

ORIGINAL ARTICLE

AR101 Oral Immunotherapy
for Peanut Allergy

The PALISADE Group of Clinical Investigators*

ABSTRACT

BACKGROUND

Peanut allergy, for which there are no approved treatment options, affects patients who are at risk for unpredictable and occasionally life-threatening allergic reactions.

METHODS

In a phase 3 trial, we screened participants 4 to 55 years of age with peanut allergy for allergic dose-limiting symptoms at a challenge dose of 100 mg or less of peanut protein (approximately one third of a peanut kernel) in a double-blind, placebo-controlled food challenge. Participants with an allergic response were randomly assigned, in a 3:1 ratio, to receive AR101 (a peanut-derived investigational biologic oral immunotherapy drug) or placebo in an escalating-dose program. Participants who completed the regimen (i.e., received 300 mg per day of the maintenance regimen for approximately 24 weeks) underwent a double-blind, placebo-controlled food challenge at trial exit. The primary efficacy end point was the proportion of participants 4 to 17 years of age who could ingest a challenge dose of 600 mg or more, without dose-limiting symptoms.

RESULTS

Of the 551 participants who received AR101 or placebo, 496 were 4 to 17 years of age; of these, 250 of 372 participants (67.2%) who received active treatment, as compared with 5 of 124 participants (4.0%) who received placebo, were able to ingest a dose of 600 mg or more of peanut protein, without dose-limiting symptoms, at the exit food challenge (difference, 63.2 percentage points; 95% confidence interval, 53.0 to 73.3; $P < 0.001$). During the exit food challenge, the maximum severity of symptoms was moderate in 25% of the participants in the active-drug group and 59% of those in the placebo group and severe in 5% and 11%, respectively. Adverse events during the intervention period affected more than 95% of the participants 4 to 17 years of age. A total of 34.7% of the participants in the active-drug group had mild events, as compared with 50.0% of those in the placebo group; 59.7% and 44.4% of the participants, respectively, had events that were graded as moderate, and 4.3% and 0.8%, respectively, had events that were graded as severe. Efficacy was not shown in the participants 18 years of age or older.

CONCLUSIONS

In this phase 3 trial of oral immunotherapy in children and adolescents who were highly allergic to peanut, treatment with AR101 resulted in higher doses of peanut protein that could be ingested without dose-limiting symptoms and in lower symptom severity during peanut exposure at the exit food challenge than placebo. (Funded by Aimmune Therapeutics; PALISADE ClinicalTrials.gov number, NCT02635776.)

The members of the writing committee (Brian P. Vickery, M.D., Andrea Vereda, M.D., Ph.D., Thomas B. Casale, M.D., Kirsten Beyer, M.D., George Du Toit, M.B., B.Ch., Jonathan O. Hourihane, M.D., Stacie M. Jones, M.D., Wayne G. Shreffler, M.D., Annette Marcantonio, M.B.A., Rezi Zawadzki, Dr.P.H., Stephen G. Dilly, M.B., B.S., Ph.D., Daniel C. Adelman, M.D., and A. Wesley Burks, M.D.) assume responsibility for the overall content and integrity of the article. The affiliations of the members of the writing committee and the full names and degrees of all the authors are provided in the Appendix.

Address reprint requests to Dr. Adelman at Aimmune Therapeutics, 8000 Marina Blvd., Suite 300, Brisbane, CA 94005.

*A complete list of the members of the PALISADE Group of Clinical Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 18, 2018, at NEJM.org.

DOI: 10.1056/NEJMoa1812856

Copyright © 2018 Massachusetts Medical Society.

THE PREVALENCE OF PEANUT ALLERGY among children in the United States and other industrialized countries is on the rise.¹⁻⁴ Peanut allergy usually persists into adulthood,⁵⁻⁸ is occasionally life-threatening, and accounts for the majority of deaths related to food allergy.⁹ Because there is no approved treatment for peanut allergy,¹⁰ the standard of care has been a strict elimination diet and the timely administration of rescue medications in case of an allergic reaction on accidental exposure.¹¹⁻¹³ However, despite vigilance, accidental exposures may occur^{14,15} and cause reactions of unpredictable severity, even with small amounts of allergen,¹⁶ leading to a lifelong risk of severe reactions. Previous studies have suggested that oral immunotherapy is a potential strategy for the treatment of peanut allergy by inducing desensitization, which is generally understood as a transient upward shift in threshold reactivity to an allergen as a result of ongoing controlled exposure to that same allergen.¹⁷⁻²¹ Since the evidence from multiple early-stage trials is limited by small sample sizes and differing methods,^{22,23} most practice guidelines currently recommend against oral immunotherapy in routine clinical settings.^{11,12,24}

AR101 is a new peanut-derived, oral biologic drug that delivers a target daily maintenance dose of 300 mg of peanut protein with a characterized protein profile. We conducted the Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization (PALISADE), an international, randomized, double-blind, placebo-controlled, phase 3 trial, to evaluate the efficacy and safety of AR101 in children and adults with peanut allergy.

METHODS

TRIAL DESIGN AND PARTICIPANTS

We conducted this multicenter, double-blind, placebo-controlled, phase 3 trial at 66 sites in 10 countries in North America and Europe. Persons 4 to 55 years of age who had a clinical history of peanut allergy and supportive test results were considered to be eligible for participation in the trial if they had a serum peanut-specific IgE level of at least 0.35 kUA (allergen-specific unit) per liter according to ImmunoCAP (Thermo Fisher Scientific), a mean wheal diameter that was at least 3 mm larger than the negative control on skin-prick testing for peanut, or both. Although we enrolled participants 4 to 55 years of age in the trial, the prespecified primary

analysis population was participants 4 to 17 years of age, and these results constitute the bulk of what is presented here. At screening, all the participants had an allergic reaction, with dose-limiting symptoms, to no more than 100 mg of peanut protein (equivalent to approximately one third of a peanut kernel) during a double-blind, placebo-controlled food challenge. The complete enrollment criteria are listed in Sections 4.1 and 4.2 in the protocol (available with the full text of this article at NEJM.org).

Aimmune Therapeutics designed and sponsored the trial, with advice from the persons listed in the Acknowledgments section. The site principal investigators, who are authors, collected the data; of the 13 members of the writing committee, who conducted the data analysis and vouch for the completeness and accuracy of the data and the analyses, 5 are employees of the sponsor (see the Supplementary Appendix, available at NEJM.org). The members of the writing committee vouch for the fidelity of the trial to the protocol. An external data and safety monitoring committee provided independent oversight of the safety of the participants, and a separate, independent event-review committee adjudicated all allergy-related adverse events that were serious or severe, that involved dose-limiting gastrointestinal toxic effects, or that were consistent with the protocol definition of anaphylaxis.

The first member of the writing committee wrote the first draft of the manuscript with assistance from 12 others, 5 of whom are employees of the sponsor (see the Supplementary Appendix). Professional assistance with formatting and coordinating author reviews was paid for by the sponsor and provided by the Curry Rockefeller Group. All the authors reviewed the manuscript and made the decision to submit the manuscript for publication. There were no agreements between the sponsor and the authors or their institutions that treated the trial data as confidential information of the sponsor.

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.

RANDOMIZATION AND BLINDING

Eligible participants were randomly assigned, in a 3:1 ratio, to receive either AR101, a peanut-derived pharmaceutical product that was manufactured

in accordance with current Good Manufacturing Practice standards (see the Supplementary Appendix), or matching placebo. Randomization was performed according to a central randomization schedule of randomly permuted blocks, with the use of an interactive online system. An unbalanced randomization was chosen in order to maximize the number of observations of participants receiving active treatment and to minimize the number of participants who were randomly assigned to an inactive regimen for 1 year.

The investigational product and placebo were administered daily as an oral powder in graduated doses that were provided in pull-apart capsules (doses of 0.5, 1, 10, 20, or 100 mg) or foil-laminate sachets (300 mg). The quantities of the investigational product administered are reported as milligrams of peanut protein (or equivalent weight for placebo). Capsules or sachets were opened, and the content was mixed thoroughly with a few spoonfuls of age-appropriate, unheated food in a vehicle of the participant's choice (see the Supplementary Appendix). Persons who were living at the same address were excluded from the trial to minimize the chances of inadvertent unblinding or dosing error.

PROCEDURES

Details of the trial procedures are provided in Section 6 in the protocol. In brief, all the participants underwent a double-blind, placebo-controlled food challenge at screening, which was performed in accordance with the Practical Allergy (PRACTALL) consensus report²⁵ and which consisted of challenges with taste-masked peanut flour (not AR101) and oat flour done on separate days and in random order (Table S1 in the Supplementary Appendix). Qualifying participants proceeded through a 1-day, supervised, initial dose-escalation phase (from 0.5 mg to 6 mg); an increasing-dose phase, during which the dose was increased gradually every 2 weeks from 3 mg to 300 mg; and a 24-week maintenance phase, during which the dose was 300 mg (Fig. S1 in the Supplementary Appendix). The total duration of the trial was approximately 12 months.

At the end-of-trial visit, an exit double-blind, placebo-controlled food challenge was conducted in a similar fashion to the screening food challenge, but the exit food challenge included additional doses of 300 mg, 600 mg, and 1000 mg of peanut protein, as tolerated (i.e., as could be ingested without dose-limiting symptoms) (Table

S1 in the Supplementary Appendix). The results were independently assessed by a physician at the site who was experienced in the procedure, who was unaware of the trial-group assignments, and who had not participated in clinically meaningful care of that participant throughout the trial. At each trial visit, all the participants were reminded to continue a strict peanut-elimination diet and to carry epinephrine that they could inject themselves, which was provided to any participant who lacked it.

During the trial, safety and adherence were monitored with the use of daily diaries. The severity of adverse events was determined by the investigator with the use of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) with the modification previously used by the Consortium of Food Allergy Research (CoFAR) for hypersensitivity events²⁶ and with the use of the NCI-CTC for all other events. Anaphylaxis was defined in the protocol according to National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network criteria.²⁷ We used the term "systemic allergic reactions" to be inclusive of these events as well as other clinically important systemic allergic reactions that were not classified as anaphylaxis according to this definition, consistent with guidance from the Food and Drug Administration. Information regarding specific participant-level and trial-level rules for dose modification and stopping is provided in Section 7.10 in the protocol.

END POINTS AND ASSESSMENTS

Participants were considered not to have had a response to the trial regimen if they were unable to complete the increasing-dose phase by week 40 or the entire trial by week 68 or if they did not undertake the exit food challenge. All the participants who completed the maintenance phase and underwent the exit food challenge were considered to have data that could be evaluated. The primary efficacy end point was the proportion of participants 4 to 17 years of age who had a response to the trial regimen, which was defined as the ability to ingest a single dose of at least 600 mg of peanut protein (cumulative dose, ≥ 1043 mg) during the exit food challenge, with no dose-limiting symptoms, according to the judgment of the investigator (Section 6.6 in the protocol). Mild symptoms involving the skin, upper respiratory tract, or gastrointestinal tract that might not be considered to be dose-limiting

were derived from PRACTALL guidance and are outlined in Section 6.7.1 in the protocol.

The key secondary end points, which are reported here in hierarchical order (see below), included the proportion of participants who could tolerate single doses of 300 mg and 1000 mg at the exit food challenge and the maximum severity of symptoms that occurred at any dose level of peanut protein during the exit food challenge. Other secondary end points involving participants 4 to 17 years of age that are reported here include the use of epinephrine as a rescue medication at the exit food challenge and comparison with its use at the screening food challenge, changes in peanut-specific IgE and IgG4 levels, and changes in the mean wheal diameters on skin-prick testing for peanut.

STATISTICAL ANALYSIS

The primary efficacy analysis was the between-group difference in response rates among participants 4 to 17 years of age. We used the Farrington–Manning test to test the null hypothesis that the absolute difference in response rates (active-drug group minus placebo group) would be equal to 15 percentage points at the 0.05 significance level.²⁸ The trial was considered to have met the primary objective if the lower boundary of the corresponding test-based 95% confidence interval was greater than the prespecified margin of 15 percentage points. At a two-sided alpha level of 0.05, and assuming a response rate of 20% or less in the placebo group and a response rate of at least 50% in the active-drug group, we estimated that a sample of 500 participants would provide the trial with 89% power to show between-group differences exceeding 15 percentage points for the primary end point. The intention-to-treat population, which included all the participants 4 to 17 years of age who underwent randomization and received at least one dose of active drug or placebo, was used as the primary population for the analysis of all the end points, and a closed testing procedure²⁹ with a prespecified hierarchy was used for the primary efficacy analysis and all the secondary end points to maintain the overall trial type I error rate at 0.05.

The protocol identified four key secondary end points: the percentage of participants 4 to 17 years of age who could ingest a dose of at least 300 mg without dose-limiting symptoms, the percentage of participants 4 to 17 years of age

who could ingest a dose of at least 1000 mg without dose-limiting symptoms, the maximum severity of symptoms at the exit food challenge, and the percentage of participants 18 to 55 years of age who could tolerate a dose of at least 600 mg. The other secondary end points are listed above. In the closed testing procedure, once a nonsignificant result (i.e., $P > 0.05$) is obtained, all the subsequent analyses are considered to be exploratory rather than confirmatory; point estimates and 95% confidence intervals are reported, and these intervals were not corrected for multiple testing. All the analyses were performed with the use of SAS software, version 9.4 (SAS Institute). The full statistical analysis plan is provided in the protocol.

RESULTS

PARTICIPANTS

The trial sites screened 842 persons, 750 of whom were 4 to 17 years of age, in order to identify 555 eligible participants with peanut allergy who then underwent randomization. Of the 555 eligible participants, 499 were 4 to 17 years of age. A total of 551 participants received at least one dose of AR101 or placebo (Fig. 1). Among the 92 persons older than 17 years of age who underwent screening, 56 were eligible for inclusion and underwent randomization, and 55 received at least one dose of AR101 or placebo. Other than the primary end point, no other data regarding this cohort are reported here.

The baseline characteristics of the participants 4 to 17 years of age were consistent with peanut allergy and were well balanced between the two trial groups (Table 1). A majority of participants had a history of peanut anaphylaxis (72%), asthma (53%), and multiple food allergies (66%). The median maximum tolerated dose of peanut protein at the screening food challenge was 10 mg. Among participants 4 to 17 years of age, 294 of 372 (79.0%) in the active-drug group and 115 of 124 (92.7%) in the placebo group completed the trial regimen per the protocol and had data from the exit food challenge that could be evaluated.

EFFICACY

Among participants 4 to 17 years of age, 250 of 372 participants (67.2%) in the active-drug group were able to ingest a single dose of at least 600 mg

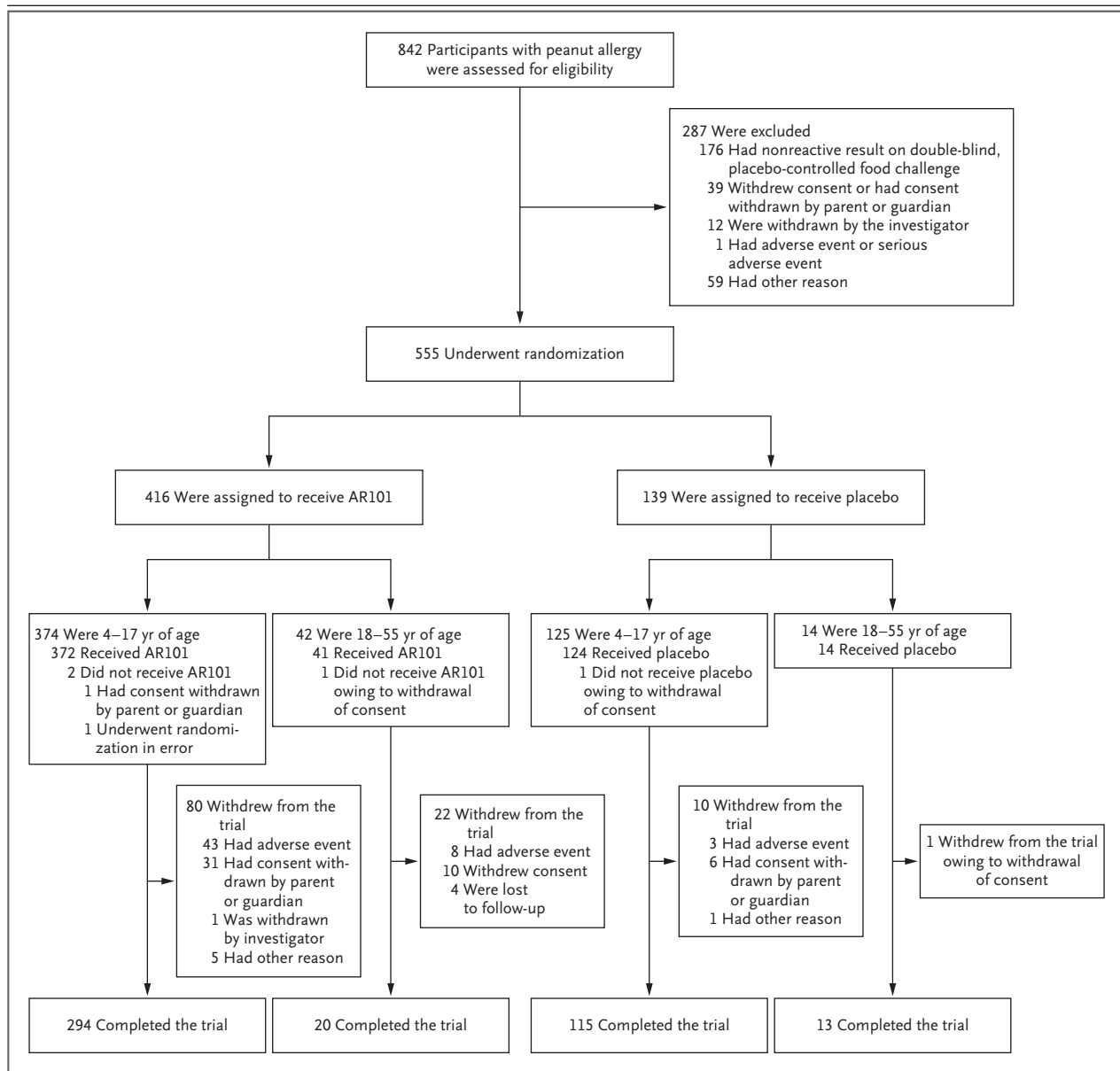


Figure 1. Screening, Randomization, and Follow-up of the Participants.

One person had an allergic reaction during the double-blind, placebo-controlled food challenge at trial entry that resulted in hospitalization (serious adverse event), so this person did not undergo randomization. Other reasons for exclusion were scheduling conflicts, time-commitment issues, and parental concerns regarding food-challenge reactions. Reasons for withdrawal from the trial among participants 4 to 17 years of age in the active-drug group included nonadherence to the regimen in two participants and relocation, schedule conflict, and randomization in error in one participant each. One participant 4 to 17 years of age in the placebo group withdrew because of relocation. Additional reasons for withdrawal from the trial after randomization because of adverse events are listed in Table S7 in the Supplementary Appendix.

of peanut protein during the exit food challenge with no more than mild symptoms, as compared with 5 of 124 (4.0%) in the placebo group, which yielded a between-group difference of 63.2 percentage points (95% confidence interval [CI],

53.0 to 73.3; $P < 0.001$) (Fig. 2). For the first two key secondary end points of tolerating the 300-mg dose and the 1000-mg dose during the exit food challenge, the response rates in the active-drug group were 76.6% and 50.3%, respectively, as

Table 1. Demographic and Clinical Characteristics of the Participants 4 to 17 Years of Age at Baseline (Intention-to-Treat Population).*

Characteristic	AR101 (N=372)	Placebo (N=124)	Total (N=496)
Sex — no. (%)			
Male	208 (56)	76 (61)	284 (57)
Female	164 (44)	48 (39)	212 (43)
Age group — no. (%)			
4–11 yr	238 (64)	89 (72)	327 (66)
12–17 yr	134 (36)	35 (28)	169 (34)
Baseline peanut sensitivity			
Median size of average wheal on skin-prick testing (IQR) — mm [†]	11 (9–14)	12 (9–15)	11 (9–15)
Median level of peanut-specific IgE (IQR) — kUA/liter	69 (19–194)	75 (29–251)	71 (20–202)
Median maximum tolerated dose of peanut protein (IQR) — mg	10 (3–30)	10 (3–30)	10 (3–30)
History of peanut anaphylaxis — no. (%)	269 (72)	89 (72)	358 (72)
Previous or current asthma — no. (%)	198 (53)	65 (52)	263 (53)
Multiple food allergies — no. (%)	245 (66)	80 (65)	325 (66)

* No significant differences were found between the active-drug group (which received AR101, a peanut-derived, oral biologic drug product) and the placebo group with regard to any of the demographic and clinical characteristics of the participants at baseline. The demographic and clinical characteristics of the full trial population of participants 4 to 55 years of age are provided in Table S2 in the Supplementary Appendix. IQR denotes interquartile range, and kUA allergen-specific unit.

[†] The average wheal diameter was calculated by measuring the longest dimension of the wheal and its orthogonal perpendicular in the peanut test and by calculating its mean, followed by subtraction of the mean wheal that occurred in the negative (saline) control test.

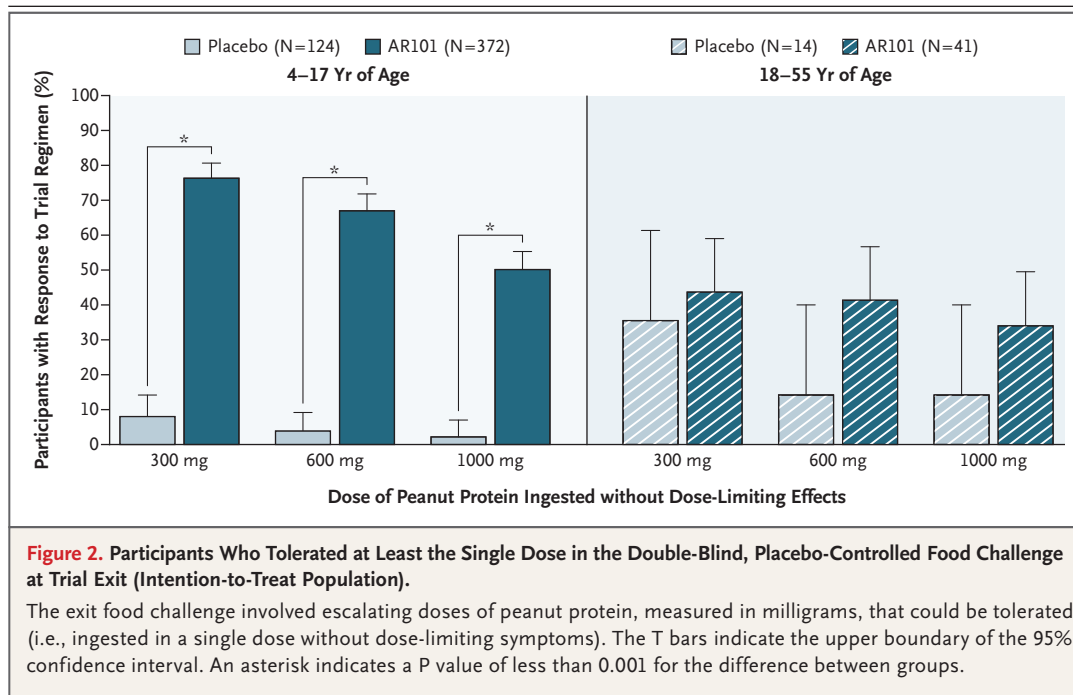
compared with 8.1% and 2.4%, respectively, in the placebo group ($P<0.001$ for both comparisons) (Fig. 2). During the exit food challenge, the maximum severity of symptoms was moderate in 25% of the participants in the active-drug group and 59% of those in the placebo group and severe in 5% and 11%, respectively ($P<0.001$ for both between-group differences) (Fig. S2 in the Supplementary Appendix). The maximum severity of symptoms was also lower in the active-drug group than in the placebo group at each dose level during the exit food challenge (Fig. S3 in the Supplementary Appendix).

The fourth key secondary analysis compared the percentages of participants 18 to 55 years of age who could tolerate a dose of 600 mg during the exit food challenge. The difference between the rate in the active-drug group (41.5%) and the rate in the placebo group (14.3%) did not reach statistical significance. Thus, the fixed-sequence testing procedure was terminated, and the results of all the subsequent analyses are presented as point estimates and 95% confidence intervals without adjustment for multiple comparisons.

Among participants 4 to 17 years of age in the active-drug group, the serum peanut-specific IgG4 levels increased from baseline (geometric least-squares mean ratio of active-drug group vs. placebo group, 1.0; 95% CI, 0.9 to 1.1), and the mean wheal diameters on skin-prick testing for peanut decreased from baseline (least-squares mean ratio of active-drug group vs. placebo group, -4.0 ; 95% CI, -4.9 to -3.2). The between-group difference regarding the change in the level of peanut-specific IgE from baseline to the end of the trial was not significant (Fig. S4 in the Supplementary Appendix).

The data for participants 4 to 17 years of age were divided according to age (children [4 to 11 years] vs. adolescents [12 to 17 years]). The between-group difference at the 600-mg challenge dose was 58.3 percentage points (95% CI, 39.7 to 76.9) among adolescents, as compared with 66.1 percentage points (95% CI, 53.9 to 78.3) among children (Fig. S5 in the Supplementary Appendix).

Among all the participants 4 to 17 years of age, 10% of the participants in the active-drug group received rescue epinephrine during the



exit food challenge, as compared with 53% of those in the placebo group, despite a similar rate of use of rescue epinephrine at the baseline screening food challenge (Fig. S6 in the Supplementary Appendix). A total of 1% of the participants in the active-drug group received a second dose of epinephrine during the exit food challenge, as compared with 15% of those in the placebo group (Fig. S7 in the Supplementary Appendix).

SAFETY

Excluding events that occurred during the exit food challenge, we found that 98.7% of the participants 4 to 17 years of age in the active-drug group and 95.2% of those in the placebo group had an adverse event during the intervention period (Table 2). In the active-drug group, 34.7% of the participants had events with a highest severity of mild, and 59.7% had events with a highest severity of moderate, as compared with 50.0% and 44.4%, respectively, in the placebo group. (Table S3 in the Supplementary Appendix). Severe reactions were reported in 4.3% of the participants in the active-drug group and in 0.8% of those in the placebo group. Participants in the active-drug group had a higher incidence than those in the placebo group of adverse events affecting the gastrointestinal tract (85.8%

vs. 69.4%), respiratory tract (81.2% vs. 71.8%), skin (66.9% vs. 55.6%), and immune system (16.9% vs. 8.9%) (Table S4 in the Supplementary Appendix).

The exposure to the trial regimen was 307.0 participant-years in the active-drug group and 108.8 participant-years in the placebo group; the exposure-adjusted rates of adverse events during the intervention period declined from the initial dose-escalation day through the increasing-dose phase and the maintenance phase in the two groups (Table S5 in the Supplementary Appendix). There were nine serious adverse events among eight participants (2.2%) in the active-drug group and one event in one participant (0.8%) in the placebo group (Table S6 in the Supplementary Appendix). Overall, serious or severe adverse events occurred in 5.6% of the participants in the active-drug group and in 1.6% of those in the placebo group (Table S10 in the Supplementary Appendix). There were no deaths or adverse events that occurred during the intervention period that were graded as life-threatening in severity.

Overall, 43 participants (11.6%) in the active-drug group and 3 (2.4%) in the placebo group withdrew from the trial because of adverse events during the intervention period. Reasons for withdrawal are shown in Table S7 in the

Table 2. Adverse Events Affecting More Than 5% of the Participants 4 to 17 Years of Age in Either Group, According to Trial Phase.*

Event	Initial Dose-Escalation Phase		Increasing-Dose Phase		Maintenance Phase		Overall	
	AR101 (N = 372)	Placebo (N = 124)	AR101 (N = 366)	Placebo (N = 123)	AR101 (N = 310)	Placebo (N = 118)	AR101 (N = 372)	Placebo (N = 124)
≥1 Adverse event	189 (50.8)	36 (29.0)	353 (96.4)	108 (87.8)	270 (87.1)	94 (79.7)	367 (98.7)	118 (95.2)
Abdominal pain	83 (22.3)	8 (6.5)	156 (42.6)	25 (20.3)	46 (14.8)	7 (5.9)	194 (52.2)	30 (24.2)
Vomiting	15 (4.0)	0	127 (34.7)	22 (17.9)	50 (16.1)	14 (11.9)	154 (41.4)	30 (24.2)
Upper abdominal pain	9 (2.4)	3 (2.4)	136 (37.2)	17 (13.8)	41 (13.2)	9 (7.6)	152 (40.9)	26 (21.0)
Oral pruritus	36 (9.7)	8 (6.5)	131 (35.8)	15 (12.2)	39 (12.6)	5 (4.2)	151 (40.6)	20 (16.1)
Nausea	31 (8.3)	1 (0.8)	128 (35.0)	22 (17.9)	45 (14.5)	8 (6.8)	146 (39.2)	29 (23.4)
Oral paresthesia	4 (1.1)	2 (1.6)	57 (15.6)	5 (4.1)	23 (7.4)	2 (1.7)	65 (17.5)	8 (6.5)
Lip swelling	2 (0.5)	0	25 (6.8)	3 (2.4)	13 (4.2)	2 (1.7)	38 (10.2)	5 (4.0)
Cough	10 (2.7)	0	117 (32.0)	30 (24.4)	61 (19.7)	22 (18.6)	152 (40.9)	42 (33.9)
Throat irritation	28 (7.5)	5 (4.0)	131 (35.8)	26 (21.1)	43 (13.9)	11 (9.3)	152 (40.9)	34 (27.4)
Rhinorrhea	6 (1.6)	1 (0.8)	82 (22.4)	25 (20.3)	46 (14.8)	9 (7.6)	113 (30.4)	28 (22.6)
Sneezing	16 (4.3)	3 (2.4)	76 (20.8)	15 (12.2)	33 (10.6)	5 (4.2)	98 (26.3)	18 (14.5)
Throat tightness	14 (3.8)	3 (2.4)	70 (19.1)	6 (4.9)	20 (6.5)	0	86 (23.1)	8 (6.5)
Dyspnea	2 (0.5)	1 (0.8)	32 (8.7)	3 (2.4)	17 (5.5)	1 (0.8)	44 (11.8)	5 (4.0)
Dysphonia	1 (0.3)	0	19 (5.2)	2 (1.6)	8 (2.6)	1 (0.8)	25 (6.7)	2 (1.6)
Pruritus	25 (6.7)	8 (6.5)	117 (32.0)	25 (20.3)	45 (14.5)	14 (11.9)	153 (41.1)	34 (27.4)
Urticaria	16 (4.3)	3 (2.4)	115 (31.4)	23 (18.7)	63 (20.3)	17 (14.4)	143 (38.4)	30 (24.2)
Rash	12 (3.2)	1 (0.8)	61 (16.7)	15 (12.2)	24 (7.7)	7 (5.9)	81 (21.8)	18 (14.5)
Chest discomfort	2 (0.5)	0	19 (5.2)	1 (0.8)	8 (2.6)	0	24 (6.5)	1 (0.8)
Systemic allergic reaction†	1 (0.3)	0	31 (8.5)	2 (1.6)	27 (8.7)	2 (1.7)	53 (14.2)	4 (3.2)
Ear pruritus	3 (0.8)	0	23 (6.3)	0	7 (2.3)	0	25 (6.7)	0

number of participants with event (percent)

* The data in the maintenance-phase and overall columns exclude symptoms that were recorded during the exit double-blind, placebo-controlled food challenge.

† Events of systemic allergic reaction included one case of severe anaphylaxis in the active-drug group during the maintenance phase.

Supplementary Appendix. A total of 16 participants in the active-drug group (4.3%) withdrew from the trial owing to chronic or recurrent dose-limiting gastrointestinal symptoms, which were prespecified adverse events of interest. Of these participants, 3 underwent esophagogastroduodenoscopy (EGD), and eosinophilic esophagitis was confirmed in 1 participant. An additional 8 participants withdrew because of more-acute gastrointestinal adverse events during the intervention period, for a total gastrointestinal-related withdrawal rate of 6.5% in the active-drug group, as compared with 1.6% (2 participants) in the placebo group. The gastrointestinal symptoms resolved, on average, within 10 days (range, 1 to 42) in all the participants after the discontinuation of AR101; the participant with eosinophilic esophagitis did not undergo a follow-up EGD by the time of the database lock, and so this adverse event was considered to be ongoing although the participant's clinical symptoms had resolved fully. Peripheral-blood eosinophil counts did not change significantly in either trial group (Fig. S8 in the Supplementary Appendix).

A total of 53 participants (14.2%) in the active-drug group and 4 (3.2%) in the placebo group had a systemic allergic reaction during the intervention period. Of these events, one was severe (grade 3 anaphylaxis) and occurred in the active-drug group, with the remainder of the events in the active-drug group being mild, occurring in 6.2% of the participants, or moderate, occurring in 7.8% of the participants (Table S3 in the Supplementary Appendix). Systemic allergic reactions leading to withdrawal from the trial occurred in 7 participants (1.9%) in the active-drug group and in no participants in the placebo group (Table S7 in the Supplementary Appendix). All the events were considered by the investigators to be related to the trial intervention, including one event of severe anaphylaxis, which occurred in the active-drug group (Table S8 in the Supplementary Appendix).

During the course of the trial, excluding during the food challenges, epinephrine was administered in 52 participants (14.0%) in the active-drug group and in 8 (6.5%) in the placebo group. In the active-drug group, 93.9% of the events for which epinephrine was administered were of grade 1 or 2 in severity, according to the CoFAR-modified NCI-CTC, and a single dose of epinephrine was administered in 92.7% of the

events. Details regarding epinephrine use are provided in Table S9 in the Supplementary Appendix.

DISCUSSION

In this phase 3 trial of peanut oral immunotherapy, AR101 showed superiority over placebo in children and adolescents 4 to 17 years of age. The effect in participants 18 to 55 years of age was not significant. Overall, 67% of the participants 4 to 17 years of age in the active-drug group could tolerate a single dose of at least 600 mg of peanut protein, the equivalent of approximately two whole peanut kernels, during the exit food challenge. All these participants had had dose-limiting symptoms at a challenge dose of 100 mg or less at baseline, which meant that before treatment they could tolerate no more than 30 mg of peanut protein, the equivalent of one tenth of one peanut kernel. A total of 50% of the participants 4 to 17 years of age in the active-drug group were able to complete the entire double-blind, placebo-controlled exit food challenge, which was capped by a 1000-mg single dose (the equivalent of approximately three or four peanut kernels). These data show that, in the context of a clinical trial, among participants 4 to 17 years of age, AR101 had immunomodulatory activity, raised the threshold dose of peanut exposure triggering the onset of clinically significant allergic symptoms (among participants having symptoms) during the double-blind, placebo-controlled exit food challenge, and attenuated the severity of those symptoms when they occurred.

The safety profile of AR101 was similar to that observed in a phase 2 trial.¹⁹ In contrast to many previous studies of peanut oral immunotherapy, our trial did not allow the use of medical prophylaxis (e.g., antihistamines or proton-pump inhibitors) to mitigate allergy symptoms. Adverse events were common in the two trial groups, and events that were considered by the investigators to be serious or severe occurred in less than 6% of the participants in the active-drug group and in less than 2% of those in the placebo group (Table S10 in the Supplementary Appendix), and exposure-adjusted event rates declined with use. These adverse events most frequently affected the skin, respiratory tract, and gastrointestinal tract, as has been previously observed during oral immunotherapy use, but the rate of withdrawals due to gastrointestinal-related

adverse events of 6.5% was lower than expected on the basis of published literature,^{30,31} perhaps in part owing to the stringent exclusion criteria in our trial. Although new-onset eosinophilic esophagitis has been estimated to occur in 2.7% of persons receiving oral immunotherapy,³² one participant received a diagnosis during the trial, whereas two other participants had negative results on endoscopy. However, not all the participants with dose-limiting gastrointestinal symptoms underwent upper endoscopy; as a result, the incidence of eosinophilic esophagitis during the trial may be underestimated. The recorded adverse events highlight both the atopic background of the participants and the immunostimulatory nature of oral immunotherapy. The clinical features that are associated with adverse events during treatment require further study.

There are several limitations to the trial. The prespecified primary analysis in this trial limited the age range of the participants to 4 to 17 years; among the older participants who were enrolled in the trial, the improvement in the exit food challenge in the active-drug group was not significantly better than that in the placebo group. The participants in this trial were selected on the basis of their sensitivity to no more than 100 mg of peanut protein. Thus, they may not be representative of the entire population of persons with peanut allergy, 50% of whom have a reaction to doses above 100 mg,¹⁶ but these persons are among those at high risk for reaction to accidental exposure in daily life. The majority of the participants in this trial were male and white — demographic characteristics that are similar to those in other studies of oral immunotherapy.

Patients with severe or poorly controlled asthma or with chronic gastrointestinal symptoms were excluded for safety reasons. Desensitization was evaluated after 6 months of the maintenance regimen, which limits the conclusions that can be drawn regarding long-term safety and efficacy after years of use, which would be necessary in the clinical treatment of patients, given that food allergen immunotherapy is generally not considered to be a curative treatment. Open-label studies of extended maintenance therapy (ClinicalTrials.gov numbers, NCT02993107 and NCT03292484) and new placebo-controlled trials (NCT03126227 and NCT03201003) are ongoing.

In conclusion, evidence from PALISADE, an international, phase 3 trial of peanut oral immunotherapy that was conducted to a regulatory standard, showed that AR101 was an immunomodulatory treatment that resulted in desensitization in children and adolescents who were highly allergic to peanut. No significant effect was found in participants 18 to 55 years of age.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

Supported by Aimmune Therapeutics.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the participants and their families; the trial coordinators, nurses, dietitians, and other personnel at all the trial sites; colleagues at Syneos Health, the clinical research organization that was hired to assist with the trial; Robert Elfont, M.D., Ph.D., for input into the protocol design; Robert A. Wood, M.D., for contributions to the conduct of the trial; Allan Rosen, Ph.D., and Brian Beus, M.S., for contributions to the statistical analysis plan; Noelle M. Griffin, Ph.D., for contributions to the data interpretation; Tmirah Haselkorn, Ph.D., for editorial assistance with an earlier version of the manuscript; and Eileen Rodríguez, C.M.P., for assistance with the logistics and coordination of the author review process.

APPENDIX

The affiliations of the members of the writing committee are as follows: Emory University School of Medicine, Atlanta (B.P.V.); Aimmune Therapeutics, London (A.V.); University of South Florida Morsani College of Medicine, Tampa (T.B.C.); Charité Universitätsmedizin Berlin, Berlin (K.B.); Guy's and St. Thomas' NHS Foundation Trust, London (G.D.T.); Irish Centre for Fetal and Neonatal Translational Research (INFANT) Centre and Paediatrics and Child Health, University College Cork, Cork, Ireland (J.O.H.); University of Arkansas for Medical Sciences, and Arkansas Children's Hospital, Little Rock (S.M.J.); Massachusetts General Hospital, Boston (W.G.S.); Aimmune Therapeutics, Brisbane, CA (A.M., R.Z., S.G.D., D.C.A.); and University of North Carolina at Chapel Hill, Chapel Hill (A.W.B.).

The full list of the authors is as follows: Brian P. Vickery, M.D., Andrea Vereda, M.D., Ph.D., Thomas B. Casale, M.D., Kirsten Beyer, M.D., George du Toit, M.B., B.Ch., Jonathan O. Hourihane, M.D., Stacie M. Jones, M.D., Wayne G. Shreffler, M.D., Annette Marcantonio, M.B.A., Rezi Zawadzki, Dr.P.H., Lawrence Sher, M.D., Warner W. Carr, M.D., Stanley Fineman, M.D., Leon Greos, M.D., Rima Rachid, M.D., M. Dolores Ibáñez, M.D., Ph.D., Stephen Tilles, M.D., Amal H. Assa'ad, M.D., Caroline Nilsson, M.D., Ph.D., Ned Rupp, M.D., Michael J. Welch, M.D., Gordon Sussman, M.D., Sharon Chinthrajah, M.D., Katharina Blumchen, M.D., Ellen Sher, M.D., Jonathan M. Spergel, M.D., Ph.D., Frederick E. Leickly, M.D., M.P.H., Stefan Zielen, M.D., Julie Wang, M.D., Georgiana M. Sanders, M.D., Robert A. Wood, M.D., Amarjit Cheema, M.D., Carsten Bindslev-Jensen, M.D., Ph.D., Stephanie Leonard, M.D., Rita Kachru, M.D., Douglas T. Johnston, D.O., Frank C. Hampel, Jr., M.D., Edwin H. Kim, M.D., Aikaterini Anagnostou, M.D., Ph.D., Jacqueline A. Pon-

gracic, M.D., Moshe Ben-Shoshan, M.D., Hemant P. Sharma, M.D., M.H.S., Allan Stillerman, M.D., Hugh H. Windom, M.D., William H. Yang, M.D., Antonella Muraro, M.D., Ph.D., José M. Zubeldia, M.D., Ph.D., Vibha Sharma, M.D., Morna J. Dorsey, M.D., M.M.Sc., Hey J. Chong, M.D., Ph.D., Jason Ohayon, M.D., J. Andrew Bird, M.D., Tara F. Carr, M.D., Dureen Siri, M.D., Montserrat Fernández-Rivas, M.D., Ph.D., David K. Jeong, M.D., David M. Fleischer, M.D., Jay A. Lieberman, M.D., Anthony E.J. Dubois, M.D., Ph.D., Marina Tsoumani, M.D., Christina E. Ciaccio, M.D., Jay M. Portnoy, M.D., Lyndon E. Mansfield, M.D., Stephen B. Fritz, M.D., Bruce J. Lanser, M.D., Jonathan Matz, M.D., Hanneke N.G. Oude Elberink, M.D., Ph.D., Pooja Varshney, M.D., Stephen G. Dilly, M.B., B.S., Ph.D., Daniel C. Adelman, M.D., and A. Wesley Burks, M.D. The affiliations of the authors are listed in the Supplementary Appendix, available at NEJM.org.

REFERENCES

- Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011;128(1):e9-e17.
- Sicherer SH, Muñoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. *J Allergy Clin Immunol* 1999;103:559-62.
- Sicherer SH, Muñoz-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.
- Grimshaw KE, Bryant T, Oliver EM, et al. Incidence and risk factors for food hypersensitivity in UK infants: results from a birth cohort study. *Clin Transl Allergy* 2016;6:1.
- Crespo JF, James JM, Fernandez-Rodriguez C, Rodriguez J. Food allergy: nuts and tree nuts. *Br J Nutr* 2006;96:Suppl 2: S95-S102.
- Moreno MA. Guidelines for children with peanut allergy. *JAMA Pediatr* 2017; 171:100.
- 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.
- Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;107:191-3.
- Yu W, Freeland DMH, Nadeau KC. Food allergy: immune mechanisms, diagnosis and immunotherapy. *Nat Rev Immunol* 2016;16:751-65.
- Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;126: Suppl:S1-S58.
- Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update — 2014. *J Allergy Clin Immunol* 2014; 134(5):1016-25.e43.
- Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014;69:1008-25.
- Rimbaud L, Heraud F, La Vieille S, Leblanc J-C, Crépet A. Quantitative risk assessment relating to the inadvertent presence of peanut allergens in various food product. *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.
- Allen KJ, Remington BC, Baumert JL, et al. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. *J Allergy Clin Immunol* 2014; 133:156-64.
- Varshney P, Jones SM, Scurlock AM, 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, 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.
- Bird JA, Spergel JM, Jones SM, et al. Efficacy and safety of AR101 in oral immunotherapy for peanut allergy: results of ARC001, a randomized, double-blind, placebo-controlled phase 2 clinical trial. *J Allergy Clin Immunol Pract* 2018;6(2): 476-485.e3.
- Blumchen K, Ulbricht H, Staden U, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol* 2010;126(1):83-91.e1.
- Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy* 2017;72:1133-47.
- Nurmatov U, Venderbosch I, Devereux G, Simons FE, Sheikh A. Allergen-specific oral immunotherapy for peanut allergy. *Cochrane Database Syst Rev* 2012;9: CD009014.
- Wood RA. Food allergen immunotherapy: current status and prospects for the future. *J Allergy Clin Immunol* 2016; 137:973-82.
- Pajno GB, Fernandez-Rivas M, Arasi S, et al. EAACI guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy* 2018;73:799-815.
- Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, 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.
- Burks AW, Jones SM, Wood RA, et al. Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med* 2012; 367:233-43.
- Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report — Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.
- Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. *Stat Med* 1990;9:1447-54.
- Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. *J Stat Plan Inference* 2001;99:25-40.
- Virkud YV, Burks AW, Steele PH, et al. Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. *J Allergy Clin Immunol* 2017;139(3):882-888.e5.
- Vazquez-Ortiz M, Turner PJ. Improving the safety of oral immunotherapy for food allergy. *Pediatr Allergy Immunol* 2016;27:117-25.
- 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.

Copyright © 2018 Massachusetts Medical Society.