Administration of a probiotic with peanut oral immunotherapy: A randomized trial

Mimi L. K. Tang, PhD,[a,b,c] Anne-Louise Ponsonby, PhD,[d] Francesca Orsini, MSc,[e] Dean Tey, FRACP,[a,c] Marnie Robinson, FRACP,[a,c] Ee Lyn Su, FRACP,[a,c] Paul Licciardi, PhD,[c] Wesley Burks, MD,[f] and Susan Donath, MA[b,e]

Melbourne, Australia, and Chapel Hill, NC

Background: Coadministration of a bacterial adjuvant with oral immunotherapy (OIT) has been suggested as a potential treatment for food allergy.

Objective: To evaluate a combined therapy comprising a probiotic together with peanut OIT.

Methods: We performed a double-blind, placebo-controlled randomized trial of the probiotic *Lactobacillus rhamnosus* CGMCC 1.3724 and peanut OIT (probiotic and peanut oral immunotherapy [PPOIT]) in children (1-10 years) with peanut allergy. The primary outcome was induction of sustained unresponsiveness 2 to 5 weeks after discontinuation of treatment (referred to as possible sustained unresponsiveness). Secondary outcomes were desensitization, peanut skin prick test, and specific IgE and specific IgG_4 measurements.

Results: Sixty-two children were randomized and stratified by age (≤5 and >5 years) and peanut skin test wheal size (≤10 and >10 mm); 56 reached the trial's end. Baseline demographics were similar across groups. Possible sustained unresponsiveness was achieved in 82.1% receiving PPOIT and 3.6% receiving placebo ($P < .001$). Nine children need to be treated for 7 to achieve sustained unresponsiveness (number needed to treat, 1.27; 95% CI, 1.06-1.59). Of the subjects, 89.7% receiving PPOIT and 7.1% receiving placebo were desensitized ($P < .001$). PPOIT was associated with reduced peanut skin prick test responses and peanut-specific IgE levels and increased peanut-specific IgG_4 levels (all $P < .001$). PPOIT-treated participants reported a greater number of adverse events, mostly with maintenance home dosing.

Conclusion: This is the first randomized placebo-controlled trial evaluating the novel coadministration of a probiotic and peanut OIT and assessing sustained unresponsiveness in children with peanut allergy. PPOIT was effective in inducing possible sustained unresponsiveness and immune changes that suggest modulation of the peanut-specific immune response. Further work is required to confirm sustained unresponsiveness after a longer period of secondary peanut elimination and to clarify the relative contributions of probiotics versus OIT. (J Allergy Clin Immunol 2015;135:737-44.)

Key words: *Peanut allergy, oral immunotherapy, probiotic, immune-modifying adjuvant, tolerance, sustained unresponsiveness, desensitization, peanut-specific IgE, peanut-specific IgG_4*

The prevalence of food allergy has increased, particularly in westernized countries.[1-3] Food allergy is estimated to affect up to 8% of children and 2% of adults,[4,5] and a recent Australian study reported challenge-proved food allergy in 10% of 12-month-old infants, with 3% of infants having peanut allergy.[6] The need for a curative treatment is greatest for peanut allergy because this is usually lifelong and the most common cause of anaphylaxis-related fatality.[3,7,8]

Oral immunotherapy (OIT) has been explored as a strategy to induce tolerance.[9] Although studies have shown that OIT for egg, milk, or peanut can consistently induce desensitization (ie, the transient ability to tolerate a food that is lost when OIT is stopped), its ability to induce tolerance (ie, the sustained ability to tolerate a food even after OIT is stopped) remains uncertain.[9-12] Desensitization might not be an optimal outcome for some patients with food allergy because they remain allergic to their food allergen, and serious allergic reactions to maintenance OIT doses can occur despite months to years of treatment.[13,14] Although an effective treatment for food allergy would be

From [a]the Department of Allergy and Immunology, Royal Children's Hospital, Melbourne; [b]the Department of Paediatrics, University of Melbourne; [c]Allergy and Immune Disorders, [d]Environmental and Genetic Epidemiology, [e]the Clinical Epidemiology and Biostatistics Unit, Murdoch Childrens Research Institute, Melbourne; and [f]the Department of Pediatrics, University of North Carolina, Chapel Hill.

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Corresponding author: Mimi L. K. Tang, PhD, Department of Allergy and Immunology, Royal Children's Hospital, Flemington Rd, Parkville, Victoria 3052, Australia. E-mail: mimi.tang@rch.org.au.

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Abbreviations used
AE: Adverse event
DBPCFC: Double-blind, placebo-controlled food challenge
FDA: US Food and Drug Administration
IQR: Interquartile range
NIAID: National Institute of Allergy and Infectious Diseases
NNT: Number needed to treat
OIT: Oral immunotherapy
OR: Odds ratio
PPOIT: Probiotic and peanut oral immunotherapy
RCH: Royal Children's Hospital
RCT: Randomized controlled trial
RR: Risk ratio
SAE: Serious adverse event
sIgE: Specific IgE
$sIgG_4$: Specific IgG_4
SPT: Skin prick test

expected to induce a sustained ability to tolerate a food, few studies have assessed for this outcome after OIT, and results have been conflicting.[15-19] Moreover, it is increasingly recognized that the ability to tolerate a food after discontinuation of OIT might not be maintained; hence the term sustained unresponsiveness has been proposed in preference to tolerance when describing food allergy immunotherapy trial outcomes.[16,20]

Studies of subcutaneous and sublingual immunotherapy for allergic rhinitis using novel combinations of allergen together with bacterial adjuvants or Toll-like receptor ligands have reported enhanced tolerogenic effect.[21-26] Therefore we postulated that such a combined immunotherapy approach incorporating a probiotic bacterial adjuvant together with allergen OIT might offer an effective treatment for food allergy. Moreover, because there was no convincing evidence that allergen OIT alone was effective in promoting sustained unresponsiveness at the time our randomized controlled trial (RCT) was designed and initiated, we elected to undertake a clinical trial evaluating whether coadministration of *Lactobacillus rhamnosus* CGMCC 1.3724 (NCC4007) and peanut OIT can induce sustained unresponsiveness to peanut among children with peanut allergy (Australian New Zealand Clinical Trials Registry ACTRN 12608000594325, 25/11/2008). This probiotic was selected based on its demonstrated tolerance-promoting effects, including induction of regulatory T and T_H1 cytokine responses.[27-30]

METHODS

Study design

We performed a double-blind, placebo-controlled randomized trial combining the probiotic *Lactobacillus rhamnosus* and peanut OIT (ie, probiotic and peanut oral immunotherapy [PPOIT]) for 18 months in 62 children aged 1 to 10 years with peanut allergy (see Fig E1 in this article's Online Repository at www.jacionline.org). Additional details of the study protocol and recruitment are available in the Methods section and Table E1 in this article's Online Repository at www.jacionline.org.

Randomization and masking

Randomization was stratified by age (≤5 or >5 years) and peanut skin prick test (SPT) wheal size (≤10 or >10 mm) by using random block sizes of 2 or 4 because most children who outgrow peanut allergy do so in the first 5 years of life[31] and because smaller SPT wheal size is associated with a greater likelihood of natural resolution.[16] The study statistician generated the randomization schedule, which was provided to the Royal Children's Hospital (RCH) clinical trials pharmacist, who prepared individual treatment doses for each randomized child coded by sequential study number. Participants, outcome assessors, and statisticians were blinded to the randomized allocation.

Study conduct

The active treatment group received *Lactobacillus rhamnosus* CGMCC 1.3724 (NCC4007; provided by Nestlé Health Science, Konolfingen, Switzerland) at a fixed dose of 2×10^{10} colony-forming units (freeze-dried powder) once daily together with peanut OIT (peanut flour, 50% peanut protein; Byrd Mill, Ashland, Va) once daily according to the peanut OIT protocol (Table I) for 18 months. The placebo group received placebo (maltodextrin) and placebo (maltodextrin, brown food coloring, and peanut essence) once daily. Active and placebo OIT products were similar in taste, color, and smell. The peanut OIT protocol (Table I) comprised a 1-day rush induction phase, a build-up phase with updosing every 2 weeks to a maintenance dose of 2 g of peanut protein (8 months), and a maintenance phase (10 months); total OIT was 18 months. Where the build-up phase was longer than 8 months (because of treatment reactions, see the footnote in Table I) but less than 12 months, the maintenance phase was adjusted to preserve a total of 18 months of OIT. For subjects taking more than 12 months to reach maintenance, the total duration of OIT was extended to ensure a minimum of 6 months of maintenance dosing.

An oral peanut double-blind, placebo-controlled food challenge (DBPCFC; cumulative dose, 4 g of peanut protein) was performed on the last day of study treatment (T1) to assess for desensitization. Children who passed the T1 DBPCFC underwent a second DBPCFC performed after an interval of 2 or more weeks off study treatment (T2), during which time they continued a peanut elimination diet, to assess for sustained unresponsiveness. This interval of secondary peanut elimination was selected based on the published recommendation by the National Institute of Allergy and Infectious Diseases (NIAID)–US Food and Drug Administration (FDA) Workshop on Food Allergy Clinical Trial Design[32]; however, it is acknowledged that a longer period of at least 4 weeks would now be advisable. DBPCFC failure occurred if objective symptoms were noted during the challenge procedure.[33] Subjects who failed the T1 DBPCFC were classified as allergic; those who passed the T1 DBPCFC were classified as desensitized. Subjects who passed both the T1 and T2 DBPCFCs were classified as having attained sustained unresponsiveness. Subjects returned for clinical interviews (including questionnaire) and SPTs at 3 months after treatment (T3). Additional details of study conduct are available in the Methods section in this article's Online Repository.

Data collection

SPTs to peanut and other common food and inhalant allergens were performed, and blood samples were collected at baseline (T0), completion of PPOIT treatment (T1), and 3 months after treatment (T3). Serum peanut-specific IgE (sIgE) and peanut-specific IgG_4 ($sIgG_4$) levels were measured by using the ImmunoCAP 250 (provided in part by Phadia AB, Uppsala, Sweden).

Severe adverse events (AEs) were defined as any symptom that prevents daily activities and might require therapeutic intervention. A serious adverse event (SAE) was defined according to standard criteria (see the Methods section in this article's Online Repository). An independent safety and data monitoring committee maintained trial observation. Parents of participating children provided written consent. The RCH Human Research and Ethics Committee provided ethics approval. The trial was registered with the Australian New Zealand Clinical Trials Registry before commencement (ACTRN 12608000594325, 25/11/2008).

Outcome measures

The primary outcome was sustained unresponsiveness (passed the T1 and T2 DBPCFCs). The term tolerance was assigned for the primary outcome in

TABLE I. Peanut OIT protocol

Dose	Peanut protein	Cumulative peanut protein
Modified rush day 1*		
1	0.1 mg	0.1 mg
2	0.2 mg	0.3 mg
3	0.4 mg	0.7 mg
4	0.8 mg	1.5 mg
5	1.5 mg	3.0 mg
6	3.0 mg	6.0 mg
7	6.0 mg	12 mg
8	12 mg	24 mg
Build-up phase†		
9	25 mg	
10	50 mg	
11	75 mg	
12	100 mg	
13	125 mg	
14	150 mg	
15	200 mg	
16	260 mg	
17	330 mg	
18	425 mg	
19	550 mg	
20	715 mg	
21	925 mg	
22	1.2 g	
23	1.55 g	
24	2.0 g	
Maintenance phase‡		
Ongoing	2.0 g	

*In the modified rush phase subjects received increasing doses of peanut protein every 30 minutes to reach a final dose of 12 mg of peanut protein.
†In the build-up phase a daily dose was taken, with dose increases (performed in hospital) every 2 weeks until a maintenance dose of 2 g was reached. If mild allergic symptoms developed (urticaria, angioedema, vomiting, diarrhea, and abdominal pain), the daily dose was continued for a further 2 weeks before increasing. If severe allergic symptoms developed (stridor, wheeze, and difficulty breathing), the daily OIT dose was reduced to the previous tolerated dose.
‡During the maintenance phase, subjects continued to receive 2 g of peanut protein daily. If 1 to 2 days of OIT were missed, the subject could continue with the usual dose at home. If 3 to 4 days of OIT were missed, the next dose had to be administered at RCH. If more than 4 days were missed, subjects were required to recommence OIT at day 1.

the study protocol; however, the term sustained unresponsiveness has more recently been proposed in preference to tolerance because OIT-induced unresponsiveness might not be long lasting.[16] Secondary outcomes were desensitization (passed the T1 DBPCFC), and peanut SPT wheal size, peanut sIgE levels, and peanut $sIgG_4$ levels at T1 and T3.

Statistical analysis

Statistical power estimates with a 2-group continuity-corrected χ^2 test with 2-sided significance of .05 indicated 39 participants in each group would provide 80% power to detect the difference between a 4% rate of sustained unresponsiveness in the placebo group[31,34] and a 30% rate in the treatment group. Allowing for 10% loss to follow-up, we aimed to recruit 90 participants. Because of slower than expected recruitment and budget constraints, recruitment was closed after 27 months (62 enrolled). A sample size of 25 in each group would provide 80% power at a 2-sided significance of .05 to detect the difference between 4% sustained unresponsiveness in the placebo group and 40% sustained unresponsiveness in the treatment group.

Analysis was by intention to treat where outcome data were available. For the primary and secondary outcomes of sustained unresponsiveness and desensitization, the effect of treatment was estimated by using the risk ratio

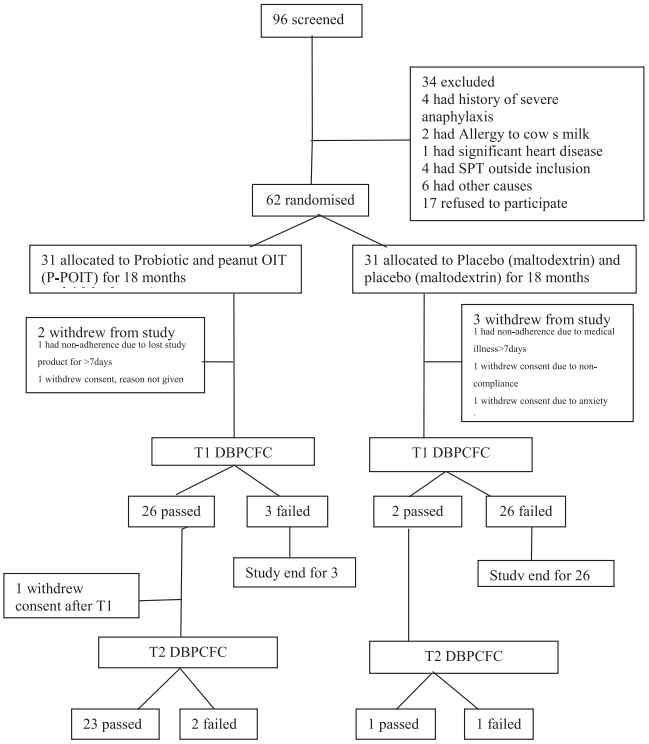

FIG 1. CONSORT diagram of participant flow in the PPOIT RCT. Oral peanut DBPCFC (cumulative dose, 4 g of peanut protein) was performed on the last day of study treatment (T1) to assess desensitization. Children who passed the T1 DBPCFC underwent a second DBPCFC performed after an interval of 2 to 5 weeks off study treatment (T2), during which time they continued a peanut elimination diet to assess sustained unresponsiveness.

(RR) and number needed to treat (NNT), each with 95% CIs. The hypothesis of no difference between treatment groups was tested by using the χ^2 test. For the primary outcome, the effect of treatment after adjustment for age and peanut SPT size at randomization and oral or inhaled steroid administration at baseline or during treatment was estimated by using a logistic regression model. For the main analyses, participants with missing outcome data were excluded. Sensitivity analyses that included all randomized participants, with missing outcome data imputed, were also performed.

Peanut SPT wheal size was normally distributed and reported as the mean (SD) by treatment group, with *P* values for group comparison from the *t* test. All other continuous secondary outcomes (non–peanut-induced SPT wheal sizes; peanut-sIgE and $sIgG_4$ levels at baseline, T1, and T3; and change in peanut-sIgE and $sIgG_4$ level from baseline at T1 and T3) have skewed distributions and are summarized as medians and interquartile ranges (IQRs), with the Wilcoxon rank sum (Mann-Whitney) test used to test the hypothesis of no difference between groups. Peanut-sIgE and $sIgG_4$ levels at baseline, T1, and T3 are also summarized by using geometric means and compared by using a *t* test on logarithmic scaled data. Data were analyzed with Stata release 12.0 software (StataCorp, College Station, Tex).

RESULTS

Trial conduct

Sixty-two children were randomized to the PPOIT and placebo groups (Fig 1). Children in the PPOIT and placebo groups were similar with regard to age, sex, and history of allergic disease (Table II). The length of treatment administration was similar for both groups (median duration, 18.8 months [IQR, 18.2-19.9 months] for the PPOIT group and 18.2 months [IQR, 17.7-19.4 months] for the placebo group; see Table E2 in this article's

TABLE II. Demographic characteristics at study entry

	PPOIT group (N = 31)	Placebo group (N = 31)
Age (y)		
Mean (SD), n	6.1 (2.4), 31	5.8 (2.6), 31
Weight (kg)		
Mean (SD), n	24.9 (9), 31	24.6 (11.3), 31
Male sex		
n (%)	17 (54.8)	20 (64.5)
History of doctor-diagnosed eczema (ever)		
n (%)	24 (77.4)	24 (77.4)
If ever eczema, medication for eczema in last 12 mo		
n (% of ever eczema)	18/24 (75)	20/24 (83.3)
History of doctor-diagnosed asthma (ever)		
n (%)	16 (51.6)	14 (45.2)
If ever asthma, medication for asthma in last 12 mo		
n (% of ever asthma)	13 (81.3)	13 (92.9)
Child ingested peanut not as part of a challenge		
n (%)	18 (58.1)	21 (67.7)
Child completed a peanut challenge at screening		
n (%)	14 (45.2)	11 (35.5)
History of anaphylaxis to peanut*		
n (%)	14 (45.2)	10 (33.3)
Peanut-induced SPT wheal size (mm)		
Mean (SD), n	17.6 (6.58), 31	18 (6.89), 31
sIgE (kU/L)		
Median (IQR), n	14.3 (2.11-181), 31	8.25 (1.12-39.3), 31

*One missing value in the placebo group.

Online Repository at www.jacionline.org). The median interval between the T1 and T2 DBPCFCs (for those who passed the T1 DBPCFC) was 2.3 weeks (range, 2-5.3 weeks). Only 2 placebo-treated participants proceeded to the T2 challenge.

Six participants withdrew from the study, 3 in the PPOIT group and 3 in the placebo group (Fig 1). The mean percentage of doses taken by participants was 97% in both groups. Protocol violations were infrequent (see Table E3 in this article's Online Repository at www.jacionline.org). Three placebo-treated participants had 5 episodes of accidental peanut ingestion, and 5 participants ingested the probiotic (3 in the PPOIT group and 2 in the placebo group). The median number of missed doses was 12 (IQR, 4-25) in the PPOIT group and 10 (IQR, 4-15) in the placebo group; the mean number of doses taken per participant was 515.9 (SD, 113.1) and 477.1 (SD, 119.4) for the PPOIT and placebo groups, respectively.

Clinical outcomes

Sustained unresponsiveness (assessed 2-5 weeks after discontinuation of PPOIT, hereafter referred to as possible sustained unresponsiveness) was achieved in 23 (82.1%) of 28 PPOIT-treated participants and 1 (3.6%) of 28 placebo-treated participants ($P < .001$, Table III). The relative RR of achieving possible sustained unresponsiveness with PPOIT was 23 (95% CI, 3.33-158.8), providing an NNT of 1.27 (95% CI, 1.06-1.59). Thus if 9 children were given PPOIT therapy, 7 would achieve possible sustained unresponsiveness. We performed 2 sensitivity analyses that confirmed the robustness of these findings to nonresponse: (1) setting all who withdrew before the T2 DBPCFC as allergic (RR, 23 [95% CI, 3.3-159.9] and NNT, 1.4 [95% CI, 1.1-1.8]; $P < .001$) and (2) setting all withdrawn PPOIT-treated participants as allergic and withdrawn placebo-treated participants as sustained unresponsive (RR, 5.8 [95% CI, 2.3-14.7] and NNT, 1.6 [95% CI, 1.2-2.4]; $P < .001$; Table III). Adjusting for age and peanut-induced SPT wheal size at randomization and inhaled or ingested steroid medication commenced during or at trial completion did not substantially alter the trial findings (see the Results section in this article's Online Repository at www.jacionline.org). We did not identify any baseline clinical predictors for later acquisition of possible sustained unresponsiveness; in particular, peanut-induced SPT wheal sizes and peanut sIgE levels at study entry did not predict possible sustained unresponsiveness. At the T3 clinical interview conducted 3 months after discontinuation of study treatment, all but 1 subject who achieved possible sustained unresponsiveness at the T2 DBPCFC reported continued intake of peanut in varying amounts (from as little as 5 peanuts a week to 3 tablespoons of peanut butter a week) without reaction (see Table E4 in this article's Online Repository at www.jacionline.org).

Desensitization was achieved in 26 (89.7%) of 29 PPOIT-treated and 2 (7.1%) of 28 placebo-treated participants (RR, 12.55 [95% CI, 3.28-47.99] and NNT, 1.21 [95% CI, 1.03-1.47]; $P < .001$).

At the T1 DBPCFC, the median cumulative dose at which a reaction occurred for placebo-treated participants in whom the challenge failed was 437.5 mg (IQR, 187.5-937.5 mg); 3 participants in the PPOIT group in whom the challenge failed reacted at cumulative doses of 1937.5, 2937.5, and 4000 mg.

Peanut SPT. The baseline distribution of peanut-induced SPT wheal size was similar across groups (Table II). At the end of treatment (T1 DBPCFC), the mean peanut-induced SPT wheal size was 4.83 mm (SD, 3.98 mm) in the PPOIT-treated and 14.54 mm (SD, 5.63 mm) in the placebo-treated participants ($P < .001$); the difference between means in the 2 groups was 9.7 mm (95% CI, −7.1 to 12.3 mm; Table III). At 3 months after treatment (T3), the mean peanut-induced wheal sizes were 4.46 mm (SD, 4.44 mm) and 14.75 mm (SD, 6.09 mm) in the PPOIT and placebo groups, respectively ($P < .001$); the difference between group means was maintained (10.3 mm; 95% CI, 7.4-13.4 mm). In contrast, SPT wheal sizes for other non-peanut antigens tested did not differ by group at T1 or T3, with the exception of egg-induced SPT wheal size at T1 (see Table E5 in this article's Online Repository at www.jacionline.org).

Asthma and eczema. At baseline, the numbers of children with doctor-diagnosed asthma (16 in the PPOIT and 14 in the placebo groups) or eczema (24 in the PPOIT and 24 in the placebo groups) were similar between groups (Table II). No new-onset asthma was observed during the study period, but 1 child (in the PPOIT arm) reported new-onset eczema. At trial completion, asthma was ongoing in 9 PPOIT-treated and 12 placebo-treated participants, whereas 16 in both groups reported ongoing eczema.

AEs. At least 1 severe AE was reported in 45.2% of children in the PPOIT group and 32.3% in the placebo group ($P = .3$, Table IV). The total number of severe AEs was greater in PPOIT-treated compared with placebo-treated children (34 and 15, respectively), but this reflected 1 child in the PPOIT group who had 13 severe AEs. The number of severe AEs per participant

TABLE III. Clinical outcomes

	PPOIT group	Placebo group	RR,* NNT,† or mean difference‡
2-wk Sustained unresponsiveness			
n (%)	23/28 (82.1)	1/28 (3.6)	23 (3.33-158.84)*§
			1.27 (1.06-1.59)†
2-wk Sustained unresponsiveness, sensitivity 1			
n (%)	23/31 (74.2)	1/31 (3.2)	23 (3.31-159.93)*§
			1.41 (1.14-1.84)†
2-wk Sustained unresponsiveness, sensitivity 2			
n (%)	23/31 (74.2)	4/31 (12.9)	5.75 (2.25-14.69)*§
			1.63 (1.24-2.39)†
Desensitization			
n (%)	26/29 (89.7)	2/28 (7.1)	12.55 (3.28-47.99)*§
			1.21 (1.03-1.47)†
Peanut SPT at T1			
Mean (SD), n	4.83 (3.98), 29	14.54 (5.63), 27	−9.71 (−12.31 to −7.11)‡§
Peanut SPT at T3			
Mean (SD), n	4.46 (4.44), 28	14.75 (6.09), 28	−10.29 (−13.14 to −7.43)‡

T1 refers to the last day of treatment, and T3 refers to 3 months after the end of treatment.
*RR (95% CI).
†NNT (95% CI).
‡Mean difference (95% CI).
§$P < .001$.

did not differ by group ($P = .9$). Reactions during rush induction and build-up were similarly distributed between groups (additional details of reactions during rush induction are shown in Table E6 in this article's Online Repository at www.jacionline.org); however, reactions during the maintenance phase were more common in PPOIT-treated than placebo-treated participants.

Ten SAEs related to study product occurred in 7 participants. Six SAEs occurred in 3 PPOIT-treated participants, and 4 occurred in 4 placebo-treated participants (Table V). All but 1 AE and SAE occurred during the Australian pollen season (August-February).

Immune indices

Table VI shows serum peanut sIgE and $sIgG_4$ data by group at baseline (T0), end of treatment (T1), and after treatment (T3). From baseline to after treatment, PPOIT-treated participants demonstrated an overall reduction in peanut sIgE levels (median, −4.45 kU/L; IQR, −108.1 to −0.35 kU/L) and an overall increase in peanut $sIgG_4$ levels (median, 3.24 mgA/L; IQR, 1-28.48 mgA/L) but the placebo-treated participants did not ($P < .001$ for both the comparisons).

DISCUSSION

This is the first double-blind RCT evaluating the effect of a combined probiotic and peanut OIT intervention in children with peanut allergy and the first double-blind RCT to report outcomes of a DBPCFC performed following a 2- to 5-week period of secondary peanut elimination with the aim of assessing sustained unresponsiveness (referred to as possible sustained unresponsiveness). Intention-to-treat analysis demonstrated the treatment was highly efficacious: just over 80% of subjects receiving active treatment compared with less than 4% of control subjects achieved possible sustained unresponsiveness, providing an NNT of 9 to produce clinical benefit in 7 children. The induction of possible sustained unresponsiveness was accompanied by a marked reduction in peanut-induced SPT wheal size for the PPOIT but not the placebo groups. Furthermore, PPOIT (but not placebo) treatment was associated with decreased peanut sIgE levels and increased peanut $sIgG_4$ levels, indicating that clinical benefit from PPOIT was through resolution of peanut sIgE–mediated allergy.

Strengths of this RCT include high-quality trial conduct with minimal noncompliance. A placebo-treated group was incorporated for the entire study, and blinding was preserved for participants and the study team until trial completion, whereas previous reports of peanut OIT assessing for sustained unresponsiveness lacked a placebo control group.[15,16] Baseline characteristics were distributed evenly across the 2 groups, and potential postrandomization confounding, such as differential use of steroids, was taken into account. The very low rate of possible sustained unresponsiveness in the placebo group is consistent with the reported natural history of peanut allergy.[31,34] DBPCFCs were performed to assess for clinical outcomes, as recommended by the NIAID–US FDA Workshop on Food Allergy Clinical Trial Design.[32] A range of both clinical and immunologic outcomes was evaluated, with a consistent pattern of reduced peanut sIgE–mediated allergy observed across all outcomes.

Few OIT RCTs (all in egg or milk OIT, no peanut OIT) have assessed for sustained unresponsiveness, and those that have done so have not provided conclusive evidence of OIT-induced sustained unresponsiveness.[17-19] Two placebo-controlled RCTs of peanut OIT have evaluated desensitization, reporting high rates of desensitization compared with placebo.[10,35] An open pilot study of peanut OIT reported sustained unresponsiveness (after a 4-week secondary elimination period) in 50% (24/48) of subjects, although a control group was not included for comparison.[16] Our study is the first placebo-controlled RCT of peanut OIT to perform a DBPCFC after a 2- to 5-week period of secondary peanut elimination, with a high proportion of PPOIT-treated participants achieving possible sustained

TABLE IV. Characteristics of severe AEs

		PPOIT group (N = 31)	Placebo group (N = 31)	*P* value
Patients who experienced ≥1 severe AE	n (%)	14 (45.16)	10 (32.26)	.3
No. of severe AEs per patient				
0	n (%)	17 (54.8)	21 (67.7)	
1	n (%)	8 (25.8)	6 (19.4)	
2	n (%)	3 (9.7)	3 (9.7)	
3	n (%)	1 (3.2)	1 (3.2)	
4	n (%)	1 (3.2)	0 (0)	
13	n (%)	1 (3.2)*	0 (0)	.9
Total no. of severe AEs	n	34	15	
No. of severe AEs by time point				
Rush induction	n (%)	0 (0)	0 (0)	
Build-up phase	n (%)	19 (55.9)	12 (80)	
Maintenance phase	n (%)	15 (44.1)	3 (20)	
Food challenge	n (%)	0 (0)	0 (0)	
No. of severe AEs by class				
Local oropharyngeal symptoms	n (%)	1 (2.9)	0 (0)	
Upper airway (rhinoconjunctivitis)	n (%)	1 (2.9)	0 (0)	
Pruritis	n (%)	0 (0)	1 (6.7)	
Urticaria	n (%)	7 (20.6)	0 (0)	
Abdominal pain	n (%)	3 (8.8)	4 (26.7)	
Diarrhea	n (%)	1 (2.9)	2 (13.3)	
Abdominal pain + diarrhea	n (%)	0 (0)	1 (6.7)	
Cough	n (%)	0 (0)	1 (6.7)	
Cough + urticaria	n (%)	6 (17.7)	0 (0)	
Asthma	n (%)	9 (26.5)	5 (33.3)	
Eczema	n (%)	1 (2.9)	0 (0)	

*One participant in the PPOIT group experienced repeated episodes of urticarial rash (with or without cough) during the maintenance phase. There was no accidental exposure to peanut or other allergens.

TABLE V. Characteristics of SAEs

		PPOIT group (N = 31)	Placebo group (N = 31)	*P* value
Patients who experienced ≥1 SAE	n (%)	3 (9.68)*	4 (12.9)†	.7
No. SAEs per patient				
0	n (%)	28 (90.3)	27 (87.1)	
1	n (%)	1 (3.2)	4 (12.9)	
2	n (%)	1 (3.2)	0 (0)	
3	n (%)	1 (3.2)‡	0 (0)	
Total no. of SAEs	n	6	4	
No. SAEs by time point				
Rush induction	n (%)	0 (0)	1 (25)	
Build-up phase	n (%)	1 (16.67)	3 (75)	
Maintenance phase	n (%)	5 (83.33)	0 (0)	
Food challenge	n (%)	0 (0)	0 (0)	
No. of SAEs by class				
Abdominal pain	n (%)	0 (0)	1 (25)	
Vomiting	n (%)	1 (16.67)	0 (0)	
Itchy throat + difficulty breathing, no objective signs	n (%)	0 (0)	1 (25)	
Asthma	n (%)	0 (0)	1 (25)	
Wheeze on auscultation	n (%)	0 (0)	1 (25)	
Urticaria + hoarse voice	n (%)	1 (16.67)	0 (0)	
Urticaria + wheeze	n (%)	2 (33.33)	0 (0)	
Urticaria + vomiting + wheeze	n (%)	1 (16.67)	0 (0)	
Urticaria + wheeze + CVS	n (%)	1 (16.67)	0 (0)	

CVS, Cardiovascular system involvement.

*Among children receiving PPOIT, 1 child experienced 3 SAEs, 1 had 2 SAEs, and 1 had 1 SAE. All SAEs in the PPOIT group occurred with doses taken at home, with 3 of these (in 2 subjects) occurring after tolerating maintenance dosing for 17.7 to 22 weeks. All SAEs in the PPOIT group were anaphylaxis, and 3 of these were treated with adrenaline.

†In the placebo group 4 SAEs occurred in 4 subjects, 2 in the hospital (one during rush induction and the other during up dosing) and 2 at home (4 and 7 days after updosing, respectively). Two were anaphylaxis treated with adrenaline (one during rush induction and one with home dose), 1 was an episode of asthma (home dose), and 1 was an episode of severe abdominal pain (updose).

‡One participant in the PPOIT group experienced 3 SAEs during the maintenance phase; the same participant reported 13 AEs. The first 2 SAEs comprised urticaria and wheeze, which each required reduction to the previous dose and updosing back to maintenance (as per protocol dose adjustment rules; for more information, see this article's Online Repository). The third SAE involved urticarial rash, wheeze, and collapse, which required stopping treatment (as per protocol stopping rules; for more information, see this article's Online Repository).

unresponsiveness. There is currently no consensus definition of sustained unresponsiveness in relation to the period of time a subject should remain off OIT before DBPCFC, and it remains uncertain exactly what duration of secondary allergen avoidance would be required to correctly identify unresponsiveness that is truly sustained. Consequently, there has been wide variation across different food allergy immunotherapy trials in the approach to assessing sustained unresponsiveness, with periods of secondary elimination ranging from 2 to 12 weeks.[19,36] To indicate the period of secondary elimination that is applied in food allergy RCTs, we would suggest the introduction of new terminology that defines the period of secondary elimination when describing sustained unresponsiveness, such as "4-week sustained unresponsiveness" or "8-week sustained unresponsiveness." We believe this would offer an ideal approach to describe the different periods of secondary avoidance used to assess sustained unresponsiveness in food allergy immunotherapy trials, while still allowing clear distinction from the assessment of desensitization that does not require any period of secondary avoidance.

Overall, the proportion of children experiencing AEs with PPOIT (45.2%) was in line with or lower than that in other reports of OIT (63% to 93%).[13,37,38] Remarkably, similar numbers of children experienced AEs or SAEs in the PPOIT and placebo groups during the rush and updosing phases, suggesting that anxiety associated with treatment might contribute to reactions. However, the absolute number of AEs was greater in the PPOIT group (34 vs 15) because 1 child reported 13 AEs (predominantly during home dosing). This participant subsequently experienced severe anaphylaxis to the study product, requiring discontinuation of treatment, which indicates that some children with peanut allergy might experience significant difficulty with PPOIT treatment. The AE data reinforce the need for high-level specialist care and parental education because the majority of AEs in the PPOIT group occurred at home.

We elected to evaluate a combined treatment intervention with probiotic and peanut OIT because at the time of study design, there was no convincing evidence that either OIT alone or probiotic alone was effective in inducing sustained unresponsiveness. Furthermore, although a factorial RCT design comprising 4 concurrent intervention arms assessing the individual contributions of OIT, probiotic, or combined therapy versus placebo offers theoretic advantages, this approach would require substantial staffing, financial resources, and patient numbers, which were not achievable in our setting and would be difficult to justify as a first-line approach to test PPOIT. Although we are

TABLE VI. Peanut sIgE and sIgG_4 values at study entry (T0), PPOIT cessation (T1), and 3 months after PPOIT cessation (T3)

	PPOIT group	Placebo group	*P* value*
sIgE (kU/L), T0			
Median (IQR), no.	14.3 (2.11 to 181), 31	8.25 (1.12 to 39.3), 31	
Geometric mean (95% CI)	15.82 (6.24 to 40.11)	7.97 (3.49 to 18.2)	
sIgE (kU/L), T1			
Median (IQR), no.	2.75 (1.21 to 35.8), 29	5.86 (1.29 to 59.9), 28	.67
Geometric mean (95% CI)	5.41 (2.21 to 13.25)	7.8 (3.06 to 19.89)	.57
sIgE (kU/L), T3			
Median (IQR), no.	3.46 (0.78 to 36.1), 27	9.98 (1.73 to 132.5), 28	.16
Geometric mean (95% CI)	4.63 (1.87 to 11.5)	13.15 (5.32 to 32.52)	.1
Difference in sIgE over time (kU/L)			
T1 vs T0			
Median (IQR)	−4.35 (−109.4 to −1.23)	−0.17 (−3.92 to 3.23)	.28
T3 vs T0			
Median (IQR)	−4.45 (−108.1 to −0.35)	0.62 (−1.6 to 25.62)	<.001
sIgG_4 (mgA/L), T0			
Median (IQR), no.	0.52 (0.13 to 0.89), 31	0.29 (0.16 to 0.75), 30	
Geometric mean (95% CI)	0.41 (0.27 to 0.61)	0.31 (0.19 to 0.51)	
sIgG_4 (mgA/L), T1			
Median (IQR), no.	6.01 (1.44 to 39.6), 29	0.23 (0.16 to 0.74), 28	<.001
Geometric mean (95% CI)	6.4 (3.08 to 13.29)	0.3 (0.18 to 0.49)	<.001
sIgG_4 (mgA/L), T3			
Median (IQR), no.	3.54 (1.24 to 29), 27	0.44 (0.19 to 1.37), 28	<.001
Geometric mean (95% CI)	4.58 (2.37 to 8.83)	0.42 (0.25 to 0.71)	<.001
Difference in sIgG_4 over time (mgA/L)			
T1 vs T0			
Median (IQR)	5.12 (1.08 to 38.97)	−0.03 (−0.13 to 0)	.001
T3 vs T0			
Median (IQR)	3.24 (1 to 28.48)	0 (−0.12 to 0.38)	.001

*The Wilcoxon rank sum (Mann-Whitney) test was applied for data expressed as medians (IQRs), The *t* test on the log scale was applied for data presented as geometric means (95% CIs).

unable to delineate the individual contributions of OIT and probiotics from our RCT, the beneficial effects in this study are likely to reflect synergistic modulation of immune responses by bacterial adjuvant and allergen OIT, with such coadministration being important for induction of clinical response. The probiotic on its own was unlikely to have produced the observed beneficial effects because PPOIT induced selective loss of peanut sensitization without modulating sensitization to other allergens; hence coadministration of peanut OIT was required. This is consistent with current understanding of oral tolerance as an active and antigen-driven immune response. Indeed, only 1 RCT has evaluated probiotic treatment for food (cow's milk) allergy and reported no effect.[39] Future RCTs comparing probiotic alone, allergen OIT alone, combined probiotic/allergen OIT, and placebo are required to clarify whether probiotic or OIT alone can provide similar beneficial or whether combined therapy yields synergistic benefits and to further investigate the underlying immune mechanisms.

Potential limitations to this trial are as follows. First, the protocol did not require a DBPCFC to confirm peanut allergy at study entry, and peanut challenges were only performed in 40% of participants. However, entry criteria were stringent and would be expected to correctly identify peanut allergy in 95% of participants. Moreover, the randomized trial design would be expected to distribute any misclassified peanut-tolerant participants evenly between the active and placebo groups, and indeed, the baseline mean peanut SPT wheal sizes and geometric mean peanut sIgE titers were similar in the 2 treatment groups. Furthermore, the rate of sustained unresponsiveness in the placebo group was 3.6%, which is consistent with the rate of natural resolution of peanut allergy and argues against the inclusion of a large number of participants who were not allergic to peanut.

Second, DBPCFCs to assess sustained unresponsiveness were performed 2 to 5.3 weeks after discontinuation of PPOIT. Although this approach was selected to be in line with NIAID-FDA recommendations for food allergy clinical trial design at the time the study was designed and registered, it is acknowledged that a longer period of at least 4 weeks after discontinuation of treatment would now be advised. We plan to conduct a long-term follow-up study (3-4 years after intervention) in which subjects will undertake a DBPCFC after 4 to 8 weeks of secondary peanut elimination to assess prolonged sustained unresponsiveness.

In conclusion, this is the first randomized trial of a novel combined therapy comprising a probiotic and peanut OIT and the first placebo-controlled RCT to perform a DBPCFC after a period of secondary peanut elimination in patients with peanut allergy. PPOIT was highly effective, with 7 children achieving possible sustained unresponsiveness if 9 are treated. The immunologic findings indicate modulation of the peanut-specific immune response. This is a promising therapy in the context of the increase in peanut allergy incidence and the unlikely natural resolution of peanut allergy. Further work is required to confirm whether subjects have attained prolonged sustained unresponsiveness and to delineate the relative contributions of probiotic and peanut OIT before this therapy should be considered for patients.

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Clinical implications: Combined administration of a probiotic immune-modifying adjuvant together with peanut OIT might offer a novel approach to induce possible sustained unresponsiveness in children with peanut allergy.

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METHODS

Recruitment

Participants were recruited between December 2008 and March 2011 from the RCH Department of Allergy and Immunology outpatient clinics and through print media.

Eligibility criteria

Children aged 1 to 10 years with peanut allergy were eligible for the study. Peanut allergy was defined as either (1) an immediate allergic reaction to peanut in the past 2 years and a positive peanut SPT response or sIgE level or (2) an immediate allergic reaction to peanut at any time previously and a positive peanut SPT response of 8 mm or greater or sIgE level of 15 kU/L or greater. These cutoffs for peanut SPT responses and sIgE levels correspond to 95% positive predictive values for clinical allergy.[E1,E2] A DBPCFC was not included in the protocol at study entry because of ethical concerns around performing 3 DBPCFCs in participants with peanut allergy, and 2 DBPCFCs were required to assess for outcomes of desensitization and sustained unresponsiveness. Nevertheless, a study entry open peanut challenge was offered to participants at study screening (Table E1).

Exclusion criteria were as follows: previous severe anaphylaxis to peanut (hypotension, collapse, and hypoxia), as required by the ethics committee because of increased risk for these subjects; use of β-blockers, cardiovascular disease, or poorly controlled asthma, which increase the risks associated with anaphylaxis; inflammatory intestinal conditions, indwelling catheters, and gastrostomies, which can increase the risk of probiotic-associated sepsis; children who are already taking probiotics; and wheat or cow's milk allergy (placebo might contain traces of wheat and probiotic might contain cow's milk protein).

Study conduct

Day 1 rush and updosing treatments were performed in the hospital. Participants' families were educated on recognition and emergency management of allergic reactions and provided with EpiPen/EpiPen Jr and an Anaphylaxis Action Plan (www.allergy.org.au). Parents completed a child diary record daily. Experienced allergy nurses conducted interviews (with completion of standardized questionnaires) at study commencement, every 2 weeks during the build-up phase, monthly during the maintenance phase, at each food challenge visit, and 3 months after the end of study treatment. Families were instructed to contact the study team for any concerns. Compliance was monitored by using diary records. Dietary instructions to trial completion were to strictly exclude peanut and probiotic supplements.

DBPCFC failure

DBPCFC failure was confirmed if the participant had objective symptoms during the challenge procedure: more than 3 urticarial lesions persisting for greater than 5 minutes, angioedema, vomiting, diarrhea, hoarse voice, stridor, wheeze, respiratory distress, pallor with hypotonia, and hypotension.

The rule for stopping the study was as follows:

- If severe allergic symptoms of reduced blood pressure or loss of consciousness develop, OIT will be discontinued.

Dose adjustment rules were as follows:

- If moderately severe allergic reactions without cardiovascular involvement, such as stridor, wheeze, or difficulty breathing, develop, the subsequent dose will be reduced to the previous dose amount, and then the reaction dose will be repeated before continuing with the protocol.
- If mild allergic reactions develop (urticaria, angioedema, vomiting, and abdominal pain) without evidence of respiratory or cardiovascular involvement, the dose will be repeated until symptoms abate before continuing with the protocol.
- There is no maximum time to reach maintenance dosing. Total duration of the treatment intervention will be a minimum of 18 months, which can be increased as required (if the build-up phase is prolonged because of reactions) to ensure a minimum of 6 months on maintenance dosing.
- If 1 to 2 days of OIT are missed, the subject can continue with the usual dose. If 3 to 4 days of OIT are missed, the next dose must be received at RCH. During updosing, if more than 4 days are missed during updosing, subjects will recommence OIT at day 1. During maintenance, if more than 5 to 7 days of OIT are missed, the participant would attend the hospital and receive his or her dose under medical supervision.

SAE

SAEs are defined as any untoward medical occurrence that:

- results in death;
- is life-threatening (note: the term life-threatening refers to an event/reaction in which the patient is at risk of death at the time of the event/reaction; it does not refer to an event/reaction that hypothetically might have caused death if it were more severe);
- requires inpatient hospitalization or prolongation of existing hospitalization (mild-to-moderate allergic reactions that were managed with over-the-counter medication, such as antihistamines and further observation in the hospitalization, were classified as severe AEs and not SAEs);
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect or a medically important event or reaction.

RESULTS

Primary outcome analysis: Adjusting for age, SPT wheal size at study entry, and use of corticosteroid medication during or at the end of the trial

Adjusting for age at randomization as a continuous outcome (odds ratio [OR], 1.4; 95% CI, 0.9-2.1), peanut-induced SPT wheal size at randomization as a continuous outcome (OR, 0.9; 95% CI, 0.8-1.1), and inhaled or ingested steroid medication commenced during (OR, 1.3; 95% CI, 0.1-21.2]) or at trial completion (OR, 2.1; 95% CI, 0.2-19.2) did not substantially alter the treatment effect ($P < .001$). Because there is little evidence of an age effect on the primary outcome, we deemed it unnecessary to investigate the effect of treatment on the primary outcome within the 2 age strata (≤5 years and >5 years).

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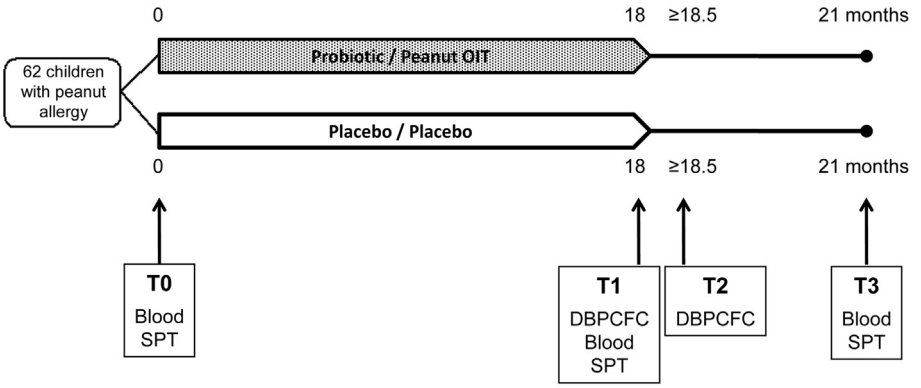

FIG E1. Study design and time lines. *T0*, Day 1, rush induction; *T1*, end of treatment intervention, DBPCFCs performed on all participants; *T2*, at least 2 weeks after discontinuation of treatment, DBPCFCs performed on participants who passed the T1 DBPCFC; and *T3*, 3 months after discontinuation of treatment.

TABLE E1. Dose of peanut protein that elicited an allergic reaction during peanut challenge at study entry

Peanut protein dose (g)	PPOIT group (N = 13)	Placebo group (N = 11)
<96.88 (smear)	1	3
96.9	6	0
193.8	0	4
387.5	2	2
775	3	1
1550	0	1
3100	1	0

TABLE E2. Time (in weeks) to reach maintenance dose

	PPOIT group (N = 30)	Placebo group (N = 30)
Mean (SD)	41.3 (11.5)	31.2 (8.2)
Median (IQR)	35.6 (33.3-47.1)	32.6 (30.4-34.1)
Missing*	1	1

*Withdrew from study during the build-up phase.

TABLE E3. Protocol violations in the PPOIT RCT

	PPOIT group (N = 31)	Placebo group (N = 31)
Missed doses		
Median (IQR)	12 (4-25)	9 (3-15)
Accidental peanut ingestion		
n (%)	0	3 (9.7)
Use of probiotics		
n (%)	3 (9.7)	2 (6.5)
Appointment rescheduled by parent or staff for nonmedical reason		
n (%)	18 (58.1)	13 (41.9)
Non–dose-related violations related to sample collection time		
n (%)	2 (6.5)	1 (3.2)
Incorrect dose		
n (%)	10 (32.3)	7 (22.6)

TABLE E4. Peanut intake at T3 in participants who achieved 2-week sustained unresponsiveness

PPOIT group
103
Two teaspoons of peanut butter weekly
204
Two tablespoons of peanut butter 3× per fortnight
207
One tablespoon of peanut butter weekly
208
Ten peanuts twice a week
212
One tablespoon of peanut butter 2 to 3 times/week
214
Twelve peanuts twice a week
218
Three peanuts daily
223
Twelve to 15 peanut M&Ms or 2 teaspoons peanut butter 2 or 3 times/week
228
Twelve to 15 frozen peanut butter buttons 2 or 3 times/week
229
Inconsistent intake because of frequent illness; no longer taking peanut
301
One tablespoon of peanut butter/1 picnic bar/week
303
One picnic bar a week
401
Twelve peanuts 1-2 times/week
404
Ten to 14 peanut M&Ms weekly
406
Four peanut M&Ms per day
407
Twelve peanut M&Ms 2 to 3 times/week
409
One satay skewer and 1 Snickers bar/week
416
Twelve peanuts weekly
418
Twelve peanut M&Ms twice a week
423
Bite-size Snickers bar daily
425
Ten to 20 peanut M&Ms 2 times a week
430
Ten to 12 ground peanuts mixed in breadcrumbs on schnitzel weekly
431
Five whole peanuts weekly
Placebo group
426
Twenty-four peanuts twice a week

TABLE E5. SPT wheal size results by study time point

	PPOIT group	Placebo group
T0		
Egg		
Median (IQR), no.	2 (0-8.5), 31	2 (0-6.5), 31
Milk		
Median (IQR), no.	0 (0-0), 31	0 (0-0), 31
Cashew		
Median (IQR), no.	2 (0-5.5), 31	3 (0-10), 31
Almond		
Median (IQR), no.	0 (0-3), 31	0 (0-4), 31
Walnut		
Median (IQR), no.	2 (0-4.5), 31	0 (0-4), 31
Der p 1		
Median (IQR), no.	10 (2-16.5), 31	8 (1-14), 31
T1		
Egg		
Median (IQR), no.	0 (0-2), 29	3 (1-10), 27
Milk		
Median (IQR), no.	0 (0-0), 29	0 (0-1), 27
Cashew		
Median (IQR), no.	1 (0-12), 29	2 (0-7), 27
Almond		
Median (IQR), no.	1 (0-2), 29	1 (0-2), 27
Walnut		
Median (IQR), no.	0 (0-2), 29	2 (0-3.5), 27
Der p 1		
Median (IQR), no.	6 (4-11), 29	5 (2-11), 27
T3		
Egg		
Median (IQR), no.	1 (0-6.5), 27	2.3 (0.5-5.8), 28
Milk		
Median (IQR), no.	0 (0-1), 27	1 (0-1), 28
Cashew		
Median (IQR), no.	2 (0-14.5), 27	2 (1-10.8), 28
Almond		
Median (IQR), no.	0 (0-2.3), 28	1.8 (0-2.8), 28
Walnut		
Median (IQR), no.	2 (0-3), 26	2 (0.5-4), 28
Der p 1		
Median (IQR), no.	6 (4.5-11.5), 27	7.8 (2-12.5), 28

Median SPT wheal sizes did not differ significantly ($P < .05$) between the children in the PPOIT and placebo groups at any time point. The only exception was egg SPT wheal size at T1 ($P = .008$).

TABLE E6. Reactions during rush induction

Study no.	Treatment group	Dose (mg peanut protein)	Reaction	Initial build-up dose (mg peanut protein)
204	PPOIT	0.4	24 min after 0.4-mg dose right: eye swollen, erythema, urticaria ×1; treated with cetirizine; symptoms resolved 2 h and 15 min after dose	0.4
227	PPOIT	3	Immediately after 1.5-mg dose: abdominal pain; 35 min after 3-mg dose: 3× urticaria; cetirizine given 50 min after 3-mg dose; abdominal pain resolved 1 h and 5 min after 3-mg dose, urticaria resolved 2 h and 5 min after 3-mg dose	1.5
416	PPOIT	6	5 min after 6-mg dose: abdominal pain; rush stopped, abdominal pain persisted for 1 hour; cetirizine given 1 h and 5 min after dose; abdominal pain resolved immediately with cetirizine but resumed 30 min later and then resolved again 30 min later	6
420	PPOIT	6	5 min after 6-mg dose: sore throat; 10 min after 6-mg dose: abdominal pain; cetirizine and ibuprofen administered 20 min after dose; symptoms resolved 1 h after dose	6
209	PPOIT	12	5 min after 6-mg dose: oral tingling, which resolved after 15 min; 30 min after 12-mg dose: itchy chin, no urticaria or erythema observed on examination	6
419	Placebo	12	35 min after 12-mg dose: soft wheeze in right anterior chest on auscultation, no audible wheeze; 0.5 mL 1:1000 adrenaline administered 40 min after dose; wheeze resolved 50 min after dose	6
203	PPOIT	12	30 min after 6-mg dose: "scratchy" tongue, nose, rhinorrhea, and urticaria ×1; 30 min after 12-mg dose: abdominal pain and itchy nose; cetirizine given 40 min after 12-mg dose; paracetamol given 1 h and 5 min after 12-mg dose; abdominal pain persisted intermittently for 3 h after dose	6
430	PPOIT	12	25 min after 6-mg dose: mild abdominal pain; 25 min after 12-mg dose: swollen left eye; cetirizine given; abdominal pain still present 2 h after 12-mg dose, eye swelling resolved	12
218	PPOIT	12	20 min after 12-mg dose: mild abdominal pain	12