guardian for minor subjects
6. Written assent from minor subjects as appropriate (eg, above the age of 7 y)
7. Use of birth control by female subjects of child-bearing potential
8. Should not be residing in the same address as another subject in this study
9. Cannot have participated in a clinical trial 30 d before randomization

Exclusion criteria

Subjects who meet any of these criteria are not eligible for enrollment as study subjects:

1. History of cardiovascular disease
2. History of frequent or repeated, severe or life-threatening episodes of anaphylaxis or anaphylactic shock
3. History of other chronic disease (other than asthma, atopic dermatitis, or rhinitis) requiring therapy (eg, heart disease, diabetes)
4. History of eosinophilic gastrointestinal disease
5. Current participation in any other interventional study
6. Subject is on “build-up phase” of immunotherapy for another allergen (ie, has not reached maintenance dosing)
7. Severe asthma (2007 NHLBI Criteria Steps 5 or 6)
8. Mild or moderate (2007 NHLBI Criteria Steps 1-4) asthma, if uncontrolled as defined by any of the following:
 - FEV1 $< 80\%$ of predicted, or FEV1/FVC $< 75\%$, with or without controller medications (only for age 6 or greater and able to do spirometry) or
 - ICS dosing of >500 mcg daily fluticasone (or equivalent inhaled corticosteroids based on NHLBI dosing chart) or
 - 1 hospitalization in the past year for asthma or
 - ER visit within 6 mo
9. Use of steroid medications (IV, IM, or oral) in the following manners:
 - history of daily oral steroid dosing for >1 mo during the past year or
 - burst or steroid course in the past 3 mo before inclusion or
 - >2 burst oral steroid course in the past year of at least 1-wk duration
10. Inability to discontinue antihistamines 5 half-lives before the initial day of escalation, skin testing, or DBPCFC
11. Lack of an available palatable vehicle food to which the subject is not allergic
12. Use of omalizumab within the past 6 mo, or current use of other investigational forms of allergen immunotherapy (eg, oral or sublingual) or immunomodulator therapy (not including corticosteroids)
13. Use of beta-blockers (oral), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB), or calcium channel blockers
14. Pregnancy or lactation
15. Having the same place of residence as another subject in the study
16. Participation in another clinical trial within 30 d before randomization

DBPCFC, Double-blind, placebo-controlled food challenge; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; NHLBI, National Heart, Lung, and Blood Institute; SPT, skin prick test.

TABLE E2. Grading system for severity of allergic reactions developed by the consortium of food allergy research²⁹

Grade 1—Mild	Grade 2—Moderate	Grade 3—Severe	Grade 4—Life Threatening	Grade 5—Death
Transient or mild discomfort (<48 h), no or minimal medical intervention/therapy required. These symptoms may include pruritus, swelling or rash, abdominal discomfort or other transient symptoms.	Symptoms that produce mild-to-moderate limitation in activity, some assistance may be needed; no or minimal intervention/therapy is required. Hospitalization is possible. These symptoms may include persistent hives, wheezing without dyspnea, abdominal discomfort/increased vomiting or other symptoms	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible. Symptoms may include bronchospasm with dyspnea, severe abdominal pain, throat tightness with hoarseness, and transient hypotension among others. Parenteral medication(s) are usually indicated	Extreme limitation in activity, significant assistance required; significant medical/therapy. Intervention is required; hospitalization is probable. Symptoms may include persistent hypotension and/or hypoxia with resultant decreased level of consciousness associated with collapse and/or incontinence or other life-threatening symptoms	Death

TABLE E3. Changes in maximally tolerated dose

	ITT Population		Completer Population	
	AR101	Placebo	AR101	Placebo
No. of subjects	29	26	23	26
Screening MTD in mg peanut protein, Geo mean (SD)	11.87 (2.253)	15.07 (2.207)	13.14 (2.189)	15.07 (2.207)
Exit MTD in mg peanut protein, Geo mean (SD)	218.15 (5.895)*	32.20 (5.674)	516.07 (1.340)*	32.20 (5.674)
Fold MTD increase in mg peanut protein, Geo mean (SD)	18.38 (5.459)*	2.14 (4.916)	39.28 (2.380)*	2.14 (4.916)

ITT, Intent-to-treat; MTD, maximum tolerated highest single dose of peanut protein; SD, standard deviation.

* $P < .0001$, Wilcoxon rank-sum for between-group differences.

TABLE E4. Summary of treatment-related treatment-emergent adverse events reported by more than one subject (safety)

MedDRA system organ class/preferred term, n (%)	AR101 (N = 29)	Placebo (N = 26)	Overall (N = 55)
Any event	27 (93%)	12 (46%)	39 (71%)
Immune system disorders	26 (90%)	10 (38%)	36 (65%)
Hypersensitivity	26 (90%)	10 (38%)	36 (65%)
Gastrointestinal disorders	6 (21%)	1 (4%)	7 (13%)
Vomiting	3 (10%)	1 (4%)	4 (7%)
Abdominal pain	2 (7%)	0	2 (4%)
Respiratory, thoracic and mediastinal disorders	3 (10%)	2 (8%)	5 (9%)
Nasal congestion	2 (7%)	1 (4%)	3 (5%)
Oropharyngeal pain	2 (7%)	0	2 (4%)
Skin and subcutaneous tissue disorders	3 (10%)	1 (4%)	4 (7%)
Urticaria	3 (10%)	1 (4%)	4 (7%)

MedDRA, Medical Dictionary for Regulatory Activities.

TABLE E5. Summary of treatment-related hypersensitivity treatment-emergent adverse events by specific classification reported by more than one subject (safety)

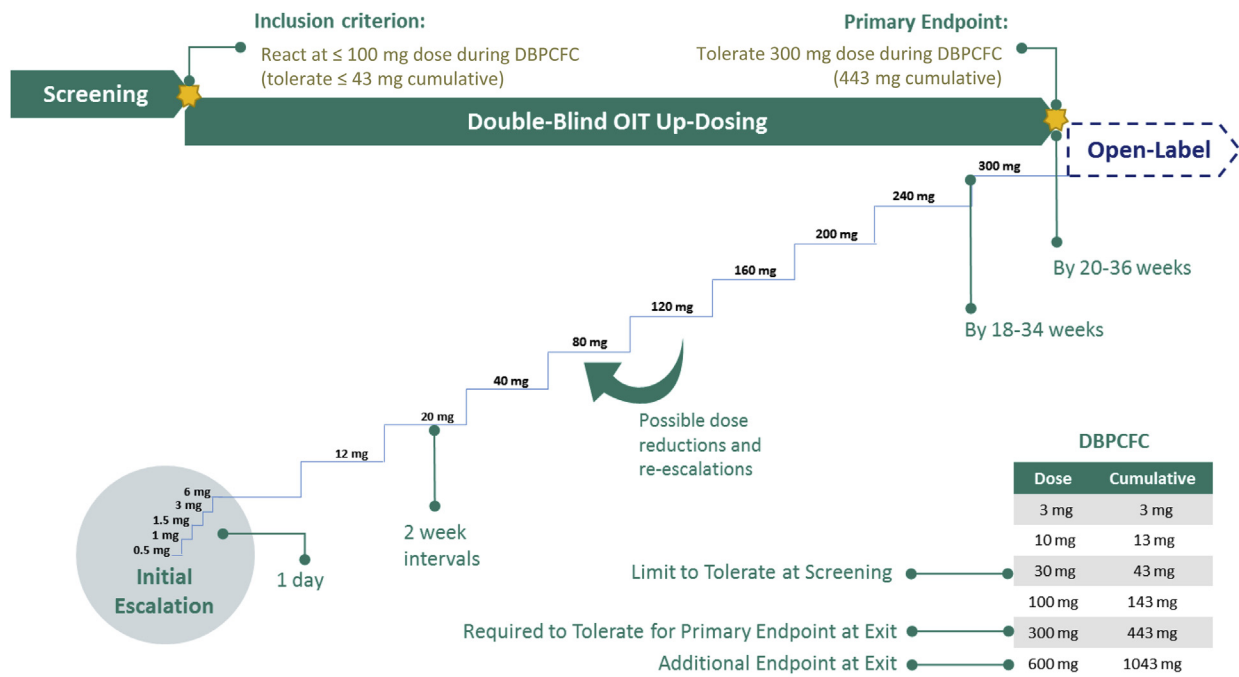
MedDRA system organ class/preferred term, n (%)	AR101 (N = 29)	Placebo (N = 26)	Overall (N = 55)
Any hypersensitivity event	26 (90%)	10 (38%)	36 (65%)
Gastrointestinal disorders	19 (66%)	7 (27%)	26 (47%)
Abdominal pain	6 (21%)	2 (8%)	8 (15%)
Abdominal pain upper	6 (21%)	2 (8%)	8 (15%)
Vomiting	7 (24%)	1 (4%)	8 (15%)
Nausea	6 (21%)	1 (4%)	7 (13%)
Oral pruritus	3 (10%)	1 (4%)	4 (7%)
Lip pruritus	2 (7%)	1 (4%)	3 (5%)
Lip swelling	2 (7%)	0	2 (4%)
Tongue pruritus	2 (7%)	0	2 (4%)
Respiratory, thoracic and mediastinal disorders	14 (48%)	3 (12%)	17 (31%)
Cough	4 (14%)	1 (4%)	5 (9%)
Oropharyngeal discomfort	4 (14%)	1 (4%)	5 (9%)
Oropharyngeal pain	4 (14%)	0	4 (7%)
Rhinorrhoea	2 (7%)	2 (8%)	4 (7%)
Sneezing	2 (7%)	2 (8%)	4 (7%)
Throat irritation	4 (14%)	0	4 (7%)
Nasal congestion	2 (7%)	0	2 (4%)
Wheezing	2 (7%)	0	2 (4%)
Immune system disorders	9 (31%)	1 (4%)	10 (18%)
Hypersensitivity	8 (28%)	1 (4%)	9 (16%)
Skin and subcutaneous tissue disorders	4 (14%)	5 (19%)	9 (16%)
Urticaria	3 (10%)	3 (12%)	6 (11%)
Erythema	2 (7%)	0	2 (4%)
Pruritus	2 (7%)	0	2 (4%)
Rash	1 (3%)	1 (4%)	2 (4%)
Swelling face	1 (3%)	1 (4%)	2 (4%)
Eye disorders	3 (10%)	2 (8%)	5 (9%)
Eye pruritus	2 (7%)	1 (4%)	3 (5%)
General disorders and administration site conditions	3 (10%)	0	3 (5%)
Chest discomfort	2 (7%)	0	2 (4%)
Ear and labyrinth disorders	1 (3%)	1 (4%)	2 (4%)
Ear pruritus	1 (3%)	1 (4%)	2 (4%)

MedDRA, Medical Dictionary for Regulatory Activities.

TABLE E6. Characteristics of withdrawn subjects

Subject	AE term	Severity	Relatedness	Onset (study day)	Last dose level (mg)	Reason for early discontinuation	Comment
002-008	EoE	Mild	Possibly	16	12	Adverse event	
003-001	Vomiting	Mild	Possibly	19	12	Adverse event	
004-001	Vomiting	Moderate	Definitely	9	6	Adverse event	
005-002	Vomiting	Mild	Probably	3	80	Adverse event	
001-007	Hypersensitivity (oropharyngeal pruritus, throat discomfort, nasal congestion, nausea, vomiting × 2, abdominal pain × 1)	Mild	Possibly	3	80	Withdrawal of consent	Subject developed increasing anxiety during up-dosing visits
007-007	Vomiting	Mild	Probably	45	80	Investigator decision	Site PI concerned about nonadherence with study product and asthma medication

AE, Adverse event; EoE, eosinophilic esophagitis.

**FIGURE E1.** ARC001 study schematic. *DBPCFC*, Double-blind, placebo-controlled food challenge; *OIT*, oral immunotherapy.