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# Efficacy and Safety of Oral Immunotherapy in a Randomized, Placebo-Controlled Study of 1–3-Year Old Children with Peanut Allergy: Findings from the Immune Tolerance Network IMPACT Trial

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Contributors

SMJ, AWB, MP, MK, JLP, SS, DL, RY and JJ designed the study. SMJ, EHK, KCN, ANW, RAW, HAS, AMS, SC, JW, RDP, SBS, and AWB did the study. JJ, KS, DCB, HC, and MLS analyzed data. MK, DL, and TQ did the immune assays. SMJ, EHK, KCN, ANW, RAW, HAS, AMS, SC, JW, RDP, SBS, MK, JJ, KS, DCB, HC, JLP, 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.



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 the Immune Tolerance Network, 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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## SUMMARY

**Background.—**For young, peanut-allergic children, dietary avoidance is the current standard of care. We evaluated whether peanut oral immunotherapy (PnOIT) can induce desensitization (an increased allergic reaction threshold while on therapy) and/or remission (a state of nonresponsiveness following discontinuation of immunotherapy) in this population.

**Methods.—**A randomized, double-blind, placebo-controlled study was conducted in 5 US centers among children (ages 12–<48 months), reactive to ≤500 mg peanut protein during double-blind, placebo-controlled food challenge (DBPCFC). Participants were computer-randomized using a 2:1 allocation ratio to receive PnOIT or placebo for 134 weeks (2000 mg peanut protein/day) followed by 26 weeks of avoidance with participants and study staff/investigators blinded to treatment arm assignment. Desensitization at the end of treatment (week 134), as the primary outcome, and remission after avoidance (week 160), as the key secondary outcome, were assessed by DBPCFC to 5000 mg. Safety and immunological parameters were assessed.

**Findings.—**Of 146 children, with a median age of 39.3 (IQR:30.8,44.7) months, randomized from August 2013 to October 2015, 96 were assigned and analyzed in the PnOIT-treatment arm and 50 in the placebo-treatment arm. At week 134, 68/96 (71%; 95% CI:61%,80%) PnOIT-treated compared to 1/50 (2%; 95% CI:0.05%,11%) placebo-treated participants met the primary outcome of desensitization (risk difference (RD)=69%; 95% CI:59%,79%; p<0.0001). The median cumulative tolerated dose (CTD) during the week 134 DBPCFC was 5005 mg (Interquartile Range (IQR):3755,5005) for PnOIT-treated versus 5 mg (IQR:0,105) for placebo-treated (p<0.0001). After avoidance, 20/96 (21%; 95% CI:13%,30%) on PnOIT compared to 1/50 (2%; 95% CI:0.05%,11%) on placebo met remission criteria (RD:19%; 95% CI:10%,28%; p=0.0021). The median CTD during the week 160 DBPCFC was 755 mg (IQR:0,2755) for the PnOIT-treated and 0 mg (IQR:0,55) for placebo-treated (p<0.0001). A significant proportion of PnOIT participants who passed the 5000 mg DBPCFC at week 134 could no longer tolerate 5000 mg at week 160 (p<0.001). The placebo participant who was desensitized at week 134 also achieved remission at week 160. Compared to placebo treatment, peanut- and Ara h2-specific-IgE, skin prick test, and basophil activation decreased, while peanut- and Ara h2-specific-IgG4 increased in PnOIT-treated participants at weeks 134 and 160. Using multivariable regression analysis of PnOIT-treated participants, younger age and lower baseline peanut-specific IgE was predictive of remission. Most participants (98% PnOIT vs. 80% placebo) experienced at least 1 OIT dosing reaction, predominantly mild-moderate and occurring more frequently in PnOIT-treated participants; 35 OIT dosing events with moderate symptoms were treated with epinephrine in 21 PnOIT participants.

**Interpretation.—**In peanut-allergic children, initiation of PnOIT before age 4 years is associated with an increase in both desensitization and remission. Development of remission correlates with immunologic biomarkers. The outcomes suggest a window of opportunity at a young age for intervention to induce remission.

**Funding.—**National Institute of Allergy and Infectious Disease, Immune Tolerance Network

**Trial registration:** The trial is registered on clinicaltrials.gov (NCT03345160).

## INTRODUCTION

Peanut allergy remains an important health and economic concern, affecting ~2% of the US pediatric population.[1,2] The vast majority of peanut-allergic children remain allergic for their lifetime,[3–5] and the risk of peanut-induced anaphylaxis from accidental exposures is significant.[6] Current strategies focus on early dietary peanut introduction to reduce the risk of developing peanut allergy.[7,8] For those who are peanut-allergic, dietary restriction of peanut remains the mainstay for management. Despite efforts to employ strict allergen avoidance, one study reported that the patient-reported, annualized allergic reaction rate among food-allergic, preschool children as 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 (OIT) product has recently received US Food and Drug Administration (FDA) approval.[10–14] Peanut OIT (PnOIT) employs ingested peanut to modulate immune responses and raise the allergic reaction threshold. PnOIT trials, in school-age children and young adults, have consistently demonstrated the capacity to induce "desensitization" (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 peanut protein.[10–12,14] Investigators have sought to define the durability of reduced clinical responsiveness initially employing the term "sustained unresponsiveness," to describe a lack of clinical reactivity after discontinuing therapy for short periods of time (typically 4–8 weeks). Recently, the term "remission" has been used to better describe this nonresponsive state after completion of immunotherapy.[15,16] Remission describes the concept of disease quiescence that may be of unknown duration compared to "permanent" immune tolerance but the relationship of remission to tolerance has not been proven to date. Studies are difficult to compare due to variations noted above, but overall, they have shown a limited duration of a remission-like clinical response after PnOIT.[14,17–20]

Because OIT is immunomodulatory,[21] intervening early in life, while the immune system is maturing, might prove more effective. The DEVIL Trial, as well as a real-world safety trial of PnOIT, showed positive clinical outcomes in children with peanut allergy by starting OIT between 9 and 71 months of age, providing proof-of-concept that PnOIT may be administered safely at younger ages with a potential for enhanced effectiveness.[19,22] Therefore, we designed the first randomized, blinded, placebo-controlled, multicenter trial of PnOIT in children under age 48 months. In this study, we utilized oral food challenges after a 134-week blinded OIT treatment period to assess "desensitization" followed by a 26-week period without allergen exposure, the longest time period without allergen exposure studied to date, to assess "remission."

# METHODS

## Study design

This multicenter, randomized, double-blind, placebo-controlled study was conducted at 5 academic medical centers in the United States by the Immune Tolerance Network. Institutional Review Boards at each site approved the protocol. Access to the full study protocol can be found at https://www.itntrialshare.org/IMPACT.url. The study was conducted under US FDA investigational new drug application and monitored by an NIH-NIAID Data and Safety Monitoring Board. The trial is registered on clinicaltrials.gov (NCT03345160). Full description of all methods can be found in the Appendix. Of note, throughout the study, peanut ingestion is defined in milligrams of peanut protein.

## Participants

Children, aged 12–<48 months were screened. Inclusion criteria included: 1) clinical history of peanut allergy or avoidance without ever having eaten peanut; 2) peanut-specific IgE ≥5 $kU_A/L$; 3) skin prick test (SPT) wheal size ≥3 mm more than saline control; and 4) positive reaction to a cumulative dose of ≤500 mg peanut on double-blind, placebo-controlled food challenge (DBPCFC). Key exclusion criteria included history of severe anaphylaxis with hypotension to peanut, more than mild and/or uncontrolled asthma, uncontrolled atopic dermatitis, and eosinophilic gastrointestinal (GI) disease (see Appendix for full exclusion criteria). Participants were recruited through referral clinics, multi-media advertisements, and social media. Written informed consent was obtained from parents/guardians.

## Randomization and masking

Using a computerized system, participants were randomized 2:1 to PnOIT (n=96) or placebo (n=50). A pre-specified randomization list was generated by a statistician with no other responsibilities during the trial. The study was blinded to participants and study staff until all participants completed end of study visits and the database was locked. Lightly roasted, partially defatted (12% fat) peanut flour (Golden Peanut Company, Blakely, GA) and oat flour placebo (Arrowhead Mills, Inc., Melville, NY) were used for OIT and manufactured at the University of North Carolina Good Manufacturing Practice facility under quality-controlled protocols.[23] An unblinded site investigational pharmacist received the randomization code from the electronic data system for each participant and assigned study product to participants. All participants and study team members (except investigational pharmacists) were blinded to treatment arm assignment. The order of peanut and placebo administration during DBPCFC was randomly assigned by an unblinded site dietitian. All other study team members were blinded to challenge order. Investigational products were masked by a similar look, texture and taste of oat flour and peanut when mixed with vehicle (e.g., applesauce, pudding), and the same volume of peanut or oat flour was provided for each product at each dosing level. No cases of accidental unblinding occurred.

## Procedures

Participants were screened using standardized procedures for SPT, DBPCFCs, and immune assays, as defined in the protocol (see Appendix). Eligible participants were randomly assigned to receive PnOIT versus placebo for daily oral dosing. The OIT protocol consisted of 4 phases: 1) initial dose escalation (IDE: 0.1 mg to 6 mg), 2) build-up every 2 weeks to a maximal target dose of 2000 mg peanut daily (weeks 0–~30) with a minimum dose of 250 mg reached after 3 attempts of build-up required to continue to daily maintenance, 3) daily maintenance (weeks 30–134), and 4) OIT discontinuation (weeks 134–160). Dosing was modified, per protocol, for dose-related symptoms and illness. Adherence with 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.

DBPCFCs were conducted up to a cumulative dose of 500-mg peanut at study entry and up to a cumulative dose of 5000-mg peanut at the end of dosing (week 134) and avoidance (week 160). Per protocol, participants progressed to week 160, independent of the week 134 DBPCFC outcome. Those who passed the DBPCFC at week 134 were categorized as “desensitized” and at week 160 as “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 conducted at baseline and throughout the study. SPT was performed with peanut extract, saline, and histamine (Greer Laboratories, Inc., Lenoir, NC). Basophil activation was tested by flow cytometry on whole blood with and without stimulation with peanut extract.[24] Total IgE and peanut-specific IgE and IgG4 were measured in serum, and peanut component-specific (Ara h1, 2, 3, 6) IgE and IgG4 levels were measured in plasma at baseline and longitudinally.

## Outcomes

The primary endpoint was the proportion of participants desensitized after 134 weeks of OIT, defined as passing the 5000-mg peanut DBPCFC. Secondary endpoints included: 1) the proportion of participants who met remission, defined as passing the 5000-mg DBPCFC 26 weeks after OIT discontinuation, 2) the change in proportion of participants who passed the 5000-mg DPBCFC at weeks 134 and 160, 3) highest cumulative tolerated dose of peanut during DPBCFC, 4) safety outcomes including incidence of all adverse events, 5) rates of withdrawal from PnOIT or placebo, and 6) changes in immune mechanistic markers.

Safety assessment and adverse events, including dosing reactions within 2 hours of OIT or DBPCFC dosing, were captured and entered in the electronic database. OIT dosing reactions were scored as mild, moderate or severe. DBPCFC-related reactions were scored using a customized allergic reaction severity grading system.[25,26] While 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, thus they were not reported as adverse events unless they: 1) resulted in hypotension, cyanosis, oxygen saturation <92%, confusion, collapse,

loss of consciousness, incontinence, or required >2 epinephrine doses; 2) occurred >2 hours after OIT or DBPCFC dosing; or 3) were not expected according to the investigational plan. Adverse events related to study procedures other than OIT 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 (MedDRA, version 16.0). A GI assessment questionnaire was used to qualitatively capture change in symptoms (difficulty swallowing, refusal to eat, abdominal pain, vomiting) at each study visit. If GI symptoms were reported (see Appendix), a GI questionnaire, modified for application in young children but not validated, was used in an attempt to further capture symptoms suggestive of eosinophilic esophagitis (EoE).[27] These assessments were used by investigators to determine need for further investigation and management of GI symptoms.

## Statistical analysis

Desensitization was imputed as a failure for participants who did not complete the DBPCFC at week 134 (tolerated dose defined as 0 mg) while remission was imputed as a failure for participants who did not complete the DBPCFC at week 160 (tolerated dose defined as 0 mg). The per-protocol (PP) sample for desensitization and remission were 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 (for ITT and PP sample definitions, see Statistical Analysis Plan, https://www.itntrialshare.org/IMPACT.url).

Sample size was calculated based on a two-sample Pearson Chi-squared test of proportions at a two-sided 0.05 level of significance assuming a 15% drop out rate, 90% desensitization in the PnOIT arm and 15% desensitization in the placebo arm. To provide 80% power for the remission endpoint but with an assumed remission rate of 40% and 15% in the PnOIT and placebo arms, respectively, required a sample size of 96 in the PnOIT arm and 48 in the placebo arm. This sample size provides greater than 99% power for the primary endpoint.

Categorical and continuous variables were compared using Chi-squared and Kruskal-Wallis tests, respectively. Chi-squared and multivariable logistic regression analyses were used in the primary analysis of desensitization and remission (see Appendix). Post-hoc analyses to identify predictors of desensitization and remission in PnOIT-treated participants were also performed (see Appendix), with additional analyses performed by categorizing into 3 categories 12–23.9 months, 24–35.9 months, and 36–47.8 months. Analyses of mechanistic data were performed in the PP sample. Analyses were performed using SAS, version 9.4 (SAS Institute) and R version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria). The statistical analysis plan and datasets are available through TrialShare (https://www.itntrialshare.org/IMPACT.url).

## Role of funding source

The funder of the study (NIH/NIAID, via the Immune Tolerance Network) was involved with study design, data collection, data analysis, data interpretation, and manuscript writing. 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.

## RESULTS

209 participants were enrolled from August 2013 to October 2015; 146 were randomized (96 PnOIT, 50 placebo) (Figure 1) with a median age of 39.3 (IQR:30.8;44.7) months; predominantly male (99/146=68%) and White/Caucasian (95/146=65%) (Table 1). Post-hoc analyses grouped participants by age at screening as 12–23.9 months (17/146=12%), 24–35.9 months (40/146=27%), 36–47.9 months (89/146=61%) (Table 1). History of peanut allergy symptoms was reported in 91/146 (62%) while 55/146 (38%) reported no exposure to peanut; differences were noted between these groups in median cumulative tolerated dose at baseline DBPCFC of 25 mg versus 75 mg, respectively ($p<0.0001$). Overall, 2/146 (1%) reported a history of peanut-associated anaphylaxis, but since neither of the two children had a history of severe anaphylaxis, both were included. At baseline, median peanut-specific IgE was 53.1 $kU_A/L$ (IQR:27.3,195.0), SPT wheal size was 15 mm (IQR:11.5,19.0), and DBPCFC cumulative tolerated dose was 25 mg (IQR:5.0,75.0). Of those randomized, 70/96 (73%) PnOIT and 23/50 (46%) placebo participants completed the week 160 assessment, representing the PP sample. Among participants who did not complete the trial, 15/26 (58%) PnOIT and 15/27 (56%) placebo discontinued before the week 134 DBPCFC, and 11/26 (42%) PnOIT and 12/27 (44%) placebo discontinued during avoidance (weeks 134–160) (Figure 1; Tables S1–S2). Adjusting for treatment arm, a comparison of baseline characteristics in ITT participants who discontinued prior to completing the week 160 DBPCFC (53/146=36%) versus ITT participants who completed the week 160 DBPCFC (93/146=64%) showed that the percentage of participants who discontinued differed across sites (Arkansas=36%/JHU= 49%/Mount Sinai=41%/Stanford=6%/UNC=50% of participants discontinued; p=0.02), race (Asian=17%/Black or African American=33%/ Mixed Race=22%/White or Caucasian=44% of participants discontinued; p=0.04), and participants who discontinued prior to completing the week 160 DBPCFC had a higher SPT to peanut at screening compared to those participants who completed the week 160 DBPCFC (17.0 (SD=6.1) versus 14.5 (SD=5.3); p=0.01).

Adherence to OIT was high (Table S3). The median percentage of doses missed was 1.9 (IQR:0.9,3.8) and 2 (IQR:0.9,3.6) during build-up and 2.7 (IQR:1.1,4.4) and 1.4 (IQR:0.6,3.3) during maintenance for PnOIT and placebo arms, respectively. Among those that completed the IDE, the number of participants that missed ≥3 consecutive doses (predominantly due to concurrent illness) was 9/94 (10%) and 4/50 (8%) during build-up and 20/90 (22%) and 5/44 (11%) during maintenance for PnOIT and placebo arms, respectively. Using the PP sample, 59/81 (73%) PnOIT and 28/35 (80%) placebo participants 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 arms.

Assessment of desensitization at week 134 showed that 68/96 (71%; 95% CI:61%,80%) of PnOIT-treated participants passed the 5000-mg DPBCFC compared to 1/50 (2%; 95% CI:0.05%,11%) placebo-treated participants (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 (see Appendix). A higher percentage of placebo-treated participants dropped out of the study prior to the week 134 DBPCFC and were imputed as failures (15/50=30% placebo, 15/96=16% PnOIT), potentially artificially altering the

relative desensitization rates. However, a statistically significant difference in desensitization between the two arms was still detected when considering only those in each arm who completed the DBPCFC at week 134. In the PP sample, 68/81 (84%; 95% CI:74%,91%) PnOIT-treated participants passed the 5000-mg DBPCFC compared to 1/35 (3%; 95% CI:0.05%,15%) placebo-treated participants ($p<0.0001$). The median cumulative tolerated dose during the week 134 DBPCFC was 5005 mg (IQR:3755,5005) for PnOIT-treated versus 5 mg (IQR:0,105) for placebo-treated ($p<0.0001$) and, in the PP sample, 5005 mg (IQR:5005,5005) and 55 mg (IQR:5,255), respectively ($p<0.0001$).

At the week 160 remission assessment (26 weeks after treatment discontinuation and peanut avoidance), 20/96 (21%; 95% CI:13%,30%) of PnOIT-treated participants passed the 5000-mg DBPCFC compared to 1/50 (2%; 95% CI:0.05%,11%) placebo-treated participants (RD:19%; 95% CI:10%,28%; $p=0.0021$) (Figure 2A). Similar estimates were found after adjustment for site and age and baseline peanut-specific IgE (see Appendix). Again, a higher percentage of placebo-treated participants had dropped out of the study prior to the week 160 DBPCFC (27/50=54% placebo, 26/96=27% PnOIT). A statistically significant difference in remission between the two arms was detected in the PP sample; 20/70 (29%; 95% CI:18%,41%) PnOIT-treated and 1/23 (4%; 95% CI:0.11%,22%) placebo-treated participants were considered in remission ($p=0.0159$). The median cumulative tolerated dose during the week 160 DBPCFC was 755 mg (IQR:0,2755) for the PnOIT-treated (Figure S1) and 0 mg (IQR:0,55) for placebo-treated ($p<0.0001$) in the ITT sample and 1755 mg (IQR:755,5005) and 55 mg (IQR:5,255) in the PP sample, respectively ($p<0.0001$). Importantly, 40/70 (57%) PnOIT-treated compared to 2/23 (9%) placebo-treated, PP participants could safely consume at least 1755 mg peanut (Table S4). A significant proportion of PnOIT participants who passed the 5000 mg DBPCFC at week 134 could no longer tolerate 5000 mg at week 160 ($p<0.001$). The placebo participant who was desensitized at week 134 also achieved remission at week 160. During the 8000-mg open-label feeding, 17/20 (85%) PnOIT-treated and 1/1 (100%) placebo-treated passed; 1 PnOIT-treated participant failed the open feeding and 2 were undetermined as the full dose was not eaten though no symptoms were reported.

Immune parameters were measured longitudinally and compared between treatment arms (Figures S2, S3) and PnOIT outcome groups (Figure 3). Compared to placebo, PnOIT significantly decreased peanut-specific IgE, peanut component-specific IgE, peanut-specific IgE/total IgE and skin and basophil reactivity to peanut while increasing peanut-specific IgG4, and peanut component-specific IgG4 (Figures S2, S3). In the PnOIT arm, reductions in peanut-specific IgE and SPT from baseline were observed by week 30 (both $p<0.0001$). Notably, when comparing immune parameters in PnOIT-treated participants by treatment outcome (desensitized/remission vs. desensitized/no remission vs. not desensitized/no remission), baseline differences demarcated the different outcome groups and these differences persisted throughout the study. Specifically, the desensitized/remission group had the lowest baseline levels of peanut-specific IgE and Ara h 2-specific IgE and the highest peanut-specific IgG4/IgE ratio (Figure 3). Importantly, compared to the PnOIT arm, we observed significant increases in peanut-specific IgE, SPT and basophil activation (Figure 3, Figure S2), as well as increases in peanut component-specific IgE (Figure S3), as early as week 30, in the placebo arm.

Baseline predictors of desensitization and remission were assessed using a pre-defined, multivariable logistic regression analysis applied to PnOIT-treated participants (see Appendix). Based on the analysis, lower peanut component-specific IgE to Ara h 6 predicted desensitization (OR=0.35 per 10-fold increase; 95% CI:0.12,0.99; p=0.048) while lower baseline peanut-specific IgE (OR=0.12 per 10 fold increase; 95% CI:0.03,0.46; p=0.0017) and younger age at screening (OR=0.93 per month increase; 95% CI: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 demonstrated in Figure 2C. While the overall rate of remission in PnOIT-treated participants was 21% in the ITT and 29% in the PP sample, remission was highly enriched in younger participants with low baseline peanut-specific IgE. In PnOIT-treated participants, 5/7 (71%) aged 12–23.9 months, 7/20 (35%) aged 24–35.9 months, and 8/43 (19%) aged 36–47.9 months attained remission (Table S5; p=0.013). The single placebo-treated participant to develop remission was one of three aged 12–23.9 months.

Safety and adverse events were assessed throughout the 160-week blinded study period. Dosing reactions during OIT (Table 2) occurred in all study phases with 98% PnOIT and 80% placebo participants having at least one dosing reaction. The most frequently reported dose-related symptoms were (PnOIT versus placebo, respectively): 1) skin 88% versus 58%; 2) gastrointestinal 78% versus 54%; and 3) respiratory 72% versus 44%. Most reactions were mild-moderate and occurred more frequently in PnOIT (97% mild, 42% moderate) than placebo (80% mild, 8% moderate) participants. OIT-related dosing reactions were most frequent overall during build-up followed by maintenance then IDE (Table 2), but moderate and severe dosing reactions were most frequent during maintenance dosing (Table S6). Reactions with severe symptoms occurred only with at-home PnOIT dosing in five participants, two (2%) participants during build-up (n=1, facial swelling; n=1, laryngeal/throat symptoms of stridor/hoarseness/dysphagia) and in three (3%) during maintenance (n=2, laryngeal/throat symptoms of stridor/hoarseness/dysphagia; n=1, dyspnea/wheezing).

Dose-related epinephrine administration occurred in 21/96 (22%) PnOIT participants during 35 events including 1/35 (3%) in-clinic build-up event and 34/35 (97%) home-dosing events. Eleven of 34 (32%) home-dosing events occurred during build-up in 6/21 (29%) participants and 23/34 (68%) home-dosing events occurred during maintenance in 17/21 (81%) participants (Table 3, Figure S4, Table S7). Grade 1 (mild) symptoms were reported in 1/35 (3%) epinephrine administrations, Grade 2 (moderate) symptoms in 31/35 (89%) epinephrine administrations, and Grade 3 (severe) symptoms in 3/35 (9%) epinephrine administrations. Two epinephrine doses were administered for symptoms of laryngeal edema (stridor/hoarseness/dysphagia), cough and wheezing occurring in two participants during 1600 mg maintenance dosing. One of the two participants requiring two epinephrine doses had a previous Grade 3 reaction at 25 mg requiring one epinephrine dose. Among PnOIT-treated participants, there was a higher proportion of at-home epinephrine administrations during maintenance compared to build-up dosing and also more epinephrine administration with OIT doses >600 mg. Seven of 21 PnOIT participants requiring epinephrine administration withdrew from the study. Amongst PnOIT participants who had at least one dose-related epinephrine administration, there were site-specific differences in the frequency of administration (Mount Sinai 9/22=41%, Arkansas 4/10=40%, Stanford

4/17=24%, UNC 2/19=11%, Johns Hopkins 2/28=7%; p=0.022). In the ITT sample, there was no significant effect of age at screening on at least one administration of epinephrine related to OIT nor were there any significant associations between at least one administration of epinephrine related to OIT dosing and desensitization or remission among PnOIT participants. Epinephrine administration occurred during DBPCFC with a similar distribution between treatment arms, except for higher epinephrine use in placebo-treated participants during the week 134 DBPCFC (Table S8). Symptoms occurring with OIT or DBPCFC dosing and meeting adverse event criteria are presented in Table S9. Serious adverse events occurred in 9 participants; only 1 was study-related during week 134 DBPCFC in a placebo-treated participant (Table S10). Three of 96 (3%) PnOIT-treated participants were referred for evaluation and endoscopy for EoE due to persistent symptoms; two were documented to resolve after OIT discontinuation while one had persistent disease.

## DISCUSSION

This study is the first to evaluate efficacy and safety of PnOIT in peanut-allergic children less than age 48 months, with novel trial design features including a 134-week blinded study period and a 26-week duration of treatment discontinuation with peanut avoidance. Findings demonstrated that 134 weeks of PnOIT with a daily maintenance dose of 2000 mg induced desensitization to 5000 mg peanut (~16 peanuts) in a majority (71%) of PnOIT-treated children when compared to 2% of placebo-treated children. The most important observation from this study is the induction of protocol-defined remission in 1 out of 5 young, highly peanut-allergic participants after 134 weeks of PnOIT followed by 26 weeks of peanut avoidance. Significantly more PnOIT-treated children (21%) demonstrated protocol-defined remission compared to placebo-treated children (2%). Importantly, 29% of PnOIT-treated children who completed the study per-protocol achieved the remission outcome. An inverse relationship between age at screening and remission was also observed in PnOIT participants during post-hoc analysis by age group, with 71% of those aged <24 months, 35% of those aged 24–35.9 months and 19% of those aged 36–47.9 months achieving remission.

Although findings from a natural history study conducted in children ≥4 years of age demonstrate that ~20% may develop natural tolerance without treatment,[28] most of the children in that study were not challenged at diagnosis and many that resolved 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 ~one-twelfth peanut). After treatment, 29% of PP PnOIT-treated participants defined as achieving remission were able to consume 5000 mg (~16 peanuts) while an additional 20 participants of those defined as not achieving remission could safely consume 1755–3755 mg (~6–12 peanuts, a child-size serving portion) 26 weeks after treatment discontinuation. Thus, a total of 40/70 (57%) of children could safely consume 1755–3755 mg peanuts, indicating a substantial increase in peanut tolerability in PnOIT-treated participants when compared to study entry tolerability of 25 mg (~1/12$^{th}$ peanut). This increase in peanut tolerability was not seen in placebo-treated participants (only 4% consumed 1755–3755 mg). PnOIT-induced remission in the PnOIT-treated participants was predicted by lower pretreatment peanut-specific IgE and younger age. The remission data,

when combined with the observation that in the placebo arm compared to the PnOIT arm, as early as week 30, there were increases in IgE and reactivity to peanut, suggest a “window of opportunity” for more successful intervention at an early age in the course of peanut allergy.

To date, the only PnOIT studies that have assessed treatment outcomes by DPBCFC after prolonged 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 (IQR:8,15) years, demonstrated that following 104 weeks of PnOIT, 20% of participants had sustained unresponsiveness to a cumulative dose of 4000 mg peanut and 32% to 900 mg peanut as assessed by DBPCFC after a 26-week treatment discontinuation.[20] In IMPACT’s age group, which is younger than the group in POISED, 21% of PnOIT treated participants were able to consume 5000 mg peanut and 40/70 (57%) in the PP sample consumed at least 1755 mg (equivalent to a child-size serving portion) 26 weeks after treatment discontinuation. Interestingly, post-hoc analysis in IMPACT suggested an inverse relationship between age and remission outcome with 71% remission noted in the youngest, PnOIT-treated subgroup. It may be that the enhanced window for remission closes very early. The 19% rate of remission in the oldest IMPACT participants, aged 36–47.9 months is similar to the overall rate of sustained unresponsiveness in POISED (20%). Although IMPACT did not stratify randomization of treatment arms by age, these findings on age effects may help guide the ideal design for future studies, including recommendations for including children under age 24 months and following PnOIT in older children/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 PnOIT in young children. As in the DEVIL Trial,[19] a recent real-world, study of PnOIT in Canadian preschool children showed that two-thirds developed at least 1 allergic reaction during dosing, 4% received epinephrine, and 10% dropped from the study.[22] The IMPACT Trial studied a well-defined, randomized, controlled, young population over 160 weeks of blinded treatment and assessment. Overall, 98% of PnOIT-treated participants in IMPACT experienced at least one dose-related reaction during treatment but no dose-related serious adverse events. Most OIT dosing reactions were mild-moderate in severity, occurred during at-home dosing and were managed without epinephrine administration or study withdrawal. Epinephrine administration during OIT dosing was more frequent during at-home maintenance compared to at-home build-up dosing and was associated with doses greater than 600 mg. Compared to the PALISADE trial, epinephrine was administered more for dose-related symptoms among PnOIT-treated participants in IMPACT (PALISADE=52/372, 14% vs. IMPACT=21/92, 22%) as well as during maintenance.[10,14] Gastrointestinal symptoms were common and similar to those reported in prior PnOIT studies.[10,19,22] Biopsy-confirmed EoE was noted in 3% of PnOIT-treated participants in IMPACT. Importantly, the Aceves assessment tool used in IMPACT to monitor for symptoms of EoE was not validated and was modified for use in young children, and in combination with the GI assessment questionnaire used, may have under-reported the incidence of EoE-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 those treated with PnOIT. Of special interest was the steady rise in peanut- and peanut component-specific IgE over time in the placebo arm, indicating increasing sensitization in untreated peanut-allergic young children and a potential closing of an important therapeutic window. In contrast, PnOIT-induced immunomodulation was characterized by a decline in peanut-specific IgE occurring by the end of build-up at week 30, earlier in the treatment course, compared to OIT studies involving older children.[10,19,29,30]

This study has important limitations. Although we included children ages 12–<48 months, only 12% of children randomized were aged <24 months. The small number of children under the age of 24 months results in larger confidence intervals around the probability of remission in this sub-group. There was a high drop-out rate during the required 26-week avoidance period with a substantial differential between treatment arms that may have affected the outcome. Additionally, 27% of PnOIT-treated participants and 20% of placebo participants did not reach the maximal maintenance dose of 2000 mg, a factor that could have impacted 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.[15,16] There are several terms that have been used recently to describe possible surrogates for tolerance; however, there are currently no biomarkers that separate “sustained unresponsiveness” from “remission” from tolerance.[15,16] Although attaining desensitization is a goal that offers significant relief to patients and their families, attaining true tolerance would eliminate the need for regular allergen exposure as well as 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 optimize family and participant preferred options 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 and at that time was felt to be the best way to determine if these young children were tolerant. However, following the food challenge, the IMPACT study did not attempt to re-introduce peanut into the diet or to follow the participants after the challenge, so the study was unable to assess whether permanent tolerance was reached. Additionally, our definition of remission for this study as 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 (40/70) consumed at least 1755–3755 mg peanut (~6–12 peanuts, a child-size serving portion) after treatment discontinuation, a level that has clinical relevance for young children.

In summary, the IMPACT Trial shows that PnOIT resulted in desensitization in the vast majority and remission in a substantial proportion of children compared to placebo and remission was predicted by younger age and lower baseline peanut-specific IgE. Further exploration of PnOIT 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The authors 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 the Immune Tolerance Network (ITN), with Drs. Jones and Burks as study chairs. The data were gathered by the investigators, and analyzed by biostatisticians at Rho, Inc. The manuscript was written collaboratively by Drs. 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, Inc. and the NIAID leadership.

### Declaration of interests

SMJ reports grants from NIH-NIAID, Food Allergy Research & Education (FARE), Aimmune Therapeutic, DBV Technologies, Astellas, Inc., Sanofi, Inc., Regeneron, Inc., and Genentech, Inc. and personal fees from Food Allergy Research and Education, EMMES Corporation, Aimmune Therapeutics. EHK reports personal fees from DBV Technologies, Aimmune Therapeutics, AllerGenis, Ukko, Inc, Vibrant America, Allakos, Kenota Health, and Duke Clinical Research Institute, and grants from Food Allergy Research & Education (FARE), and the Wallace Research Foundation. KCN reports grants from National Institute of Allergy and Infectious Diseases (NIAID), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Environmental Health Sciences (NIEHS), Food Allergy Research & Education (FARE), other fees from World Allergy Organization (WAO), Cour Pharma, other Before Brands, Alladapt, Latitude, IgGenix, Immune Tolerance Network (ITN), National Institutes of Health (NIH) clinical research centers and KCN has a patent Inhibition of Allergic Reaction to Peanut Allergen using an IL-33 Inhibitor pending, a patent Special Oral Formula for Decreasing Food Allergy Risk and Treatment for Food Allergy pending, a patent Basophil Activation Based Diagnostic Allergy Test pending, a patent Granulocyte-based methods for detecting and monitoring immune system disorders pending, a patent Methods and Assays for Detecting and Quantifying Pure Subpopulations of White Blood Cells in Immune System Disorders pending, a patent Mixed Allergen Compositions and Methods for Using the Same pending, and a patent Microfluidic Device and Diagnostic Methods for Allergy Testing Based on Detection of Basophil Activation pending. ANW reports grants from NIH NIAID, DBV Technologies, Astellas Pharma, Food Allergy Research and Education, grants and personal fees from Nestle, and grants and personal fees from Nutricia. RAW reports grants from NIAID, Aimmune, Astellas, DBV, Genentech, Regeneron, Sanofi, and personal fees from UpToDate. HAS receives funding to his institution for grants from NIH/NIAID and has received consulting fees from DBV Technologies, S.A., N-Fold Therapeutics, LLC, and Siolta, Inc, and stock options from DBV Technologies and N-Fold Therapeutics. AMS reports grants from NIAID-Immune Tolerance Network, Food Allergy Research and Education, grants from Aimmune Therapeutics, DBV Technologies, Astellas, Inc., Sanofi, Regeneron and Genentech and personal fees from DBV Technologies. RSC reports grants from NIAID, Aimmune Therapeutics, DBV Technologies, Astellas, and Regeneron and is an advisory member for Alladapt, Genentech, Novartis, and Sanofi. JW reports grants from NIAID and personal fees from DBV Technologies, ALK Abello, Genentech, and UpToDate. SBS reports grants from NIAID, Regeneron, DBV, Aimmune, Novartis, and Sanofi, and personal fees from AstraZeneca. MK reports grants from National Institutes of Health and Department of Defense. JJ reports grants from National Institute of Allergy and Infectious Diseases. KS reports grants from NIAID/NIH. DCB reports grants from NIH/NIAID. HC reports grants from NIH/NIAID. DL reports grants from NIH-NIAID. EW reports grants from NIH-NIAID. MLS reports grants from NIAID/NIH. AWB reports personal fees from Aimmune Therapeutics, Inc., Astella Pharma Global Development, Consortia TX, Inc., DBV Technologies, Intrommune Therapeutics, Prota Therapeutics, N-Fold, LLC, Aravax, Hycor Biomedical and grants from NIH, Johns Hopkins/NIH, FARE, other fees from Allertein stock, Mastcell Pharmaceuticals, UpToDate royalties, personal fees from AllerGenis, kaléo, UKKO, Inc., ALK-Abelló, Inc. In addition, AWB has a patent US #7879977 with royalties paid, a patent US #6835824 with royalties paid, a patent US #6486311 with royalties paid, a patent US #6441142 with royalties paid, a patent US #5973121 with royalties paid, and a patent US #5558869 with royalties paid. All other authors report no competing interests

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## Research in Context with Previous Work

### Evidence before this study

Peanut oral immunotherapy (PnOIT) has been studied predominantly in school-age children with the exception of two small, single-center studies in preschool children. Findings from these trials have shown that PnOIT is protective against accidental ingestion. In particular, daily PnOIT induces increases in the amount of peanut required to induce a reaction. Previous research has also demonstrated 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 performed without a treated control group, and another conducted in a "real world" setting, demonstrated 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 were also associated with adverse events in many participants.

### Added value of this study

This study is the first randomized, controlled, long-term blinded study of PnOIT in children less than age 4 years conducted in a multi-center (5 US academic centers) trial design. The study provides long-term clinical efficacy, safety and novel immunologic data, along with predictors of response, among young children that can inform clinicians about the potential benefits and risks of PnOIT for these patients.

### Implications of the available evidence

The IMPACT Trial shows that PnOIT induces desensitization in the majority of 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. Though the majority of the children, both PnOIT-treated and placebo-treated, had dosing reactions during OIT, most were mild-to-moderate with epinephrine given in 21 participants for 35 PnOIT 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 PnOIT may improve treatment outcomes for patients with peanut allergy.

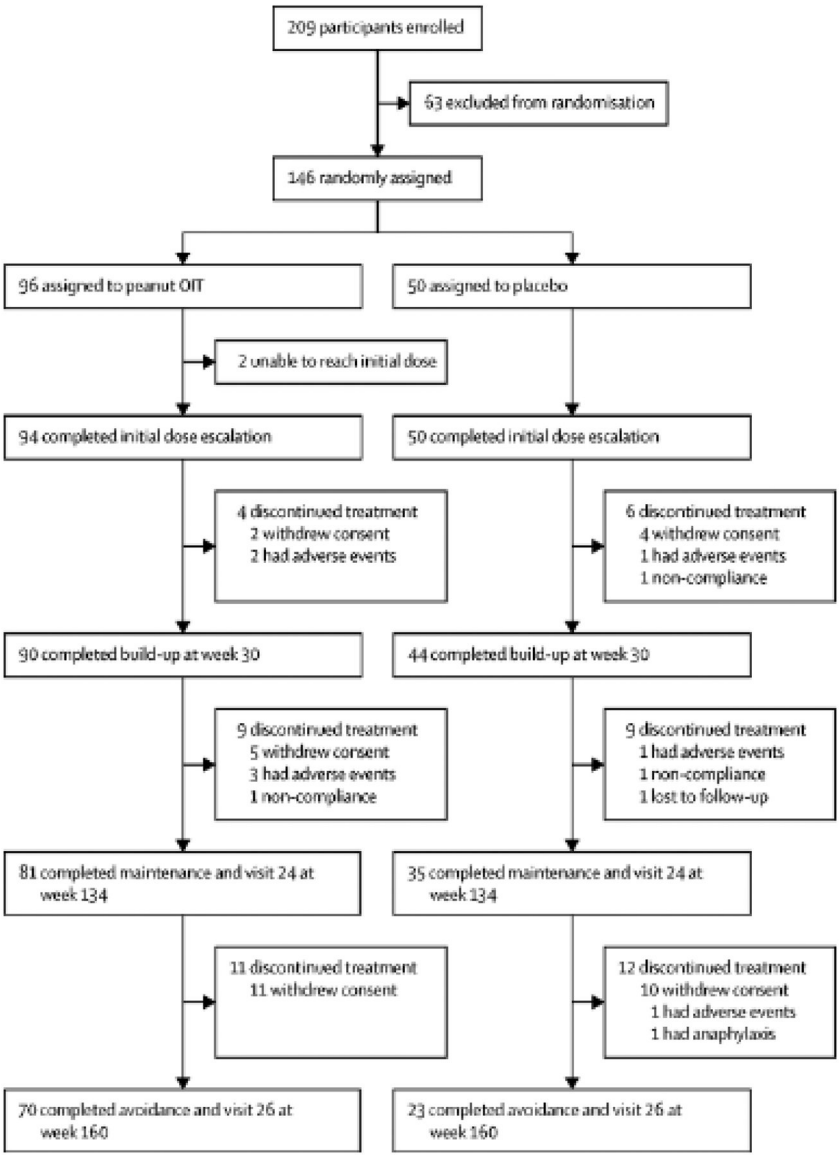
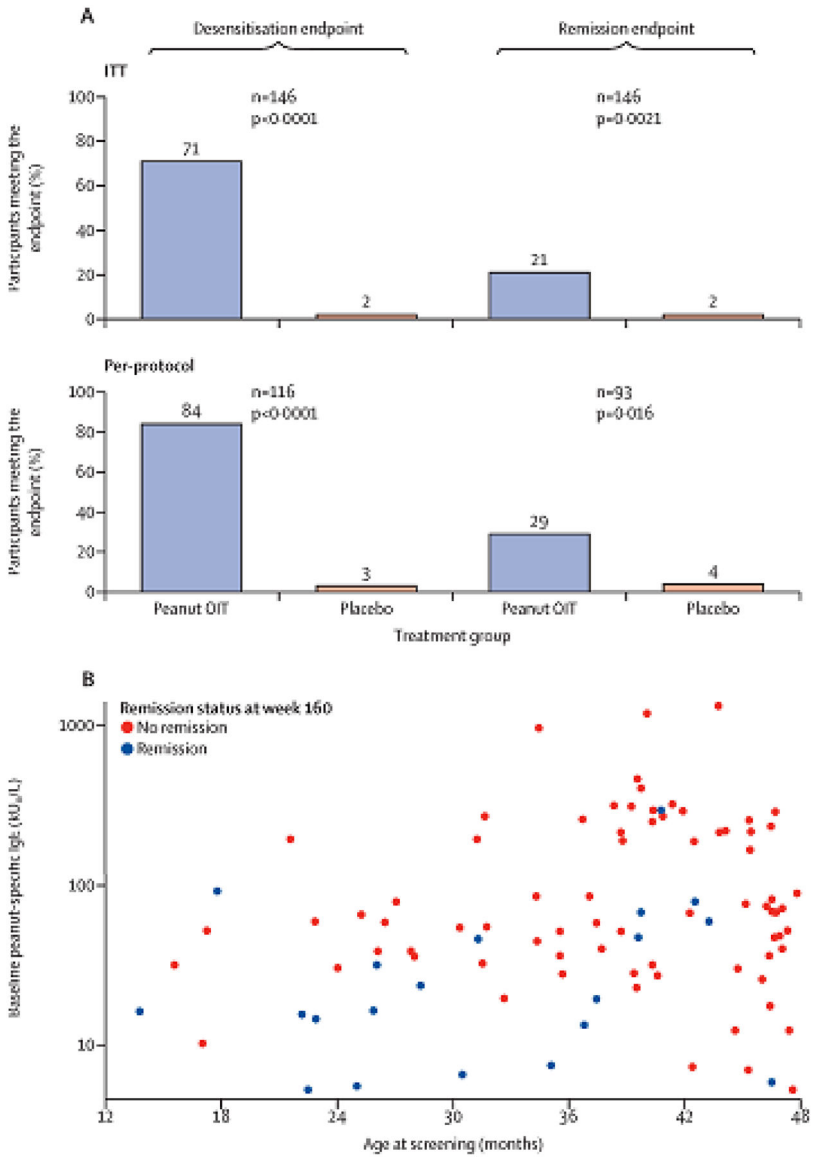



**Figure 1. Trial Profile.**

Participants were screened and randomized (2:1) to receive PnOIT or placebo in a blinded study protocol through week 160 and database lock. Following the study entry DBPCFC to 500 mg peanut protein, participants consumed daily, blinded OIT through week 134 per protocol then were assessed for protocol-defined clinical outcomes by DBPCFC to 5000 mg peanut protein at week 134 (desensitization) and after peanut avoidance for 26 weeks at week 160 (remission).



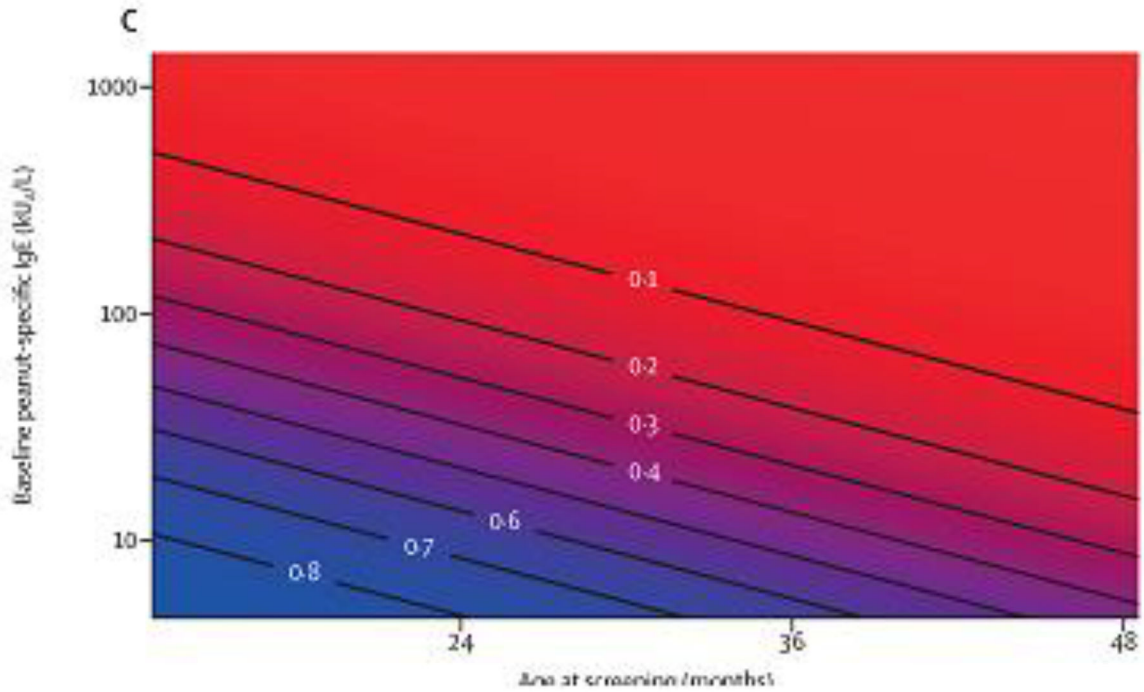



**Figure 2. Primary and Secondary Outcomes.**

(A) Data are shown for primary (desensitization, in left panels) and secondary (remission, in right panels) endpoints measured by DBPCFC at weeks 134 and 160, respectively, for the ITT sample (upper panels) and PP sample (lower panels) comparing PnOIT (purple) and placebo (orange) arms. (B) Data are shown for the PnOIT arm. Baseline peanut-specific IgE ($kU_AL$) is plotted on the y axis and age at screening (months) on the x axis; AUC=0.8072. Participants not achieving remission at the week 160 DBPCFC are shown in red, while those achieving remission at the week 160 DBPCFC are shown in blue. (C) A contour plot of predicted probability of remission from the logistic regression model plotted against baseline peanut-specific IgE ($kU_A/L$) on the y axis and age at screening (months) on the x axis. Values in blue show >50% probability of remission, while values in red show <50% probability of remission.

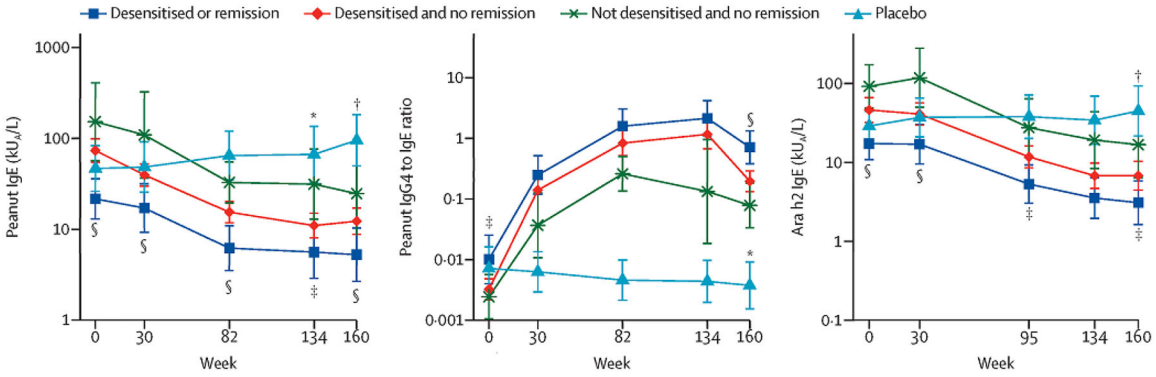



**Figure 3. Immunologic Changes over the Course of the Study.**

Data are shown for the sample of PP participants that were evaluable while on treatment, during the avoidance phase and by DBPCFC after avoidance. Data are shown for time points including before treatment, week 30, week 82 or 95, week 134, and week 160 of the study. PnOIT participants were categorized as “desensitized, remission” (blue squares), “desensitized, no remission” (red diamonds), “not desensitized and no remission” (black asterisks) based on the results of the week 134 and week 160 DBPCFC. Panels A through C 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 PnOIT outcome groups and placebo participants (orange triangles). (n=23 placebo, n=10 not desensitized, no remission, n=40 desensitized, no remission (panel C, n=39), and n=19 desensitized, remission, (panel C, n=18). Data are shown as means with 95% confidence intervals. +p≤0.05, ++p≤0.01 change from pretreatment in placebo participants. #p<0.05, ##p<0.01 for desensitized, remission vs both desensitized, no remission and not desensitized, no remission.

**Table 1.**

Demographics and Baseline Characteristics

| | 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%) |
| UNC | 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 | | | |
| 12–23.9 months | 10 (10%) | 7 (14%) | 17 (12%) |
| 24–35.9 months | 26 (27%) | 14 (28%) | 40 (27%) |
| 36–47.9 months | 60 (63%) | 29 (58%) | 89 (61%) |
| Sex | | | |
| Male | 66 (69%) | 33 (66%) | 99 (68%) |
| Race | | | |
| Asian | 15 (16%) | 3 (6%) | 18 (12%) |
| Black or African American | 1 (1%) | 5 (10%) | 6 (4%) |
| Mixed Race | 16 (17%) | 11 (22%) | 27 (18%) |
| White/Caucasian | 64 (67%) | 31 (62%) | 95 (65%) |
| Atopic Dermatitis History | | | |
| Yes | 81 (84%) | 41 (82%) | 122 (84%) |
| Allergic Rhinitis History | | | |
| Yes | 28 (29%) | 14 (28%) | 42 (29%) |
| Asthma History | | | |
| Yes | 22 (23%) | 7 (14%) | 29 (20%) |
| History of Peanut Allergy Symptoms | 62 (65%) | 29 (58%) | 91 (62%) |
| Never Exposed to Peanut | 34 (35%) | 21 (42%) | 55 (38%) |

| | Peanut OIT (N=96) | Placebo (N=50) | Total (N=146) |
|---|---|---|---|
| History of Anaphylaxis to Peanut | | | |
| Yes | 0 (0%) | 2 (4%) | 2 (1%) |
| History of Other Food Allergies | | | |
| Yes | 50 (52%) | 33 (66%) | 83 (57%) |
| Peanut-specific IgE at Baseline (kUA/L) | | | |
| Median (IQR) | 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) | | | |
| Median (IQR) | 14.0 (12.0, 18.0) | 15.8 (10.0, 20.0) | 15.0 (11.5, 19.0) |
| Cumulative Tolerated Dose of Blinded OFC to Peanut at Baseline (mg) | | | |
| Median (IQR) | 75.0 (5.0, 175.0) | 25.0 (25.0, 75.0) | 25.0 (5.0, 75.0) |

Note: This table includes all participants in the Intent-To-Treat sample.

**Table 2.**

Dosing Reactions During OIT

| | IDE Phase | | Build-Up Phase | | Maintenance Phase | | Overall | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Peanut OIT (N=96) n (%)** | **Placebo (N=50) n (%)** | **Peanut OIT (N=94) n (%)** | **Placebo (N=50) n (%)** | **Peanut OIT (N=90) n (%)** | **Placebo (N=44) n (%)** | **Peanut OIT (N=96) n (%)** | **Placebo (N=50) n (%)** | |
| 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 Epi | 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 | | | | | | | | | |
| 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/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 Gl 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 Gl 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) | +^‡ |

| | IDE Phase | | Build-Up Phase | | Maintenance Phase | | Overall | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Peanut OIT (N=96) n (%)** | **Placebo (N=50) n (%)** | **Peanut OIT (N=94) n (%)** | **Placebo (N=50) n (%)** | **Peanut OIT (N=90) n (%)** | **Placebo (N=44) n (%)** | **Peanut OIT (N=96) n (%)** | **Placebo (N=50) n (%)** | |
| 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/throat symptoms | 0 | 0 | 6 (6) | 0 | 6 (7) | 0 | 12 (13) | 0 | ‡ |
| Mouth/throat discomfort | 1 (1) | 0 | 17 (18) | 0 | 25 (28) | 0 | 33 (34) | 0 | +^‡ |
| Rhinitis/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/ 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/pruritis | 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/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 | |

Note: This table includes all participants in the safety sample for IDE, build-up, and maintenance.

* represents a statistically significant difference between the treatment groups in the IDE phase using a Fisher's exact test.

+ represents a statistically significant difference between the treatment groups in the Build-Up phase using a Fisher's exact test.

^ represents a statistically significant difference between the treatment groups in the Maintenance phase using a Fisher's exact test.

**Table 3.**

Summary of Epinephrine Administration

| | Peanut OIT | | Placebo | |
|---|---|---|---|---|
| | Events n (%) | Participants (N=96) n (%) | Events n (%) | Participants (N=50) n (%) |
| At Least One Epinephrine Dose Given [1] | 109 | 61 (64) | 58 | 35 (70) |
| Associated with Study Product Dosing [2] | 35 (32) | 21 (34) | 0 | 0 |
| In-clinic Dosing [3] | 1 (3) | 1 (5) | 0 | 0 |
| Dosing during IDE [4] | 0 | 0 | 0 | 0 |
| Dosing during Build-up [4] | 1 (100) | 1 (100) | 0 | 0 |
| Out-of-clinic Dosing [3] | 34 (97) | 21 (100) | 0 | 0 |
| Dosing during Build-up [5] | 11 (32) | 6 (29) | 0 | 0 |
| Dosing during Maintenance [5] | 23 (68) | 17 (81) | 0 | 0 |
| Associated with a Study Procedure [2] | 97 (89) | 57 (93) | 54 (93) | 34 (97) |
| Overall Oral Food Challenge DBPCFC [6] | 62 (64) | 48 (84) | 54 (100) | 34 (100) |
| Screen (Baseline-500 mg DBPCFC) [7] | 36 (58) | 36 (75) | 23 (43) | 23 (68) |
| Desensitization (Week 134-5 g DBPCFC) [7] | 4 (6) | 4 (8) | 21 (39) | 21 (62) |
| Tolerance (Week 160-5 g DBPCFC) [7] | 22 (35) | 22 (46) | 10 (19) | 10 (29) |
| Not Associated with Study Product Dosing or a Study Procedure [2] | 12 (11) | 11 (18) | 4 (7) | 3 (9) |
| Accidental Exposure to Peanut [8] | 4 (33) | 4 (36) | 1 (25) | 1 (33) |
| Other Allergen Exposure [8] | 8 (67) | 8 (73) | 3 (75) | 2 (67) |

Note: This table includes all participants in the Intent-To-Treat sample.

Note: Participants may be counted in more than one row if the participant experienced multiple types of event.

[1] The denominator used to calculate percentages is the number of participants randomized.

[2] The denominator used to calculate percentages Is either the number of events or participants with at least one administration of epinephrine.

[3] The denominator used to calculate percentages is either the number of events or participants with at least one administration of epinephrine associated with study product dosing.

[4] The denominator used to calculate percentages is either the number of events or participants with at least one administration of epinephrine associated with in-clinic dosing.

[5]The denominator used to calculate percentages is either the number of events or participants with at least one administration of epinephrine associated with out-of-clinic dosing.

[6]The denominator used to calculate percentages is either the number of events or participants with at least one administration of epinephrine associated with a study procedure.

[7]The denominator used to calculate percentages is either the number of events or participants with at least one administration of epinephrine associated with an oral food challenge DBPCFC.

[8]The denominator used to calculate percentages is either the number of events or participants with at least one administration of epinephrine not associated with study product dosing or a study procedure.