Efficacy and safety of oral immunotherapy in children aged 1–3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study

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Summary

Background For young children with peanut allergy, dietary avoidance is the current standard of care. We aimed to assess whether peanut oral immunotherapy can induce desensitisation (an increased allergic reaction threshold while on therapy) or remission (a state of non-responsiveness after discontinuation of immunotherapy) in this population.

Methods We did a randomised, double-blind, placebo-controlled study in five US academic medical centres. Eligible participants were children aged 12 to younger than 48 months who were reactive to 500 mg or less of peanut protein during a double-blind, placebo-controlled food challenge (DBPCFC). Participants were randomly assigned by use of a computer, in a 2:1 allocation ratio, to receive peanut oral immunotherapy or placebo for 134 weeks (2000 mg peanut protein per day) followed by 26 weeks of avoidance, with participants and study staff and investigators masked to group treatment assignment. The primary outcome was desensitisation at the end of treatment (week 134), and remission after avoidance (week 160), as the key secondary outcome, were assessed by DBPCFC to 5000 mg in the intention-to-treat population. Safety and immunological parameters were assessed in the same population. This trial is registered on ClinicalTrials.gov, NCT03345160.

Findings Between Aug 13, 2013, and Oct 1, 2015, 146 children, with a median age of 39·3 months (IQR 30·8–44·7), were randomly assigned to receive peanut oral immunotherapy (96 participants) or placebo (50 participants). At week 134, 68 (71%, 95% CI 61–80) of 96 participants who received peanut oral immunotherapy compared with one (2%, 0·05–11) of 50 who received placebo met the primary outcome of desensitisation (risk difference [RD] 69%, 95% CI 59–79; p<0·0001). The median cumulative tolerated dose during the week 134 DBPCFC was 5005 mg (IQR 3755–5005) for peanut oral immunotherapy versus 5 mg (0–105) for placebo (p<0·0001). After avoidance, 20 (21%, 95% CI 13–30) of 96 participants receiving peanut oral immunotherapy compared with one (2%, 0·05–11) of 50 receiving placebo met remission criteria (RD 19%, 95% CI 10–28; p=0·0021). The median cumulative tolerated dose during the week 160 DBPCFC was 755 mg (IQR 0–2755) for peanut oral immunotherapy and 0 mg (0–55) for placebo (p<0·0001). A significant proportion of participants receiving peanut oral immunotherapy who passed the 5000 mg DBPCFC at week 134 could no longer tolerate 5000 mg at week 160 (p<0·001). The participant receiving placebo who was desensitised at week 134 also achieved remission at week 160. Compared with placebo, peanut oral immunotherapy decreased peanut-specific and Ara h2-specific IgE, skin prick test, and basophil activation, and increased peanut-specific and Ara h2-specific IgG4 at weeks 134 and 160. By use of multivariable regression analysis of participants receiving peanut oral immunotherapy, younger age and lower baseline peanut-specific IgE was predictive of remission. Most participants (98% with peanut oral immunotherapy *vs* 80% with placebo) had at least one oral immunotherapy dosing reaction, predominantly mild to moderate and occurring more frequently in participants receiving peanut oral immunotherapy. 35 oral immunotherapy dosing events with moderate symptoms were treated with epinephrine in 21 participants receiving peanut oral immunotherapy.

Interpretation In children with a peanut allergy, initiation of peanut oral immunotherapy before age 4 years was associated with an increase in both desensitisation and remission. Development of remission correlated with immunological biomarkers. The outcomes suggest a window of opportunity at a young age for intervention to induce remission of peanut allergy.

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See **Comment** page 336

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Research in context

Evidence before this study

We actively monitor relevant publications and do literature reviews on a regular basis to ensure the most relevant, evidence-based information was included in the study design and manuscript. Peanut oral immunotherapy has been studied predominantly in school-age children, except for two small, single-centre studies in preschool children. Findings from these trials have shown that peanut oral immunotherapy is protective against accidental ingestion. Particularly, daily peanut oral immunotherapy induces increases in the amount of peanut required to induce a reaction. Previous research has also shown that some study participants can discontinue treatment and maintain the increased reaction threshold for short periods of time (4–8 weeks). One trial in young children done without a treated control group and another done in a real-world setting showed an ability to maintain the protection and to introduce peanut into the diet after treatment was discontinued. The beneficial protective clinical changes noted in these studies were associated with immune modulation, but they were also associated with adverse events in many participants.

Added value of this study

To our knowledge, this study is the first randomised, controlled, long-term blinded study of peanut oral immunotherapy in children younger than 4 years done in a multicentre (five US academic centres) trial design. The study provides long-term clinical efficacy, safety, and novel immunological data, along with predictors of response, among young children. These findings could inform clinicians about the potential benefits and risks of peanut oral immunotherapy for these patients.

Implications of the available evidence

The IMPACT trial shows that peanut oral immunotherapy induces desensitisation in most young children treated and, in a subset of these children, induces remission, especially in the youngest children with lower peanut-specific IgE at the beginning of treatment. Although most children, from both the peanut oral immunotherapy and placebo groups, had dosing reactions during oral immunotherapy, most were mild to moderate, with epinephrine given in 21 participants for 35 peanut oral immunotherapy dosing reactions over the 134-week daily dosing period. Benefits noted in the youngest participants suggest that there is a therapeutic window of opportunity for inducing remission such that intervention at a young age with peanut oral immunotherapy might improve treatment outcomes for patients with peanut allergy.

Introduction

Peanut allergy remains an important health and economic concern, affecting about 2% of the US paediatric population.[1,2] Most children with peanut allergy remain allergic for their lifetime,[3–5] and the risk of peanut-induced anaphylaxis from accidental exposure is substantial.[6] Existing preventive strategies focus on early dietary peanut introduction to reduce the risk of developing peanut allergy.[7,8] For individuals who are peanut allergic, dietary restriction of peanut remains the mainstay for management. Despite efforts to use strict allergen avoidance, one study reported that the patient-reported, annualised allergic reaction rate among preschool children (aged 3–15 months) who have a food allergy was 0·81 (95% CI 0·76–0·85) per year,[9] highlighting the need for safe and effective therapies.

To address these concerns, diverse immunotherapeutic strategies have been investigated in clinical trials. One oral immunotherapy product has recently received US Food and Drug Administration (FDA) approval.[10] Peanut oral immunotherapy uses ingested peanut to modulate immune responses and raise the allergic reaction threshold. Trials in school-aged children and young adults have consistently shown the capacity of this therapy to induce desensitisation (defined as an increased allergic reaction threshold while on therapy) in the majority (50–70%) of participants treated, although few have tested a threshold as high as 5000 mg of peanut protein.[10–13] Investigators have sought to define the durability of reduced clinical responsiveness, initially using the term sustained unresponsiveness to describe the absence of clinical reactivity after discontinuing therapy for short periods of time (typically 4–8 weeks). In the past few years, the term remission has been used to better describe this non-responsive state after completion of immunotherapy.[14,15] Remission describes the concept of disease quiescence that might be of unknown duration compared with permanent immune tolerance, but the relationship of remission to tolerance has not been proven to date. Studies are difficult to compare due to the variations noted but, overall, they have shown a limited duration of a remission-like clinical response after peanut oral immunotherapy.[13,16–19]

Because oral immunotherapy is immunomodulatory,[20] intervening early in life, while the immune system is maturing, might be more effective. The DEVIL Trial,[18] as well as a real-world safety trial of peanut oral immunotherapy,[21] showed positive clinical outcomes in children with peanut allergy by starting oral immunotherapy between the ages of 9 and 71 months, providing proof of concept that peanut oral immunotherapy might be administered safely at young ages with a potential for enhanced effectiveness. Therefore, we designed the first randomised, blinded, placebo-controlled, multicentre trial of peanut oral immunotherapy in children younger than 48 months. In

this study, children underwent a 134-week blinded oral immunotherapy treatment period followed by a 26-week period without allergen exposure. We used oral food challenges to assess desensitisation after the 134-week treatment period and to assess remission after the 26-week no-exposure period, the longest period without allergen exposure studied to date.

Methods

Study design and participants

This multicentre, randomised, double-blind, placebo-controlled study was done at five academic medical centres in the USA by the Immune Tolerance Network. Institutional Review Boards at each site approved the protocol, which can be found online. Full description of all methods can be found in the appendix (pp 2–12). Throughout this study, peanut ingestion is defined in mg of peanut protein.

Children aged 12 months or older and younger than 48 months were screened for inclusion in the study. Inclusion criteria included the following: a clinical history of peanut allergy or avoidance without ever having eaten peanut, peanut-specific IgE levels of 5 kU_A/L or higher, a skin prick test (SPT) wheal size greater than that of saline control by 3 mm or more, and a positive reaction to a cumulative dose of 500 mg or less of peanut in a double-blind, placebo-controlled food challenge (DBPCFC). Key exclusion criteria included a history of severe anaphylaxis with hypotension to peanut, more than mild asthma or uncontrolled asthma, uncontrolled atopic dermatitis, and eosinophilic gastrointestinal disease (the full list of exclusion criteria is presented in the appendix p 2). Participants were recruited through referral clinics, multimedia advertisements, and social media. Written informed consent was obtained from the parents or guardians of the participating children.

Randomisation and masking

We used a computerised system to randomly assign participants (2:1) to peanut oral immunotherapy or placebo. A prespecified randomisation list was generated by a statistician with no other responsibilities during the trial. The study was masked to participants and study staff until all participants completed the end-of-study visits and the database was locked. An unmasked site investigational pharmacist received the randomisation code from the electronic data system for each participant and assigned study product to participants. All participants and study team members (except the investigational pharmacists) were masked to treatment group assignment. The order of peanut and placebo administration during DBPCFC was randomly assigned by an unmasked site dietitian, who also prepared the food challenge. All other study team members were masked to the challenge order. Investigational products were masked by a similar look, texture, and taste of oat flour and peanut when mixed with the vehicle (eg, applesauce or pudding), and the same volume of peanut or oat flour was provided for each product at each dosing level. No cases of accidental unmasking occurred.

Procedures

Participants were screened with standardised procedures for SPT, DBPCFCs, and immune assays, as defined in the protocol (appendix pp 3–10). Eligible participants were randomly assigned to receive peanut oral immunotherapy or placebo for daily oral dosing. We used lightly roasted, partly defatted (12% fat) peanut flour (Golden Peanut Company, Blakely, GA, USA) and oat flour placebo (Arrowhead Mills, Melville, NY, USA) for oral immunotherapy, manufactured at the University of North Carolina Good Manufacturing Practice facility under quality-controlled protocols.[22] The oral immunotherapy protocol consisted of four phases: first, an initial dose escalation (0·1 mg to 6·0 mg); second, a build-up every 2 weeks to a maximal target dose of 2000 mg peanut daily (week 0 to about week 30), with a minimum dose of 250 mg reached after three attempts of build-up required to continue to daily maintenance; third, daily maintenance (weeks 30–134); and fourth, oral immunotherapy discontinuation (weeks 134–160). Dosing was modified, per protocol, for dose-related symptoms and illness. Adherence with the study product dosing was monitored by daily diaries and drug accountability logs. During all phases of the trial, participants were instructed to avoid dietary peanut consumption.

For more on the **study protocol** see https://www.itntrialshare.org/IMPACT.url

See **Online** for appendix

DBPCFCs were done up to a cumulative dose of 500 mg of peanut at study entry and up to a cumulative dose of 5000 mg of peanut at the end of dosing (week 134) and avoidance (week 160). Per protocol, participants progressed to week 160, independent of the DBPCFC outcome at week 134. Participants who passed the DBPCFC at week 134 were categorised as desensitised, and those who passed the DBPCFC at week 160 were categorised as being in remission (defined in the protocol as tolerant but revised to remission for clarity in this manuscript). For those passing the week 160 DBPCFC, an 8000 mg open-label feeding of peanut butter was conducted to confirm tolerability.

Immune assessments were done at baseline and throughout the study (weeks 30, 82, 134, and 160). SPT was done with peanut extract, saline, and histamine (Greer Laboratories, Lenoir, NC, USA). We tested basophil activation by flow cytometry on whole blood with and without stimulation with peanut extract.[23] We measured total IgE and peanut-specific IgE and IgG4 in serum, and we measured peanut component-specific (Ara h1, h2, h3, and h6) IgE and IgG4 levels in plasma at baseline and longitudinally.

Outcomes

The primary endpoint was the proportion of participants desensitised after 134 weeks of oral immunotherapy,

defined as passing the 5000 mg peanut DBPCFC. Secondary endpoints included the proportion of participants who met remission, defined as passing the 5000 mg DBPCFC 26 weeks after oral immunotherapy discontinuation; the change in proportion of participants who passed the 5000 mg DPBCFC at weeks 134 and 160; the highest cumulative tolerated dose of peanut during DPBCFC; safety outcomes including incidence of all adverse events; rates of withdrawal from peanut oral immunotherapy or placebo; and changes in immune mechanistic markers.

The safety assessment and adverse events, including dosing reactions within 2 h of oral immunotherapy or DBPCFC dosing, were captured and entered in the electronic database. Oral immunotherapy dosing reactions were scored as mild, moderate, or severe. DBPCFC-related reactions were scored with a customised allergic reaction severity grading system.[24,25] Although symptoms associated with anaphylaxis and systemic allergic reactions were recorded, the terms anaphylaxis and systemic allergic reactions were not defined as specified variables for this study. Dosing and challenge reactions were expected, and thus they were not reported as adverse events unless they resulted in hypotension, cyanosis, oxygen saturation lower than 92%, confusion, collapse, loss of consciousness, incontinence, or required more than two epinephrine doses; occurred more than 2 h after oral immunotherapy or DBPCFC dosing; or were not expected according to the investigational plan. Adverse events related to study procedures other than oral immunotherapy or DBPCFC or not associated with study procedures were graded according to the National Cancer Institute's *Common Terminology Criteria for Adverse Events* (version 4.03) and classified according to the Medical Dictionary for Regulatory Activities (version 16.0). We used a gastrointestinal assessment questionnaire to qualitatively capture changes in symptoms (difficulty swallowing, refusal to eat, abdominal pain, or vomiting) at each study visit. If gastrointestinal symptoms were reported (appendix pp 8–9), we used a gastrointestinal questionnaire, modified for application in young children but not validated, in an attempt to further capture symptoms suggestive of eosinophilic oesophagitis.[26] These assessments were used by investigators to determine the need for further investigation and management of gastrointestinal symptoms.

For more on the **statistical analysis plan** see https://www.itntrialshare.org/IMPACT.url

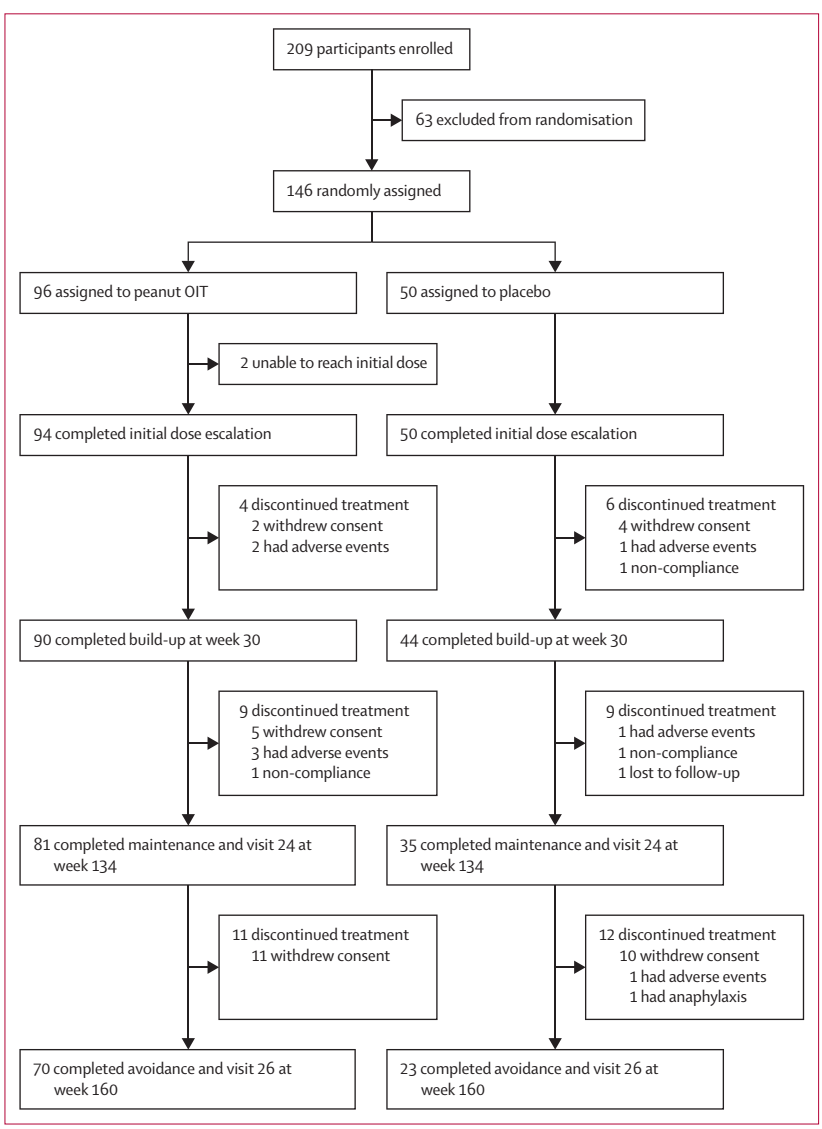


Figure 1: **Trial profile**
OIT=oral immunotherapy.

Statistical analysis

Desensitisation was imputed as a failure for participants who did not complete the DBPCFC at week 134 (with the tolerated dose defined as 0 mg), while remission was imputed as a failure for participants who did not complete the DBPCFC at week 160 (with the tolerated dose defined as 0 mg). The per-protocol sample for desensitisation and remission was defined as all intention-to-treat (ITT) participants who adhered to maintenance dosing and avoidance per protocol and had an evaluable DBPCFC at weeks 134 and 160 (ITT and per-protocol sample definitions are available in the statistical analysis plan. All assessments were done in the ITT population unless stated otherwise.

We calculated the sample size on the basis of a two-sample Pearson χ^2 test of proportions at a two-sided 0·05 level of significance, assuming a 15% dropout rate, 90% desensitisation in the peanut oral immunotherapy group, and 15% desensitisation in the placebo group. To provide 80% power for the remission endpoint but with an assumed remission rate of 40% in the peanut oral immunotherapy group and 15% in the placebo group, this required a sample size of 96 in the peanut oral immunotherapy group and 48 in the placebo group. This sample size provides greater than 99% power for the primary endpoint.

We compared categorical variables using the χ^2 test and continuous variables using the Kruskal-Wallis test. We used χ^2 and multivariable logistic regression analyses in the primary analysis of desensitisation and remission (appendix pp 11–12). Additionally, we did post-hoc analyses to identify predictors of desensitisation and remission in participants treated with peanut oral immunotherapy (appendix pp 11–12), with additional analyses done by categorising participants in three age categories: 12·0–23·9 months, 24·0–35·9 months, and 36·0–47·8 months. We did analyses of mechanistic data in the per-protocol sample. Analyses were done with SAS, version 9.4, and R, version 3.2.4. The statistical analysis plan and datasets are available through TrialShare.

The study was done under an FDA investigational new drug application and monitored by a National Institutes of Health (NIH)–National Institute of Allergy and Infectious Diseases (NIAID) Data and Safety Monitoring Board. The trial is registered on ClinicalTrials.gov, NCT03345160.

Role of the funding source

The funder of the study was involved with study design, data collection, data analysis, data interpretation, and writing of the manuscript.

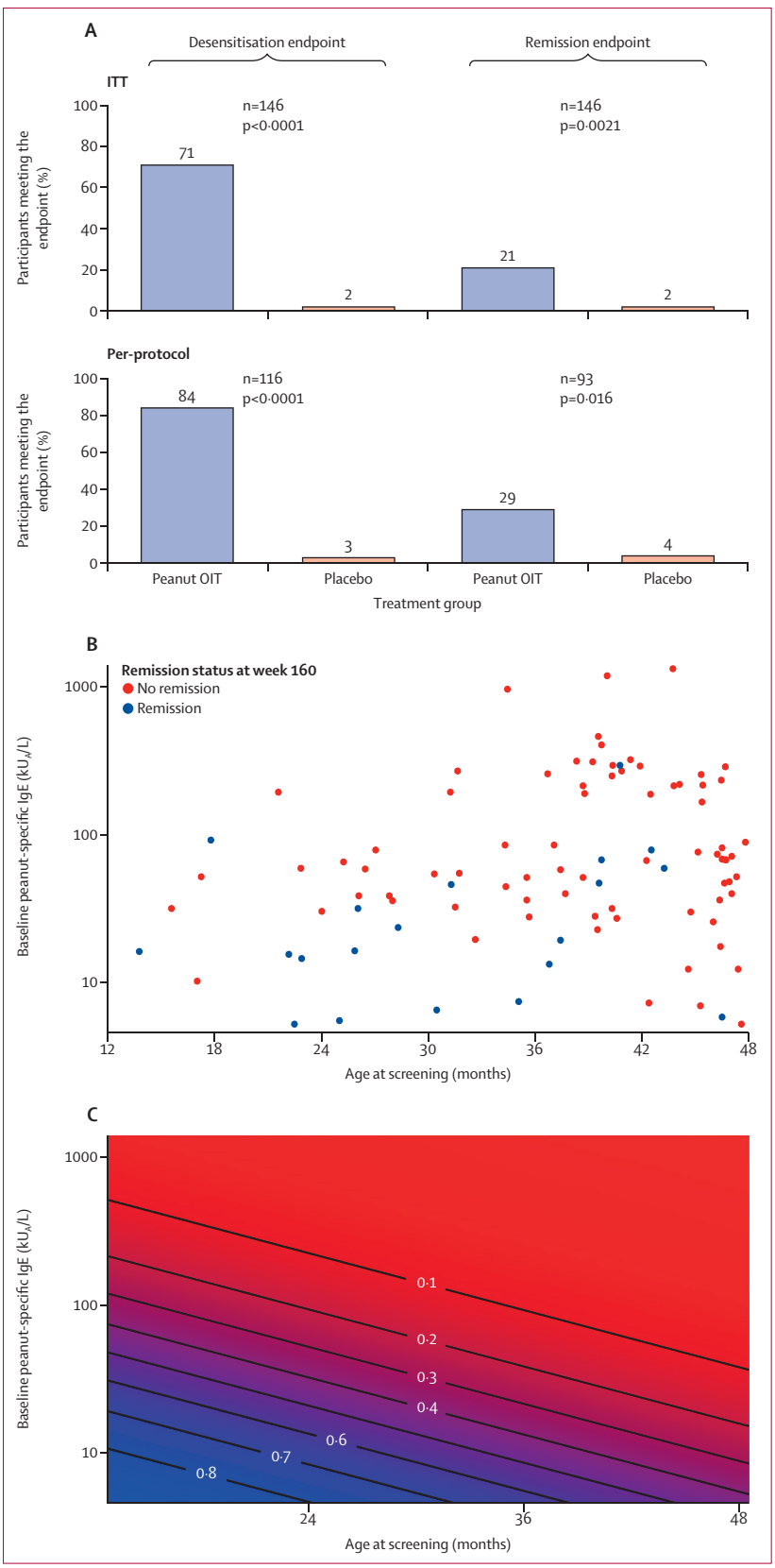
Results

Between Aug 13, 2013, and Oct 1, 2015, 209 participants were enrolled in the study. Of these, 146 were randomly assigned to peanut oral immunotherapy (96 participants) or placebo (50 participants; figure 1). Participants had a median age of 39·3 months (IQR 30·8–44·7), were predominantly White (95 [65%] of 146), and 99 (68%) were boys and 47 (32%) were girls (table 1). Post-hoc analyses grouped participants by age at screening in three groups: 12·0–23·9 months (17 [12%] participants), 24·0–35·9 months (40 [27%] participants), and 36·0–47·9 months (89 [61%] participants; table 1). History of peanut allergy symptoms was reported in 91 (62%) participants, whereas 55 (38%) reported no exposure to peanut; differences were noted between these groups in median cumulative tolerated dose at baseline DBPCFC of 25 mg for those with allergy history versus 75 mg for those with no peanut exposure ($p<0·0001$). Overall, two (1%) participants had a reported history of peanut-associated anaphylaxis, but because neither of the two children had a history of severe anaphylaxis, both were included. Of participants randomly assigned, 70 (73%) of 96 who received peanut oral immunotherapy and 23 (46%) of 50 who received placebo completed the week 160 assessment, representing the per-protocol sample. Among participants who did not complete the trial, 15 (58%) of 26 who received peanut oral immunotherapy and 15 (56%) of 27 who received placebo discontinued before the week 134 DBPCFC, and 11 (42%) who received peanut oral immunotherapy and 12 (44%) who received placebo discontinued during avoidance (weeks 134–160; figure 1, appendix pp 17–19). Adjusting for treatment group, we compared baseline characteristics in ITT participants who discontinued before completing the week 160 DBPCFC (53 [36%]

	Peanut OIT (n=96)	Placebo (n=50)	Total (n=146)
Site			
Arkansas	15 (16%)	7 (14%)	22 (15%)
Johns Hopkins	21 (22%)	12 (24%)	33 (23%)
Mount Sinai	21 (22%)	11 (22%)	32 (22%)
Stanford	21 (22%)	10 (20%)	31 (21%)
University of North Carolina	18 (19%)	10 (20%)	28 (19%)
Age at screening, months			
Median (IQR)	39·5 (31·3–45·0)	38·7 (30·1–44·5)	39·3 (30·8–44·7)
Range	(13·77–47·80)	(13·80–47·70)	(13·77–47·80)
Age group			
12·0–23·9 months	10 (10%)	7 (14%)	17 (12%)
24·0–35·9 months	26 (27%)	14 (28%)	40 (27%)
36·0–47·9 months	60 (63%)	29 (58%)	89 (61%)
Sex			
Female	30 (31%)	17 (34%)	47 (32%)
Male	66 (69%)	33 (66%)	99 (68%)
Race			
Asian	15 (16%)	3 (6%)	18 (12%)
Black	1 (1%)	5 (10%)	6 (4%)
Mixed race	16 (17%)	11 (22%)	27 (18%)
White	64 (67%)	31 (62%)	95 (65%)
Atopic dermatitis history			
Yes	81 (84%)	41 (82%)	122 (84%)
No	..	..	..
Allergic rhinitis history			
Yes	28 (29%)	14 (28%)	42 (29%)
No	..	..	..
Asthma history			
Yes	22 (23%)	7 (14%)	29 (20%)
No	..	..	..
History of peanut allergy symptoms	62 (65%)	29 (58%)	91 (62%)
Never exposed to peanut	34 (35%)	21 (42%)	55 (38%)
History of anaphylaxis to peanut			
Yes	0 (0%)	2 (4%)	2 (1%)
No	..	..	..
History of other food allergies			
Yes	50 (52%)	33 (66%)	83 (57%)
No	..	..	..
Peanut-specific IgE at baseline, kUA/L	54·6 (28·0–192·5)	44·9 (25·2–236·0)	53·1 (27·3–195·0)
Calculated wheal on skin prick test to peanut at baseline, mm	14·0 (12·0–18·0)	15·8 (10·0–20·0)	15·0 (11·5–19·0)
Cumulative tolerated dose of masked DBPCFC to peanut at baseline, mg	75·0 (5·0–175·0)	25·0 (25·0–75·0)	25·0 (5·0–75·0)

Data are n (%) or median (IQR), unless otherwise specified. This table includes all participants in the intention-to-treat sample. DBPCFC=double-blind, placebo-controlled food challenge. OIT=oral immunotherapy.

Table 1: **Demographics and baseline characteristics**



of 146) with those of ITT participants who completed the week 160 DBPCFC (93 [64%]). The percentage of participants who discontinued differed across sites (36% in Arkansas, 49% in Johns Hopkins University, 41% in Mount Sinai, 6% in Stanford, and 50% in the University of North Carolina; p=0·015), and race (three [17%] of 18 were Asian, two [33%] of six were Black, six [22%] of 27 were mixed race, and 42 [44%] of 95 were White; p=0·039), and participants who discontinued before completing the week 160 DBPCFC had a higher SPT to peanut at screening (17·0 mm, SD 6·1) than that of participants who completed the week 160 DBPCFC (14·5 mm, SD 5·3; p=0·012).

Adherence to oral immunotherapy was high (appendix p 20). The median percentage of doses missed was 1·9% (IQR 0·9–3·8) for peanut oral immunotherapy and 2·0% (0·9–3·6) for placebo during build-up and 2·7% (1·1–4·4) for peanut oral immunotherapy and 1·4% (0·6–3·3) for placebo during maintenance. Among participants who completed the initial dose escalation, the number who missed three or more consecutive doses (predominantly due to concurrent illness) was nine (10%) of 94 for peanut oral immunotherapy and four (8%) of 50 for placebo during build-up and 20 (22%) of 90 for peanut oral immunotherapy and five (11%) of 44 for placebo during maintenance. Using the per-protocol sample, 59 (73%) of 81 participants with peanut oral immunotherapy and 28 (80%) of 35 with placebo reached the 2000 mg maintenance dose; the median highest dose received between week 30 and week 134 was 2000 mg (IQR 2000–2000) in both groups.

Assessment of desensitisation at week 134 showed that 68 (71%, 95% CI 61–80) of 96 participants who received peanut oral immunotherapy passed the 5000 mg DPBCFC compared with one (2%, 0·05–11) of 50 who received placebo (risk difference [RD] 69%, 95% CI 59–79; p<0·0001; figure 2A). Similar estimates were found after adjustment for site and age and baseline peanut-specific IgE (appendix pp 11–12). Compared with participants receiving peanut oral immunotherapy, a higher percentage of those receiving placebo dropped out of the study before the week 134 DBPCFC and were imputed as failures (figure 1), potentially artificially altering the relative desensitisation rates. However, we still detected a significant difference in desensitisation

Figure 2: **Primary and secondary outcomes**
(A) Data are shown for the primary endpoint (desensitisation) at week 134 and secondary endpoint (remission) at week 160, measured by DBPCFC for the ITT sample and per-protocol sample, comparing peanut oral immunotherapy and placebo groups. (B) Data are shown for the peanut oral immunotherapy group; area under the curve=0·8072. (C) A contour plot of predicted probability of remission from the logistic regression model plotted against baseline peanut-specific IgE and age at screening; values in blue show probability of remission higher than 50%, whereas values in red show probability of remission lower than 50%. DBPCFC=double-blind, placebo-controlled food challenge. ITT=intention-to-treat. OIT=oral immunotherapy.

between the two groups when considering only participants in each groups who completed the DBPCFC at week 134. In the per-protocol sample, 68 (84%, 95% CI 74–91) of 81 participants receiving peanut oral immunotherapy passed the 5000 mg DBPCFC compared with one (3%, 0·05–15) of 35 receiving placebo (p<0·0001). The median cumulative tolerated dose during the week 134 DBPCFC was 5005 mg (IQR 3755–5005) for peanut oral immunotherapy versus 5 mg (0–105) for placebo (p<0·0001); in the per-protocol sample, these values were 5005 mg (IQR 5005–5005) for peanut oral immunotherapy and 55 mg (5–255) for placebo (p<0·0001).

At the week 160 remission assessment (26 weeks after treatment discontinuation and peanut avoidance), 20 (21%, 95% CI 13–30) of 96 participants receiving peanut oral immunotherapy passed the 5000 mg DBPCFC compared with one (2%, 0·05–11) of 50 receiving placebo (RD 19%, 95% CI 10–28; p=0·0021; figure 2A). Similar estimates were found after adjustment for site, age, and baseline peanut-specific IgE (appendix pp 11–12). Again, compared with participants receiving peanut oral immunotherapy, a higher percentage of those treated with placebo dropped out of the study before the week 160 DBPCFC (figure 1). We detected a significant difference in remission between the two groups in the per-protocol sample: 20 (29%, 95% CI 18–41) of 70 participants receiving peanut oral immunotherapy versus one (4%, 0·11–22) of 23 receiving placebo were considered in remission (p=0·016). The median cumulative tolerated dose during the week 160 DBPCFC was 755 mg (IQR 0–2755) for peanut oral immunotherapy (appendix p 13) and 0 mg (0–55) for placebo (p<0·0001) in the ITT sample, and 1755 mg (755–5005) for peanut oral immunotherapy and 55 mg (5–255) for placebo in the per-protocol sample (p<0·0001). In the per-protocol sample, 40 (57%) of 70 participants receiving peanut oral immunotherapy compared with two (9%) of 23 receiving placebo could safely consume at least 1755 mg of peanut (appendix p 22). A significant proportion of participants receiving peanut oral immunotherapy who passed the 5000 mg DBPCFC at week 134 could no longer tolerate 5000 mg at week 160 (p<0·001). The participant receiving placebo who was desensitised at week 134 also achieved remission at week 160. During the 8000 mg open-label feeding, 17 (85%) of 20 participants receiving peanut oral immunotherapy and one (100%) of one receiving placebo passed, one receiving peanut oral immunotherapy failed the open feeding, and two participants also receiving peanut oral immunotherapy had undetermined status because the full dose was not eaten, although no symptoms were reported.

We measured immune parameters longitudinally and compared them between treatment groups (appendix pp 14–15) and peanut oral immunotherapy outcome groups (figure 3). Compared with placebo, peanut oral immunotherapy significantly decreased peanut-specific IgE, peanut component-specific IgE, peanut-specific IgE to total IgE ratio, and skin and basophil reactivity to peanut while increasing peanut-specific IgG4 and peanut component-specific IgG4 (appendix pp 14–15). In the peanut oral immunotherapy group, we observed reductions in peanut-specific IgE and SPT from baseline to week 30 (both p<0·0001). When comparing immune parameters in participants receiving peanut oral immunotherapy by treatment outcome (desensitisation and remission *vs* desensitisation and no remission *vs* no desensitisation and no remission), baseline differences demarcated the different outcome groups and these differences persisted throughout the study. Specifically, the desensitisation and remission group had the lowest baseline levels of peanut-specific IgE and Ara h2-specific IgE and the highest peanut-specific IgG4 to IgE ratio (figure 3). Compared with the peanut oral immunotherapy group, we observed significant increases in peanut-specific IgE, SPT, and basophil activation (figure 3, appendix p 14), as well as increases in peanut component-specific IgE (appendix p 15), as early as week 30 in the placebo group.

We assessed baseline predictors of desensitisation and remission using a predefined, multivariable logistic regression analysis applied to participants receiving peanut oral immunotherapy (appendix pp 11–12). On the basis of this analysis, a lower peanut component-specific IgE to Ara h6 ratio predicted desensitisation (odds ratio 0·35 per 10-fold increase, 95% CI 0·12–0·99; p=0·048) whereas a lower baseline peanut-specific IgE (0·12 per ten-fold increase, 0·03–0·46; p=0·0017) and younger age at screening (0·93 per month increase, 0·88–0·99; p=0·022) predicted remission (figure 2B). The effects of age at screening and baseline peanut-specific IgE on predicting the likelihood of remission within this study population are shown in figure 2C. Although the overall rate of remission in participants receiving peanut oral immunotherapy was 21% in the ITT sample and 29% in the per-protocol sample, remission was highly enriched in younger participants with low baseline peanut-specific IgE. In those receiving peanut oral immunotherapy, five (71%) of seven aged 12·0–23·9 months, seven (35%) of 20 aged 24·0–35·9 months, and eight (19%) of 43 aged 36·0–47·9 months attained remission (p=0·013, appendix p 23). The single participant receiving placebo to develop remission was one of three aged 12·0–23·9 months.

We assessed safety and adverse events throughout the 160-week masked study period. Dosing reactions during oral immunotherapy (table 2) occurred in all study phases, with 94 (98%) of 96 participants receiving peanut oral immunotherapy and 40 (80%) of 50 receiving placebo having at least one dosing reaction. The most frequently reported dose-related symptoms were skin, gastrointestinal, and respiratory disorders (table 2). Most reactions were mild or moderate and occurred more frequently with peanut oral immunotherapy (93 [97%] of 96 mild and 40 [42%] of 96 moderate) than

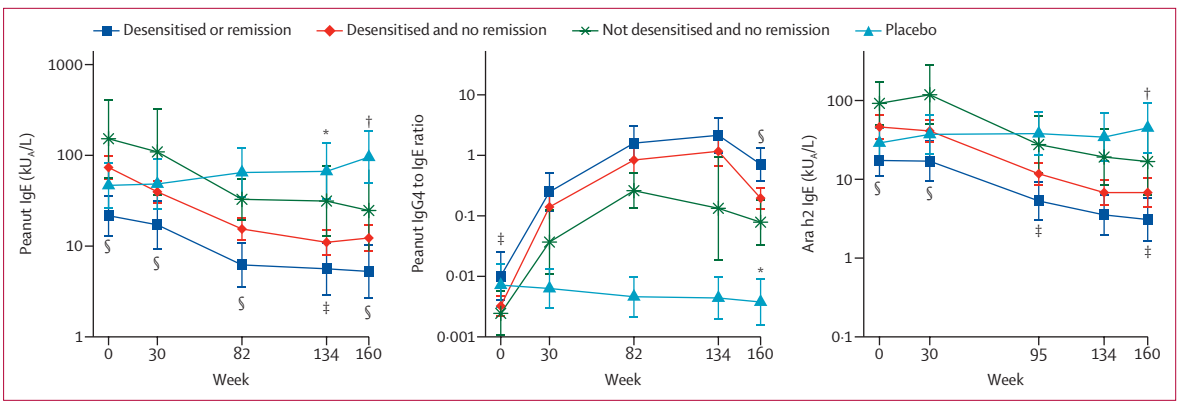


Figure 3: **Immunological changes over the course of the study**

Data are shown for the sample of per-protocol participants who were evaluable while on treatment, during the avoidance phase, and by DBPCFC after avoidance. Data are shown for timepoints including before treatment, week 30, week 82 or 95, week 134, and week 160 of the study. Participants receiving peanut oral immunotherapy were categorised as desensitised or remission, desensitised and no remission, and not desensitised and no remission on the basis of the results of the week 134 and week 160 DBPCFC. The panels show levels of peanut-specific IgE (A), peanut-specific IgG4 to IgE ratios (B), and IgE to peanut component-specific Ara h2 (C) for the peanut oral immunotherapy outcome groups and placebo. The number of participants per group is the following: 23 in placebo, ten in not desensitised and no remission, 40 in desensitised and no remission (39 in C), and 19 in desensitised or remission (18 in C). Data are shown as means with 95% CIs. DBPCFC=double-blind, placebo-controlled food challenge. *p<0·05 and †p<0·01 change from pre-treatment in the placebo group. ‡p<0·05 and §p<0·01 for desensitised and remission versus both desensitised and no remission and not desensitised and no remission.

with placebo (40 [80%] of 50 mild and 4 [8%] of 50 moderate). Oral immunotherapy-related dosing reactions were most frequent overall during build-up, followed by maintenance and initial dose escalation (table 2); however, moderate and severe dosing reactions were most frequent during maintenance dosing (appendix p 24). Reactions with severe symptoms occurred only with at-home peanut oral immunotherapy dosing in five participants, two (2%) during build-up (one facial swelling and one laryngeal or throat symptoms of stridor, hoarseness, or dysphagia) and three (3%) during maintenance (two laryngeal or throat symptoms of stridor, hoarseness, or dysphagia and one dyspnoea or wheezing).

Dose-related epinephrine administration occurred in 21 (22%) of 96 participants receiving peanut oral immunotherapy during 35 events, including one (3%) in-clinic build-up event and 34 (97%) home-dosing events. 11 (32%) of 34 home-dosing events occurred during build-up in six (29%) of 21 participants, and 23 (68%) home-dosing events occurred during maintenance in 17 (81%) participants (table 3, appendix pp 16, 25). Grade 1 (mild) symptoms were reported in one (3%) of 35 epinephrine administrations, grade 2 (moderate) symptoms in 31 (89%) administrations, and grade 3 (severe) symptoms in three (9%) administrations. Two epinephrine doses were administered to two participants during 1600 mg maintenance dosing for symptoms of laryngeal oedema (stridor, hoarseness, or dysphagia), cough, and wheezing. One of these two participants had a previous grade 3 reaction at 25 mg requiring one epinephrine dose. Among participants receiving peanut oral immunotherapy, we observed a higher proportion of at-home epinephrine administrations during maintenance compared with build-up dosing, as well as more epinephrine administrations with oral immunotherapy doses higher than 600 mg. Seven of 21 participants receiving peanut oral immunotherapy requiring epinephrine administration withdrew from the study. Among those receiving peanut oral immunotherapy who had at least one dose-related epinephrine administration, we observed site-specific differences in the frequency of administration (nine [41%] of 22 at Mount Sinai, four [40%] of ten at Arkansas, four [24%] of 17 at Stanford, two [11%] of 19 at University of North Carolina, and two [7%] of 28 at Johns Hopkins; p=0·022). In the ITT sample, we detected no significant effect of age at screening on at least one administration of epinephrine related to oral immunotherapy or any significant associations between at least one administration of epinephrine related to oral immunotherapy dosing and desensitisation or remission among participants receiving peanut oral immunotherapy. Epinephrine administration occurred during DBPCFC with a similar distribution between treatment groups, except for higher epinephrine use in the placebo group during the week 134 DBPCFC (appendix p 26). Symptoms occurring with oral immunotherapy or DBPCFC dosing and meeting adverse event criteria are presented in the appendix (pp 27–28). Serious adverse events occurred in nine participants; only one was study related during week 134 DBPCFC in a participant receiving placebo (appendix p 29). Three (3%) of 96 participants receiving peanut oral immunotherapy were referred for evaluation and endoscopy for eosinophilic oesophagitis due to persistent symptoms; two were documented to resolve after oral immunotherapy discontinuation while one had persistent disease.

	IDE phase		Build-up phase		Maintenance phase		Overall	
	Peanut OIT (n=96)	Placebo (n=50)	Peanut OIT (n=94)	Placebo (n=50)	Peanut OIT (n=90)	Placebo (n=44)	Peanut OIT (n=96)	Placebo (n=50)
At least one dosing reaction*†‡§	32 (33%)	3 (6%)	86 (91%)	38 (76%)	78 (87%)	11 (25%)	94 (98%)	40 (80%)
At least one dosing reaction requiring epinephrine‡§	0	0	8 (9%)	0	15 (17%)	0	21 (22%)	0
At least one mild dosing reaction*†‡§	30 (31%)	3 (6%)	86 (91%)	38 (76%)	78 (87%)	11 (25%)	93 (97%)	40 (80%)
At least one moderate dosing reaction†‡§	3 (3%)	0	18 (19%)	3 (6%)	30 (33%)	1 (2%)	40 (42%)	4 (8%)
At least one severe dosing reaction	0	0	2 (2%)	0	3 (3%)	0	5 (5%)	0
System organ class and dosing reaction								
Skin and subcutaneous tissue disorders*†‡§	21 (22%)	3 (6%)	71 (76%)	27 (54%)	55 (61%)	6 (14%)	84 (88%)	29 (58%)
Eczema	0	0	12 (13%)	4 (8%)	1 (1%)	0	12 (13%)	4 (8%)
Erythema, flushing, or pruritus ‡§	11 (11%)	3 (6%)	43 (46%)	18 (36%)	36 (40%)	3 (7%)	60 (63%)	20 (40%)
Facial swelling	0	0	2 (2%)	0	1 (1%)	0	3 (3%)	0
Rash	0	0	18 (19%)	7 (14%)	9 (10%)	2 (5%)	22 (23%)	8 (16%)
Urticaria*†‡§	13 (14%)	1 (2%)	53 (56%)	15 (30%)	44 (49%)	3 (7%)	71 (74%)	17 (34%)
Gastrointestinal disorders*†‡§	14 (15%)	0	64 (68%)	24 (48%)	54 (60%)	9 (20%)	75 (78%)	27 (54%)
Abdominal pain*†‡§	14 (15%)	0	46 (49%)	13 (26%)	32 (36%)	4 (9%)	56 (58%)	16 (32%)
Constipation	0	0	1 (1%)	0	0	0	1 (1%)	0
Diarrhoea	0	0	7 (7%)	8 (16%)	2 (2%)	1 (2%)	9 (9%)	8 (16%)
Foreign body	0	0	1 (1%)	0	0	0	1 (1%)	0
Lower gastrointestinal symptoms	0	0	3 (3%)	1 (2%)	1 (1%)	0	3 (3%)	1 (2%)
Oral symptoms†‡§	0	0	16 (17%)	1 (2%)	16 (18%)	0	26 (27%)	1 (2%)
Upper gastrointestinal symptoms†‡§	3 (3%)	0	41 (44%)	12 (24%)	39 (43%)	7 (16%)	53 (55%)	15 (30%)
Respiratory, thoracic, and mediastinal disorders†‡§	8 (8%)	1 (2%)	55 (59%)	20 (40%)	51 (57%)	6 (14%)	69 (72%)	22 (44%)
Cough‡§	6 (6%)	1 (2%)	37 (39%)	15 (30%)	38 (42%)	3 (7%)	57 (59%)	17 (34%)
Dyspnoea	0	0	1 (1%)	0	1 (1%)	0	2 (2%)	0
Hiccups	0	0	1 (1%)	0	0	0	1 (1%)	0
Hyperventilation	0	0	0	0	1 (1%)	0	1 (1%)	0
Laryngeal or throat symptoms§	0	0	6 (6%)	0	6 (7%)	0	12 (13%)	0
Mouth or throat discomfort †‡§	1 (1%)	0	17 (18%)	0	25 (28%)	0	33 (34%)	0
Rhinitis or nasal symptoms‡	1 (1%)	0	33 (35%)	12 (24%)	23 (26%)	4 (9%)	40 (42%)	14 (28%)
Wheezing‡§	1 (1%)	0	8 (9%)	2 (4%)	18 (20%)	1 (2%)	22 (23%)	2 (4%)
Eye disorders	0	0	11 (12%)	2 (4%)	6 (7%)	1 (2%)	15 (16%)	3 (6%)
Eye pruritus, lacrimation, pain, or erythema	0	0	9 (10%)	2 (4%)	6 (7%)	1 (2%)	15 (16%)	3 (6%)
Ocular hyperaemia	0	0	4 (4%)	1 (2%)	2 (2%)	0	6 (6%)	1 (2%)
Ear and labyrinth disorders	0	0	2 (2%)	1 (2%)	4 (4%)	0	5 (5%)	1 (2%)
Ear pain or pruritus	0	0	2 (2%)	1 (2%)	4 (4%)	0	5 (5%)	1 (2%)
Psychiatric disorders	1 (1%)	0	2 (2%)	1 (2%)	2 (2%)	0	5 (5%)	1 (2%)
Change in affect or lethargy	1 (1%)	0	2 (2%)	1 (2%)	2 (2%)	0	5 (5%)	1 (2%)
General disorders and administration site conditions	0	0	2 (2%)	0	2 (2%)	0	4 (4%)	0
Chest pain	0	0	2 (2%)	0	2 (2%)	0	4 (4%)	0
Nervous system disorders	0	0	2 (2%)	1 (2%)	1 (1%)	0	3 (3%)	1 (2%)
Headache	0	0	2 (2%)	1 (2%)	1 (1%)	0	3 (3%)	1 (2%)
Paraesthesia	0	0	0	0	1 (1%)	0	1 (1%)	0
Musculoskeletal and connective tissue disorders	0	0	2 (2%)	0	0	0	2 (2%)	0
Pain in extremity	0	0	2 (2%)	0	0	0	2 (2%)	0

Data are n (%). This table includes all participants in the safety sample for IDE, build-up, and maintenance. IDE=initial dose escalation. OIT=oral immunotherapy. *Significant difference between the treatment groups in the IDE phase with use of Fisher's exact test. †Significant difference between the treatment groups in the build-up phase with use of Fisher's exact test. ‡Significant difference between the treatment groups in the maintenance phase with use of Fisher's exact test. §Significant difference between the treatment groups overall with use of Fisher's exact test.

Table 2: **Dosing reactions during OIT**

Discussion

To our knowledge, this study is the first to evaluate efficacy and safety of peanut oral immunotherapy in children younger than 48 months with peanut allergy, with novel trial design features including a 134-week masked study period and a 26-week duration of

	Peanut OIT		Placebo	
	Events	Participants (n=96)	Events	Participants (n=50)
At least one epinephrine dose given*	109	61 (64%)	58	35 (70%)
Associated with study product dosing†	35 (32%)	21 (34%)	0	0
In-clinic dosing‡	1 (3%)	1 (5%)	0	0
Dosing during initial dose escalation§	0	0	0	0
Dosing during build-up§	1 (100%)	1 (100%)	0	0
Out-of-clinic dosing‡	34 (97%)	21 (100%)	0	0
Dosing during build-up¶	11 (32%)	6 (29%)	0	0
Dosing during maintenance¶	23 (68%)	17 (81%)	0	0
Associated with a study procedure†	97 (89%)	57 (93%)	54 (93%)	34 (97%)
Overall oral food challenge DBPCFC‖	62 (64%)	48 (84%)	54 (100%)	34 (100%)
Screen (baseline 500 mg DBPCFC)**	36 (58%)	36 (75%)	23 (43%)	23 (68%)
Desensitisation (week 134 5000 mg DBPCFC)**	4 (6%)	4 (8%)	21 (39%)	21 (62%)
Tolerance (week 160 5000 mg DBPCFC)**	22 (35%)	22 (46%)	10 (19%)	10 (29%)
Not associated with study product dosing or a study procedure†	12 (11%)	11 (18%)	4 (7%)	3 (9%)
Accidental exposure to peanut††	4 (33%)	4 (36%)	1 (25%)	1 (33%)
Other allergen exposure††	8 (67%)	8 (73%)	3 (75%)	2 (67%)

Data are n (%). This table includes all participants in the intention-to-treat sample. Participants could be counted in more than one row if the participant had multiple types of event. DBPCFC=double-blind, placebo-controlled food challenge. OIT=oral immunotherapy. *The denominators used to calculate percentages are the following: the number of participants randomly assigned (*), either the number of events or participants with at least one administration of epinephrine (†), either the number of events or participants with at least one administration of epinephrine associated with study product dosing (‡), either the number of events or participants with at least one administration of epinephrine associated with in-clinic dosing (§), either the number of events or participants with at least one administration of epinephrine associated with out-of-clinic dosing (¶), either the number of events or participants with at least one administration of epinephrine associated with a study procedure (‖), either the number of events or participants with at least one administration of epinephrine associated with an oral food challenge DBPCFC (**), or either the number of events or participants with at least one administration of epinephrine not associated with study product dosing or a study procedure (††).

Table 3: **Summary of epinephrine administration**

treatment discontinuation with peanut avoidance. Our findings showed that 134 weeks of peanut oral immunotherapy with a daily maintenance dose of 2000 mg induced desensitisation to 5000 mg peanut (about 16 peanuts) in a majority (71%) of children treated with peanut oral immunotherapy compared with 2% of children receiving placebo. The most important observation from this study was the induction of protocol-defined remission in one in five young participants highly allergic to peanut after 134 weeks of peanut oral immunotherapy followed by 26 weeks of peanut avoidance. Significantly more children receiving peanut oral immunotherapy (21%) showed protocol-defined remission than those receiving placebo (2%). Importantly, 29% of children receiving peanut oral immunotherapy who completed the study per protocol achieved the remission outcome. We also observed an inverse relationship between age at screening and remission in participants receiving peanut oral immunotherapy during post-hoc analysis by age group, with 71% of those younger than 24 months, 35% of those aged 24·0–35·9 months, and 19% of those aged 36·0–47·9 months achieving remission.

Although findings from a natural history study done in children aged 4 years or older showed that about 20% might develop natural tolerance without treatment,[27] most of the children in that study were not challenged at diagnosis and many who developed tolerance had a much lower peanut-specific IgE than participants included in the IMPACT trial. Our study enrolled children with a low peanut reaction threshold (median cumulative tolerated dose at study entry of 25 mg or about one-12th of a peanut). After treatment, 20 (29%) of 70 per-protocol participants receiving peanut oral immunotherapy defined as achieving remission were able to consume 5000 mg (about 16 peanuts) whereas an additional 20 participants of those defined as not achieving remission could safely consume 1755–3755 mg (about 6–12 peanuts, a child-size serving portion) 26 weeks after treatment discontinuation. Therefore, a total of 40 (57%) of 70 children could safely consume 1755–3755 mg peanuts, indicating a substantial increase in peanut tolerability in participants who received peanut oral immunotherapy compared with study entry tolerability of 25 mg. This increase in peanut tolerability was not seen in participants who received placebo (only 4% consumed 1755–3755 mg of peanut). Treatment-induced remission in participants who received peanut oral immunotherapy was predicted by lower pre-treatment peanut-specific IgE and younger age. The remission data, when combined with the observation that increases in IgE and reactivity to peanut were observed as early as week 30 in the placebo group compared with the peanut oral immunotherapy group, suggest a window of opportunity for more successful interventions at an early age in the course of peanut allergy.

To date, the only peanut oral immunotherapy studies that have assessed treatment outcomes by DPBCFC after a long period of treatment cessation are the current IMPACT trial and the POISED study. The POISED Study, using a different trial design in a population with a median age of 11 years (IQR 8–15), showed that after 104 weeks of peanut oral immunotherapy, 20% of participants had sustained unresponsiveness to a cumulative dose of 4000 mg peanut and 32% to 900 mg peanut, assessed by DBPCFC after a 26-week treatment discontinuation.[19] In IMPACT's age group, which is younger than that in POISED, 21% of participants who received peanut oral immunotherapy were able to consume 5000 mg peanut and 57% of those in the per-protocol sample consumed at least 1755 mg 26 weeks after treatment discontinuation. A post-hoc analysis in IMPACT suggested an inverse relationship between age and remission outcome, with 71% of remission cases noted in the youngest subgroup of those receiving peanut oral immunotherapy. It might be that the enhanced window for remission closes very early.

The 19% rate of remission in the oldest participants in IMPACT, aged 36·0–47·9 months, is similar to the overall rate of sustained unresponsiveness in POISED (20%). Although IMPACT did not stratify randomisation of treatment groups by age, these findings on age effects might help guide the ideal design for future studies, including recommendations for including children younger than 24 months and following peanut oral immunotherapy in older children or adults with continued exposure through regular or intermittent peanut dosing or dietary introduction.

In addition to meaningful efficacy findings, the IMPACT trial contributes important, long-term safety data about peanut oral immunotherapy in young children. As in the DEVIL trial,[18] a 2019 real-world study of peanut oral immunotherapy in Canadian preschool children showed that two-thirds of them developed at least one allergic reaction during dosing, 4% received epinephrine, and 10% dropped from the study.[21] The IMPACT trial studied a well defined, randomised, controlled young population during 160 weeks of masked treatment and assessment. Overall, 98% of participants who received peanut oral immunotherapy in IMPACT had at least one dose-related reaction during treatment but no dose-related serious adverse events. Most oral immunotherapy dosing reactions were mild to moderate in severity, occurred during at-home dosing, and were managed without epinephrine administration or study withdrawal. Epinephrine administration during oral immunotherapy dosing was more frequent during at-home maintenance than at-home build-up dosing and was associated with doses greater than 600 mg. Compared with the PALISADE trial, epinephrine was administered more for dose-related symptoms among participants receiving peanut oral immunotherapy in IMPACT (52 [14%] of 372 in PALISADE *vs* 21 [22%] of 92 in IMPACT), as well as during maintenance.[10,13] Gastrointestinal symptoms were common and similar to those reported in previous peanut oral immunotherapy studies.[10,18,21] Biopsy-confirmed eosinophilic oesophagitis was noted in 3% of participants who received peanut oral immunotherapy in IMPACT. Importantly, the Aceves assessment tool used in IMPACT to monitor for symptoms of eosinophilic oesophagitis was not validated and was modified for use in young children. This, in combination with the gastrointestinal assessment questionnaire used, might have led to underreporting of the incidence of eosinophilic oesophagitis-related symptoms and diagnoses. Clearly, development of age-appropriate, validated assessment tools will shed light on this issue for the future.

Outcome groups were clearly distinguishable at baseline for children treated with peanut oral immunotherapy. Of special interest was the steady rise in peanut-specific and peanut component-specific IgE over time in the placebo group, indicating increasing sensitisation in young children with untreated peanut allergy and a potential closing of an important therapeutic window. By contrast, peanut oral immunotherapy-induced immunomodulation was characterised by a decline in peanut-specific IgE occurring by the end of build-up at week 30, earlier in the treatment course compared with oral immunotherapy studies involving older children.[10,18,28,29]

This study has important limitations. Although we included children aged 12 to younger than 48 months, only 12% of children randomly assigned were younger than 24 months. The small number of children younger than 24 months resulted in larger CIs for the probability of remission in this subgroup. There was a high dropout rate during the required 26-week avoidance period, with a substantial differential between treatment groups that might have affected the outcome. Additionally, 27% of participants who received peanut oral immunotherapy and 20% of those who received placebo did not reach the maximal maintenance dose of 2000 mg, a factor that could have affected study outcomes.

A key secondary outcome of the IMPACT trial, assessed by DBPCFC after 26 weeks of allergen avoidance, is best described by the term remission.[14,15] Recently, several terms have been used to describe possible surrogates for tolerance; however, there are currently no biomarkers that separate sustained unresponsiveness from remission from tolerance.[14,15] Although desensitisation is a goal that offers substantial relief to patients and their families, attaining true tolerance would eliminate the need for regular allergen exposure and the fear of severe reactions, making it the ultimate goal of treatment. Future studies should focus on longer term follow-up, and thus should consider new designs that optimise the preferred options of families and participants for allergen avoidance or continued allergen consumption. The IMPACT design of a 26-week period of peanut allergen avoidance after treatment was designed in 2013; at that time, this was felt to be the best way to determine if these young children were tolerant. However, after the food challenge, the IMPACT study did not attempt to re-introduce peanut into the diet or to follow up the participants after the challenge, thus the study was unable to assess whether permanent tolerance was reached. Additionally, our definition of remission for this study—the ability to consume 5000 mg peanut—does not acknowledge the positive treatment effect noted in a large subset of those not achieving remission, since the majority of children consumed at least 1755–3755 mg peanut after treatment discontinuation, a level that has clinical relevance for young children.

In summary, the IMPACT Trial shows that peanut oral immunotherapy resulted in desensitisation in most children and remission in a substantial proportion of children compared with placebo, and that remission was predicted by younger age and lower baseline peanut-specific IgE. Further exploration of peanut oral immunotherapy in young children is warranted, focusing

on age-defined benefits and risks for a potential valuable therapeutic window of opportunity for early intervention to induce remission.

Contributors

SMJ, AWB, MP, MK, JL-P, SS, DL, RY, and JJ designed the study. SMJ, EHK, KCN, AN-W, RAW, HAS, AMS, SC, JW, RDP, SBS, and AWB did the study. JJ, KS, DCB, HC, and MLS analysed data. MK, DL, and TQ did the immune assays. SMJ, EHK, KCN, AN-W, RAW, HAS, AMS, SC, JW, RDP, SBS, MK, JJ, KS, DCB, HC, JL-P, RY, DL, TQ, DW, MLS, SS, MP, LMW, and AWB critically reviewed the manuscript. SMJ, EHK, KS, DCB, HC, DL, TQ, DW, MLS, SS, MP, LMW, and AWB wrote the manuscript. DCB and HC verified the study data. The corresponding author had full access to all the data in the study and has shared, final responsibility with the funder for the decision to submit for publication.

Declaration of interests

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Data sharing

The trial dataset will be available to appropriate academic parties on request from the corresponding author, in accordance with the data sharing policies of ITN, with input from the investigator group where applicable, subject to submission of a suitable study protocol and analysis plan, on publication of all initial trial results.

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We attest to the accuracy and completeness of the reported data and for the fidelity of the report, the posted protocol, and the ClinicalTrials.gov posting. The study was designed by the investigators of ITN, with Stacie M Jones and A Wesley Burks as study chairs. The data were gathered by the investigators and analysed by biostatisticians at Rho. The manuscript was written collaboratively by Jones and Burks and reviewed and edited by the authors. The decision and approval to publish was made by the authors, as investigators in ITN, Rho, and the NIAID leadership.

References

1 Bilaver LA, Chadha AS, Doshi P, O'Dwyer L, Gupta RS. Economic burden of food allergy: a systematic review. *Ann Allergy Asthma Immunol* 2019; **122:** 373–80.

2 Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011; **128:** e9–17.

3 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:** 183–89.

4 Gupta RS, Lau CH, Sita EE, Smith B, Greenhawt MJ. Factors associated with reported food allergy tolerance among US children. *Ann Allergy Asthma Immunol* 2013; **111:** 194–98.

5 Nitsche C, Westerlaken-van Ginkel CD, Kollen BJ, Sprikkelman AB, Koppelman GH, Dubois AEJ. Eliciting dose is associated with tolerance development in peanut and cow's milk allergic children. *Clin Transl Allergy* 2019; **9:** 58.

6 Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001; **107:** 191–93.

7 Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. *J Allergy Clin Immunol* 2017; **139:** 29–44.

8 Du Toit G, Sayre PH, Roberts G, et al. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med* 2016; **374:** 1435–43.

9 Fleischer DM, Perry TT, Atkins D, et al. Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. *Pediatrics* 2012; **130:** e25–32.

10 Vickery BP, Vereda A, Casale TB, et al. AR101 oral immunotherapy for peanut allergy. *N Engl J Med* 2018; **379:** 1991–2001.

11 Scurlock AM, Jones SM. Advances in the approach to the patient with food allergy. *J Allergy Clin Immunol* 2018; **141:** 2002–14.

12 Vickery BP, Ebisawa M, Shreffler WG, Wood RA. Current and future treatment of peanut allergy. *J Allergy Clin Immunol Pract* 2019; **7:** 357–65.

13 Wood RA. Food allergen immunotherapy: current status and prospects for the future. *J Allergy Clin Immunol* 2016; **137:** 973–82.

14 Burks AW, Sampson HA, Plaut M, Lack G, Akdis CA. Treatment for food allergy. *J Allergy Clin Immunol* 2018; **141:** 1–9.

15 Sampson HA, O'Mahony L, Burks AW, Plaut M, Lack G, Akdis CA. Mechanisms of food allergy. *J Allergy Clin Immunol* 2018; **141:** 11–19.

16 Jones SM, Burks AW, Keet C, et al. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. *J Allergy Clin Immunol* 2016; **137:** 1117–27.

17 Vickery BP, Scurlock AM, Kulis M, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol* 2014; **133:** 468–75.

18 Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol* 2017; **139:** 173–81.

19 Chinthrajah RS, Purington N, Andorf S, et al. Sustained outcomes in oral immunotherapy for peanut allergy (POISED study): a large, randomised, double-blind, placebo-controlled, phase 2 study. *Lancet* 2019; **394:** 1437–49.

20 Kulis MD, Patil SU, Wambre E, Vickery BP. Immune mechanisms of oral immunotherapy. *J Allergy Clin Immunol* 2018; **141:** 491–98.

21 Soller L, Abrams EM, Carr S, et al. First real-world safety analysis of preschool peanut oral immunotherapy. *J Allergy Clin Immunol Pract* 2019; **7:** 2759–67.

22 Berglund JP, Szczepanski N, Penumarti A, et al. Preparation and analysis of peanut flour used in oral immunotherapy clinical trials. *J Allergy Clin Immunol Pract* 2017; **5:** 1098–104.

23 Santos AF, Du Toit G, O'Rourke C, et al. Biomarkers of severity and threshold of allergic reactions during oral peanut challenges. *J Allergy Clin Immunol* 2020; **146:** 344–55.

24 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:** 391–97.

25 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.

26 Aceves SS, Newbury RO, Dohil MA, Bastian JF, Dohil R. A symptom scoring tool for identifying pediatric patients with eosinophilic esophagitis and correlating symptoms with inflammation. *Ann Allergy Asthma Immunol* 2009; **103:** 401–06.

27 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.

28 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:** 476–85.

29 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.

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