THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Jones SM, Kim EH, Nadeau KC, et al. Efficacy and safety of oral immunotherapy in children aged 1–3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study. *Lancet* 2022; **399:** 359–71.

APPENDIX: IMPACT Trial

TABLE OF CONTENTS

1. *INVESTIGATORS and AFFILIATIONS*

Investigators
Stacie M. Jones, MD[1], Edwin H. Kim, MD[2], Kari C. Nadeau, MD, PhD[3], Anna Nowak-Wegrzyn, MD[4,6], Robert A. Wood, MD[5], Hugh A. Sampson, MD[4], Amy M. Scurlock, MD[1], Sharon Chinthrajah, MD[3], Julie Wang, MD[4], Robert D. Pesek, MD[1], Sayantani B. Sindher, MD,[3], Mike Kulis, PhD[2], Jacqueline Johnson, DrPH[7], Katharine Spain, MS[7], Denise Babineau, PhD[7], Hyunsook Chin, MS[7], Joy Laurienzo-Panza, RN[8], Rachel Yan, MS[9] , David Larson, PhD[10], Tielin Qin, PhD[10], Don Whitehouse, MS[9], Michelle L. Sever, PhD[7], Srinath Sanda, MD[9], Marshall Plaut, MD[8], Lisa M. Wheatley, MD, MPH[8], and A. Wesley Burks, MD[2] for the Immune Tolerance Network

Affiliations
[1]Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, AR, USA; [2]Departments of Medicine and Pediatrics, University of North Carolina, Chapel Hill, NC, USA; [3]Department of Pediatrics and Sean N. Parker Center for Allergy and Asthma Research, Stanford University, Palo Alto, CA, USA; [4]Department of Pediatrics, Mount Sinai School of Medicine, New York, NY, USA; [5]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [6]Department of Pediatrics, New York University Langone Health, New York, NY, USA; [7]Rho Federal Systems Division, Durham, NC, USA; [8]National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIAID, NIH), Bethesda, MD, USA; The Immune Tolerance Network, [9]San Francisco, CA, USA and [10]Bethesda, MD, USA; [11]Benaroya Research Institute, Virginia Mason University, Seattle, WA

2. *SUPPLEMENTAL METHODS*

2a. INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria:
Patients must meet *all* of the following criteria to be eligible for this study:
1. Age 12 months to less than 48 months, either gender.
2. Clinical history of peanut allergy or avoidance of peanut without ever having eaten peanut.
3. Serum IgE to peanut of > 5 kU_A/L determined by UniCAP™.
4. Wheal ≥ 3mm on skin prick test to peanut extract compared to a negative control.
5. A clinical reaction at or below ingestion of 1 g peanut flour (500 mg peanut protein) during screening blinded OFC.
6. Written informed consent from parent/guardian.

Exclusion Criteria:
Patients who meet any of the following criteria will *not* be eligible for this study:
1. History of severe anaphylaxis with hypotension to peanut.
2. Documented clinical history of allergy to oat
3. Suspected allergy to oat and a wheal greater than or equal to 7mm on skin prick test to oat extract compared to a negative control.
4. Chronic disease other than asthma, atopic dermatitis, rhinitis requiring therapy; e.g., heart disease or diabetes.
5. Active eosinophilic gastrointestinal disease in the past 2 years.
6. Participation in any interventional study for the treatment of food allergy in the 6 months prior to visit
7. Inhalant allergen immunotherapy that has not yet reached maintenance dosing.
8. Severe asthma, as indicated by repeated hospitalizations or hospital emergency department visits.
9. Moderate asthma defined according to National Asthma Education and Prevention Program Expert Panel that requires more than fluticasone 440 mcg or its equivalent daily for adequate control.
10. Inability to discontinue antihistamines for skin testing, blinded OFC and the initial dose escalation.
11. Use of omalizumab or other non-traditional forms of allergen immunotherapy (e.g., oral or sublingual) in the 12 months prior to visit -1.
12. Any systemic therapy which in the judgment of the investigator could be immunomodulatory (e.g., rituximab) in the 12 months prior to visit -1. Systemic corticosteroid therapy of up to a total of 3 weeks is allowed.
13. Use of any investigational drug in 90 days prior to visit -1.
14. Plan to use any investigational drug during the study period.
15. The presence of any medical condition that the investigator deems incompatible with

2.b. ORAL IMMUNOTHERAPY PROTOCOL

Study Product:

Lightly roasted, partially defatted (12% fat) peanut flour was purchased from Golden Peanut Company (Blakely, GA). Peanut flour and matching placebo (oat flour, Arrowhead Mills, Inc., Melville, NY) were weighed and vialed at the University of North Carolina Chapel Hill GMP manufacturing facility, then distributed to study site pharmacies.

OIT Dosing Phases (see Dosing Table below):

Initial Dose Escalation Phase:

This occurred on a single day in which multiple doses were given. Peanut or placebo was given incrementally and increased every 15-30 minutes until a dose of 6 mg peanut protein or placebo flour (at an equivalent volume) was given. The first four doses were administered as a peanut flour extract of 0.1 to 0.8 mg peanut protein or placebo flour extract. The last three doses were given as 1.5 to 6 mg peanut protein or placebo flour. All participants started dosing at 0.1 mg. Participants were required to tolerate a dose of at least 1.5 mg peanut protein or placebo flour to remain in the study. The table below, from the protocol, shows the 3 possible outcomes from the initial dose escalation with participants reaching 6 mg versus 3 mg versus 1.5 mg as their top tolerated peanut protein dose, the dose which would initiate the first stage of build-up dosing.

	Dose Escalation for Maximum Initial Dose Escalation of:			**First day at Dose**	**Week Number**
	6 mg	**3 mg**	**1.5 mg**		
Initial Dose Escalation	0.1	0.1	0.1	0	0
	0.2	0.2	0.2	0	0
	0.4	0.4	0.4	0	0
	0.8	0.8	0.8	0	0
	1.5	1.5	1.5	0	0
	3.0	3.0		0	0
	6.0			0	0

Build-up Phase:
After the initial dose escalation day, the participant returned to the research unit the next morning for an observed dose administration of the highest tolerated dose from the initial escalation day, 6 mg versus 3 mg, versus 1.5 mg peanut protein. The participant then continued daily OIT dosing at home and return to the research unit every 2 weeks for a dose escalation. The dosing escalation table is shown below. Participants who did not reach the 2000 mg peanut protein or placebo flour dose during the build-up phase could enter the maintenance phase at their highest tolerated dose, which was required to be at least 250 mg peanut protein or placebo flour. The build-up phase comprised 30 weeks but could be extended longer if symptoms occurred during build-up dosing or if a reduction in dosing was required (either due to symptoms or due to missed doses due to illness). Build-up was stopped after 3 attempted, unsuccessful updosing events, and the maintenance phase was initiated if the participant reached at least 250 mg peanut protein dosing daily.

	Dose Escalation for Maximum Initial Dose Escalation of:			**First day at Dose**	**Week Number**
	6 mg	**3 mg**	**1.5 mg**		
Build-up	6.0	3.0	1.5	1	0
	12	6.0	3.0	14	2
	25	12	6.0	28	4
	50	25	12	42	6
	100	50	25	56	8
	150	100	50	70	10
	250	150	100	84	12
	400	250	150	98	14
	600	400	250	112	16
	900	600	400	126	18
	1200	900	600	140	20
	1600	1200	900	154	22
	2000	1600	1200	168	24
	2000	2000	1600	182	26
	2000	2000	2000	196	28

Maintenance Phase:
Participants continued on daily OIT with return visits every 13 weeks. At the end of this phase, the participant underwent a DBPCFC to 5000 mg peanut protein. The maintenance phase comprised 104 weeks.

Avoidance Phase:
In this phase, participants stopped OIT and avoided peanut consumption. They were seen 2 weeks and 26 weeks after initiating this phase. At the completion of this phase participants had a DBPCFC to 5000 mg peanut protein. The avoidance phase comprised 26 weeks.

Post-challenge:
If participants did not have a clinical reaction during the open feeding at the end of avoidance, they were allowed to consume peanut and had one visit which included peripheral blood sampling for mechanistic assays assessments. The post-challenge phase comprised 2 weeks.

Missed Doses for Non-Compliance
Missed doses at any phase of the study could pose a significant risk to the enrolled subjects.
The algorithm for missed consecutive doses is as follows:
• 1 dose — the next dose would be the current dose and could be given at home
• 2 doses in a row — the next dose would be the current dose and could be given at home
• 3 or 4 doses in a row — the next dose would be the current dose and would be given under observation in the clinical research unit
• 5 to 7 doses in a row-— the next dose would be 75% of the current dose and would be given under observation in the clinical research unit
• 8 to 14 doses in a row — initiate the next dose as approximately 50% of the last tolerated dose. This would be done under observation in the clinical research unit.
After any dose reduction, dose escalation would occur in the clinical research unit with an escalation no sooner than weekly and no longer than every 4 weeks with dose increases of 1 dose level at each escalation. If symptoms occurred, the dosing symptom rules in the build-up phase would apply. Study site staff would contact the investigator if 1 or 2 missed doses were due to an allergic reaction or symptom. Study staff contacted the investigator for all missed doses of 3 or more.

Management of Dosing During Concurrent Illness:
If a participant had gastroenteritis, nausea and vomiting, upper-respiratory infection, active wheezing, fever greater than 100.5° F, or other similar illness, the parent was instructed to hold the dose and call the study center for instructions regarding dosing. Depending on the severity of the illness, the study center could instruct the parent to hold dosing for one or more days. Re-initiation of dosing was according to the dosing algorithm.

Documentation of Dose-Related Symptoms
Dosing was modified for dose-related symptoms, illness or other circumstances per protocol. All adverse events, including dose-related and DBPCFC-related symptoms, were captured on the study diary, via contact with the study team, and case report forms and reported in the electronic data capture system. Dosing reactions were defined as related to dosing if occurring within 2 hours of dosing; otherwise, these were captured as adverse events; all were scored for severity.

2.c. ORAL FOOD CHALLENGE PROTOCOL
Oral food challenges (500 mg and 5000 mg peanut protein)
All oral food challenges conducted in the study were double-blind, placebo-controlled food challenges (DBPCFC) and were performed so that neither the participant, nor the participant's caregiver, nor the physician knew which challenge contained the peanut or the placebo. The 500 mg DBPCFC results was unblinded in order to determine eligibility for the study since the participant was required to have a clinical reaction to this DBPCFC to begin dosing.

All DBPCFC were undertaken under direct medical supervision in a clinical research center or food challenge area with emergency medications and staff immediately available and followed established study procedures. Prior to a DBPCFC, participants were off antihistamines for an appropriate length of time (5 half-lives of the antihistamine being used), and participants were assessed for an exacerbation of asthma as determined by active wheezing and for a current flare in atopic dermatitis. Participants judged by the investigator to be at significant risk of severe reaction had an intravenous line placed prior to the DBPCFC. Such participants would include those with a history of life-threatening anaphylaxis to any food, or a reaction to any food which caused dehydration and required intravenous fluid resuscitation.

A uniform approach for DBPCFC was used with the order of placebo or active peanut food challenges being randomly assigned by an unblinded dietician. The DBPCFC consisted of a total of 500 mg or 5000 mg of the peanut protein or placebo flour in gradually increasing doses at intervals of 15-30 minute. Although these minimum standards have been used safely in the past, the investigator could use clinical judgment to increase the intervals between doses or repeat lower doses, if there is a concern that a reaction was developing. For the 500 mg DBPCFC, the set of doses were comprised of the following: 1%, 4%, 10%, 20%, 20%, 20%, 25% (for a maximal cumulative dose of 505 mg). For the 5000 mg DBPCFC, the set of doses was comprised of the following: 0.1%, 1%, 4%, 10%, 20%, 20%, 20%, 25% (for a maximal cumulative dose of 5005 mg). Though many published challenges begin with 5% initial doses, the minimum dose for this study was chosen to be a lower dose according to additional recent recommendations and consensus at the time of study onset. Most DBPCFCs were conducted during two separate days. Food challenges were only conducted on a single day if the first challenge did not induce symptoms or require treatment and the second challenge was performed at least 2 hours was required to separate the last dose of the first challenge from the first dose of the second challenge.

Open Feeding of Peanut after Week 160 DBPCFC
An open feeding of peanut was conducted for all participants who passed the 5000 mg DBPCFC at week 160. The participant ingested a meal size portion (approximately 8000 mg of peanut protein) of the food in its natural form (e.g., 2 tablespoons peanut butter) in an open setting in which all of the involved parties are aware of the identity of the food to make sure that it is

tolerated. The feeding was conducted 2 hours after passing a 5000 mg DBPCFC. The peanut-containing food was consumed during a 120-minutes maximum (30-60 minute preferred) time period at the participant's own pace (i.e., not in a stepwise or graded fashion). If the participant passed the open feeding, the participant was observed for a minimum of 2 hours or longer as indicated by the participant's status. If the participant had no symptoms during open feeding but could not consume the full amount of food material, a repeat open feeding could be scheduled within 14 days to determine the outcome.

Oral Food Challenge Outcome

Frequent assessments were made for symptoms affecting the skin, gastrointestinal tract, and/or respiratory tract. Outcome of the challenge was determined by evaluating the participant at frequent intervals using the criteria in the table below: A positive food challenge was defined by the presence of the following: One or more major criteria and/or two or more minor criteria.[5] Otherwise, the food challenge was considered negative. A challenge was discontinued and considered positive if in the judgment of the investigator, the subject was experiencing an allergic reaction even though scoring criteria were not fulfilled. The investigator documented why she or he believed the subject was experiencing an allergic reaction. All symptoms were required to be of new onset and not due to ongoing disease. Symptoms were required to occur no later than 2 hours after the last dose. During a challenge, if a participant has a false positive reaction to the placebo, both the peanut and placebo challenge could be repeated, at the study physician's discretion. In the event that a conclusive 5000 mg DBPCFC outcome could not be determined at week 134, the participant was scheduled to return to the clinic for repeat 5000 mg DBPC and continued taking maintenance dose OIT. The scorer was blinded to treatment assignment through week 160.

Criteria for Determining the Outcome of Food Challenge[5]

Major Criteria
Confluent erythematous pruritic rash Respiratory signs (at least one of the following): Wheezing Inability to speak Stridor Dysphonia Aphonia At least 3 urticarial lesions At least 1 site of angioedema At least 2 distinct episodes of vomiting Hypotension for age not associated with vasovagal episode Evidence of severe abdominal pain (such as abnormal stillness or doubling over) that persists for ≥ 5 minutes
Minor Criteria
1 – 2 urticarial lesions Single episode of vomiting Diarrhea Notably distressed because of nausea and/or abdominal pain with decreased activity Dry hacking cough that lasts for at least 4 minutes Complaint of throat tightness and/or pruritus plus at least 4 episodes of throat clearing Persistent rubbing of nose or eyes that lasts for at least 5 minutes Persistent rhinorrhea that lasts for at least 5 minutes Continuous, hard scratching that lasts for at least 3 minutes Distinct change in affect: whining, crying, and/or clinging to parent

2.d. ANAPHYLAXIS STAGING SYSTEM[1]

Criteria for Diagnosis:

Anaphylaxis is likely when any *one* of the three following sets of criteria are fulfilled:

1. Acute onset of an illness (minutes to hours) with involvement of:
• Skin/mucosal tissue (e.g., *generalized* hives, itch or flush, swollen lips/tongue/uvula) *AND*
• Airway compromise (e.g., dyspnea, stridor, wheeze/ bronchospasm, hypoxia, reduced PEF) AND*/OR*
• Reduced BP or associated symptoms (e.g., hypotonia, syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to the allergen (minutes to hours):
• Skin/mucosal tissue (e.g., *generalized* hives, itch/flush, swollen lips/tongue/uvula)**

• Airway compromise (e.g., dyspnea, stridor wheeze/bronchospasm, hypoxia, reduced PEF)
• Reduced BP or associated symptoms (e.g., hypotonia, syncope, incontinence)
• *Persistent* GI symptoms (e.g., nausea, vomiting, crampy abdominal pain)
3. Reduced BP after exposure to the allergen (minutes to hours):
• Infants and Children: low systolic BP (age-specific) or > 30% drop in systolic BP*
• Adults: systolic BP < *90* mm Hg or > 30% drop from their baseline
* Low systolic BP for children is defined as < 70 mmHg from 1 month to 1 year; less than (70 mmHg + [2 x age]) from 1-10 years; and < 90 mmHg from age 11-17 years.
** Isolated skin or mucosal lesions following the ingestion of a food constitute a "food-induced allergic reaction."

Staging System of Severity of Anaphylaxis
Stage Defined by:
1. *Mild (skin & subcutaneous tissues, GI, &/or mild respiratory)*
Flushing, urticaria, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and/or emesis
2. *Moderate* (mild symptoms + features suggesting moderate respiratory, cardiovascular or GI symptoms)
Marked dysphagia, hoarseness, and/or stridor; shortness of breath, wheezing and retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness
3. *Severe* (hypoxia, hypotension, or neurological compromise)
Cyanosis or SpO2 < 92% at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence.

Of note, "anaphylaxis" was not captured as a distinct variable in this study, rather the Sampson criteria was used by investigators to manage allergic reactions noted in participants during dosing or DBPCFC reactions with severity grading recorded.

2.e. CONSORTIUM FOR FOOD ALLERGY RESEARCH (CoFAR) GRADING SYSTEM FOR ALLERGIC REACTIONS[2]

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

2.f. ASSESSMENT OF GASTROINTESTINAL SYMPTOMS

Baseline Assessments

Gastrointestinal (GI) symptoms were assessed at baseline as follows:

Question 1 "Prior to enrollment in the study, did your child have:"

	No	*Yes and active but infrequent (less than 3x/mo)*	*Yes and active (3x/month or more)*	*Yes, active, (3x/month or more) and requiring treatment**
"Colic"				
Intolerance of formula or breastmilk				
"Reflux" or frequent spitting up				
Abdominal pain				
Constipation				
Poor appetite				

**please specify any medications or diet changes*

Question 2 "Currently, does your child exhibit any of the following:"

	No	*Yes and active but infrequent (less than 3x/mo)*	*Yes and active (3x/month or more)*	*Yes, active, (3x/month or more) and requiring treatment**
Difficulty swallowing				
Refusal to eat				
Abdominal pain				
Vomiting				

**please specify any medications or diet changes*

Ongoing Assessments

GI symptoms were assessed during the study as follows:

Question 3 "Has your child experienced a change in any of the following since his/her last study visit (Mark all that apply)?

	Does Not Apply (NA)	Newly Appeared in Interval	Better	Same	Worse
Difficulty swallowing					
Refusal to eat					
Abdominal pain					
Vomiting					

Modified Aceves Questionnaire[3]

For any "yes" responses to Question 2 and for any "yes" responses to Questions 3 falling in the shaded cells, GI symptoms were further assessed with a the completion of the following questionnaire:

	0	1	2
1. Does your child ever feel food coming back up into his / her throat *And /or* Do you observe your child repetitively or forcefully swallowing?			
2. Does your child complain about stomach pains *And /or* Is your child often irritable for no apparent reason and you suspect belly pain?			
3. How often does your child complain about feeling like throwing up? *And /or* How often does your child throw up?			
4. How often does your child eat too little or get full before finishing his or her meal?			
5. How often does your child wake up during the night from belly pain?			
6. How often have you noticed blood in your child's stool during the last 3 months?			
7. Does your child have difficulty swallowing *And /or* Does swallowing feel painful to your child?			

Subsequent actions were determined by the total score as follows:
Scoring Key: 0=Not at all; 1 Mild. No problem with daily activities; medications given as needed; 2=Moderate-severe. Interferes with daily activities or requires daily medications.
A total score of 5 or more was reported to the site investigator. The investigator would follow-up with a discussion with the participant's family to collect additional history. Depending on the severity of the symptoms, the investigator could instruct the participant's family to consult with the participant's primary provider about further workup and treatment, review dosing instructions, or hold and/or adjust dosing for one or more days. In addition, the investigator could consider whether to refer the participant to a gastroenterologist. The DAIT/NIAID Medical Monitor, the Protocol Chair or co-Chair, and the ITN Clinical Trial Physician were notified based on the principal investigator's judgment.

2.g. IMMUNE ASSAYS

Statistical Analyses with Mechanistic Data

Mechanistic data were analyzed for participants in per-protocol population who were study-compliant through the avoidance phase and had an evaluable blinded DBPCFCs at the end of the maintenance and avoidance phases (per protocol population for the secondary endpoint). For comparisons between placebo and PnOIT groups, a linear mixed model was used with adjustment for baseline levels. For comparisons among PnOIT outcome groups, a linear mixed model was used without adjustment for baseline levels. The threshold for significance was $p<0.05$ (two-sided). Since all analyses were considered exploratory, p-values were not adjusted for multiple comparisons. All analyses were performed with SAS Version 9.4 (SAS Institute Inc., Cary, NC) and R version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria).

Skin prick testing

The skin prick test was performed over the course of the study on clear, eczema-free skin of the back or forearm by using a Greer Pick® (Stallergenes Greer, Inc., Cambridge, MA) to deliver a small droplet of 0.5% glycerine saline, 10 mg/mL histamine dihydrochloride (negative and positive controls, respectively), and peanut extract (Stallergenes Greer, Inc.). After 15 minutes, wheal sizes were obtained by measuring the longest and widest length of the wheal in millimeters and dividing by 2. Peanut skin prick test results were reported as "calculated wheals" (peanut wheal – the negative control wheal).

Antibody assays

The ImmunoCAP 1000 system (Viracor Eurofins, Lee's Summit, MO) was used to measure peanut-specific IgE and IgG4 levels in serum. Plasma IgE and IgG4 to peanut components (Ara h1, 2, 3, 6), were measured using the ImmunoCAP 250 system (Phadia-Thermo Fisher Scientific, Waltham, MA). Peanut IgG4 to peanut IgE ratios were calculated by using the formula IgG4 ÷ (IgE × 2.4), and peanut IgE to total IgE ratios were calculated using the formula (peanut IgE ÷ total IgE) * 100 as previously described.[4,5]

Basophil Activation Assay

Whole blood was collected in lithium heparin tubes and shipped overnight to a core facility where the basophil activation test was performed as previously described.[6] Briefly, 100µl of whole blood was incubated with the same volume of RPMI 1640 (to measure spontaneous activation) or peanut protein (Golden Peanut Company, LLC, Alpharetta, GA) diluted in RPMI 1640. After incubating for 30 minutes at 37°C, degranulation was stopped by adding cold 20 mM EDTA. Cells were then stained with anti-CD123-FITC (eBioscience, San Diego, CA), anti-CD203c-PE (BioLegend, San Diego, CA), anti-HLA-DR-PerCP (BioLegend), and anti-CD63-APC (BioLegend). Flow cytometry was performed using a BD LSRII flow cytometer (BD Biosciences, San Jose, CA) and data analyzed using FlowJo software (Tree Star Inc., Ashland, OR). Basophils were identified as SSClow/CD203c+/CD123+/HLA-DR- cells, and activation was reported as the mean percentage of CD63+ basophils following stimulation with 10 and 100 ng/mL peanut extract and after subtracting spontaneous (RPMI 1640) activation levels.

Statistical Analyses of Desensitization and Remission

Primary Analysis of Desensitization and Remission

As specified in the protocol and the SAP, the probability of desensitization (or remission) to peanut was compared between arms using a multivariable logistic regression model with site, baseline peanut-specific IgE and age at screening as covariates in the model.

Table 1 and 2 provides the results of these analyses in the ITT sample and the PP sample for desensitization (or remission). Table 1 provides the estimated probabilities of desensitization or remission (as well as the associated 95% CI and p-value) based on an unadjusted model (i.e., logistic regression model that only includes treatment arm) and the adjusted model (i.e., logistic regression model that includes treatment arm, site, baseline peanut-specific IgE, and age at screening). Table 2 provides the adjusted odds ratios (as well as the associated 95% CIs and p-value) for the covariates site, age at screening, and baseline peanut-specific IgE.

Table 1. Unadjusted and adjusted probabilities of desensitization or remission

Sample	Model	Probability of Desensitization (95% CI) p-value	Probability of Remission (95% CI) p-value
ITT	Unadjusted	Peanut OIT: 0.71 (0.61-0.79) Placebo: 0.02 (0-0.13) p<0.0001 Difference: 0.69 (0.59-0.79)	Peanut OIT: 0.21 (0.14-0.30) Placebo: 0.02 (0-0.13) p=0.014 Difference: 0.19 (0.10-0.28)
	Adjusted for site, age at screening, and baseline peanut-specific IgE	Peanut OIT: 0.74 (0.63-0.82) Placebo: 0.01 (0-0.10) p<0.0001 Difference: 0.73 (0.62- 0.83)	Peanut OIT: 0.11 (0.05-0.22) Placebo: 0 (0-0.04) p=0.0031 Difference: 0.10 (0.03-0.18)
PP	Unadjusted	Peanut OIT: 0.84 (0.74-0.90) Placebo: 0.03 (0-0.18) p<0.0001 Difference: 0.81 (0.71-0.91)	Peanut OIT: 0.29 (0.19-0.40) Placebo: 0.0435 (0-0.25) p=0.040 Difference: 0.24 (0.11-0.38)
	Adjusted for site, age at screening, and baseline peanut-specific IgE	Peanut OIT: 0.93 (0.80-0.98) Placebo: 0.01 (0-0.10) p<0.0001 Difference: 0.92 (0.83-1)	Peanut OIT: 0.20 (0.10-0.35) Placebo: 0.01 (0.0009-0.10) p=0.0080 Difference: 0.19 (0.07-0.31)

Table 2. Adjusted odds ratios of desensitization or remission for each covariate

Model	Variable	OR of Desensitization (95% CI) p-value	OR of Remission (95% CI) p-value
ITT	Site	Arkansas vs. UNC: 1.98 (0.40-9.82) Johns Hopkins vs. UNC: 2.92 (0.68-12.60) Mount Sinai vs. UNC: 1.01 (0.26-3.88) Stanford vs. UNC: 4.04 (0.89-18.35) p=0.24	Arkansas vs. UNC: 0.83 (0.11-6.44) Johns Hopkins vs. UNC: 2.52 (0.33-19.47) Mount Sinai vs. UNC: 2.09 (0.30-14.53) Stanford vs. UNC: 5.11 (0.86-30.47) p=0.29
	Age at screening (per month increase)	0.95 (0.89-1.00) p=0.065	0.91 (0.86-0.97) p=0.0045
	Baseline peanut-specific IgE (per 10 fold increase)	0.45 (0.18-1.15) p=0.095	0.08 (0.02-0.33) p=0.0006
PP	Site	Arkansas vs. UNC: 11.20 (0.24-520.93) Johns Hopkins vs. UNC: 2.13 (0.29-15.77) Mount Sinai vs. UNC: 0.62 (0.09-4.12) Stanford vs. UNC: 1.88 (0.25-13.87) p=0.46	Arkansas vs. UNC: 1.10 (0.11-11.47) Johns Hopkins vs. UNC: 2.53 (0.22-29.72) Mount Sinai vs. UNC: 1.85 (0.21-16.45) Stanford vs. UNC: 2.55 (0.36-17.95) p=0.86
	Age at screening (per month increase)	0.91 (0.82-1.01) p=0.084	0.91 (0.84-0.98) p=0.011
	Baseline peanut-specific IgE (per 10 fold increase)	0.15 (0.04-0.63) p=0.0096	0.085 (0.02-0.42) p=0.0025

Identification of Predictors for Desensitization or Remission in Peanut OIT Participants

The following post-hoc analyses were performed for each endpoint separately to identify predictors of desensitization or remission in participants randomized to peanut OIT:

1. Fit a univariate logistic regression model to the endpoint in participants randomized to peanut OIT in the ITT sample using each of the following clinical and mechanistic parameters:
    - Clinical parameters: site, age at screening, history of atopic dermatitis, history of asthma, baseline SPT size, baseline peanut-specific IgE, and baseline cumulative tolerated dose during DBPCFC to peanut
    - Mechanistic parameters: baseline peanut component-specific IgE to Ara h 1, 2, 3, and 6 components, BAT, and BAT area under the curve
2. Using any predictors that were statistically significant at the 0.05 level in the univariate analyses performed in the previous step, fit a multivariable logistic regression model to the endpoint in participants randomized to peanut OIT in the ITT sample.
3. Perform backward stepwise selection using this fitted multivariable logistic regression model to select the final list of predictors of the endpoint. The final model chosen is based on the lowest Akaike's Information Criterion.

Using the approach above, baseline peanut component-specific IgE to the Ara h 6 component was identified as the only predictor of desensitization in participants randomized to peanut OIT in the ITT sample (see Table 3). Based on the final fitted model, for every 10 fold increase in the baseline peanut component-specific IgE to Ara h 6, the odds of desensitization decreases by 65% (95% CI: (1%, 88%); p-value=0.048).

Table 3. Results of multivariable logistic regression for desensitization to peanut in participants randomized to peanut OIT in the ITT sample (n=96)

Variable	Odds Ratio (95% CI)	p-value
Baseline peanut component-specific IgE to Ara h 6 (per 10 fold increase)	0.35 (0.12-0.99)	0.048

Additionally, the approach above identified baseline peanut-specific IgE and age at screening as predictors of remission in participants randomized to peanut OIT in the ITT sample (see Table 4). Based on the final fitted model:

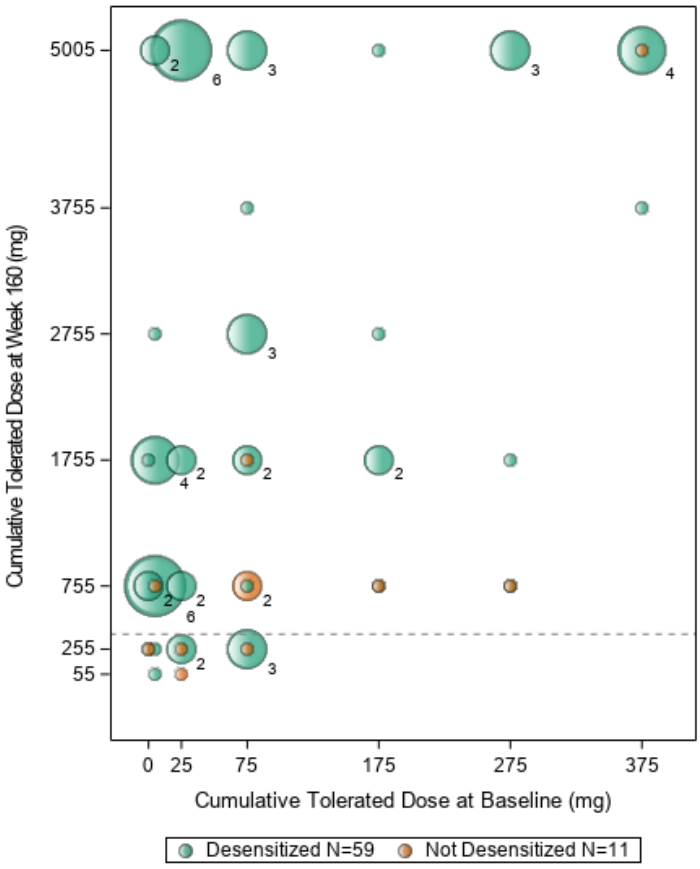
- For every 10 fold increase in baseline peanut-specific IgE, the odds of remission decreases by 88% (95% CI: (54%, 97%); p-value=0.0017).
- For every month increase in age at screening, the odds of remission decreases by 7% (95% CI: (1%, 12%); p-value=0.022).

Table 4. Results of multivariable logistic regression of remission to peanut in ITT participants randomized to peanut OIT in the ITT sample (n=96)

Variable	Odds Ratio (95% CI)	p-value
Baseline peanut-specific IgE (per 10 fold increase)	0.12 (0.03-0.46)	0.0017
Age at screening (per month increase)	0.93 (0.88-0.99)	0.022

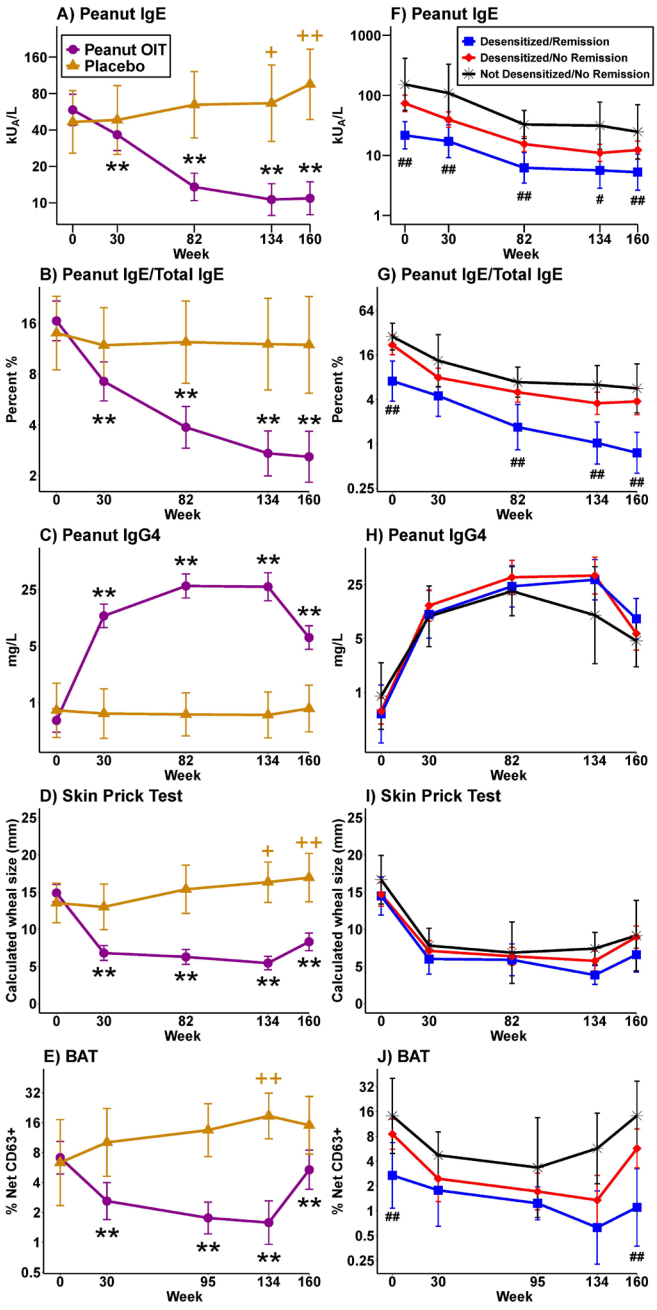
Supplemental Figures and Tables

Figure S1. Cumulative tolerated dose over time.



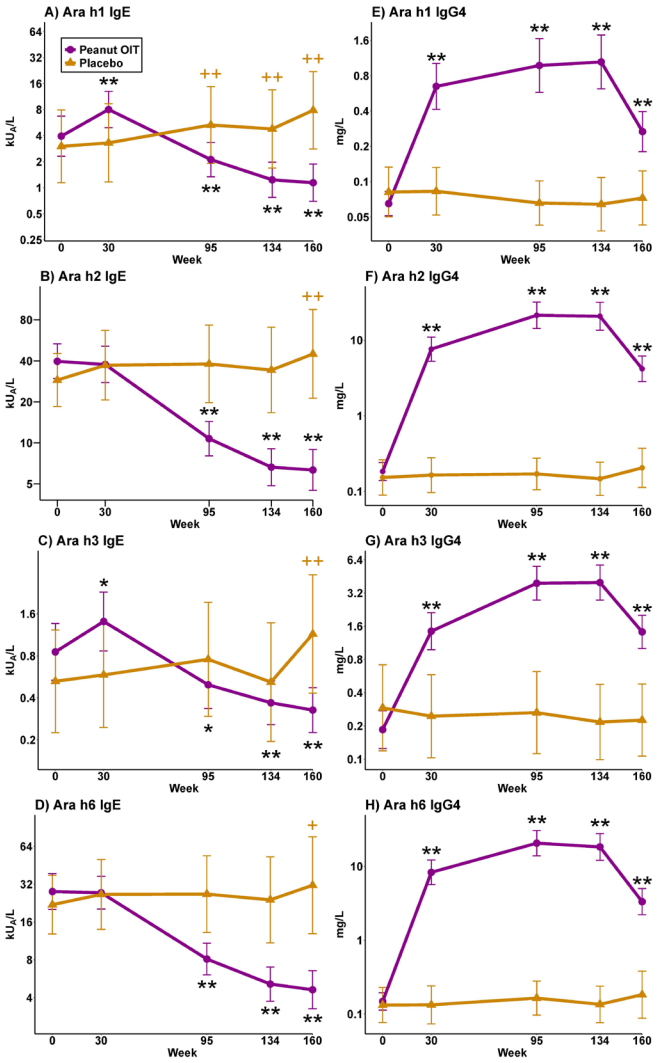
Data shown are cumulative tolerated dose (CTD) at week 160 on the y-axis and CTD at baseline on the X-axis for participants in the PnOIT arm that participated in the week 160 DBPCFC. Green bubbles represent participants who were desensitized (CTD=5005 mg) at week 134. Orange bubbles represent participants who were not desensitized at week 134. The number of participants represented by each bubble is shown to the bottom right of each bubble. Bubbles without a label represent 1 participant. A reference line is shown on the y-axis at the maximum CTD at baseline (375 mg). All PnOIT participants tolerated more peanut protein at week 160 than at baseline.

Figure S2. Immunologic Changes over the Course of the Study



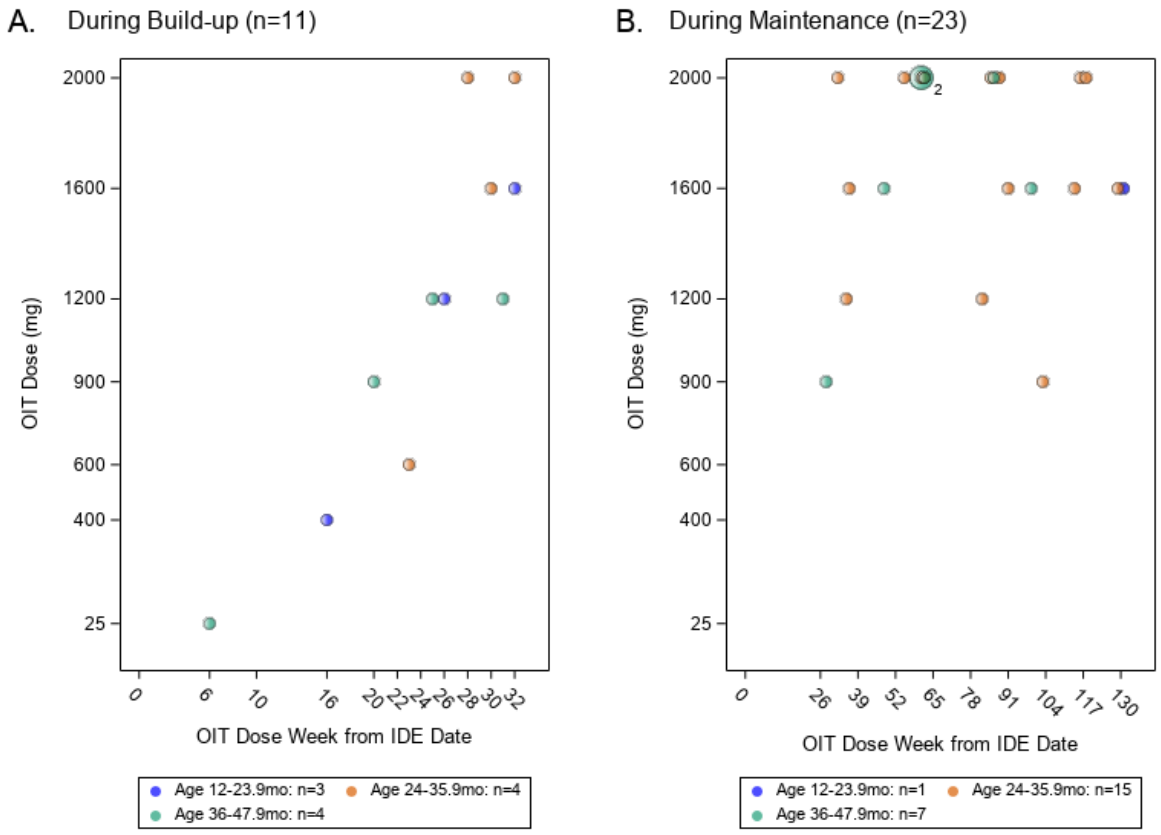
Values are displayed for the sample of PP participants that were evaluable while on treatment, during the avoidance phase, and by DBPCFC after avoidance. Data are shown for time points including before treatment, week 30, week 82 or 95, week 134, and week 160 of the study. Data shown are peanut-specific IgE levels (A, placebo data also shown in Figure 4A), peanut IgE to total IgE ratios (B), peanut-specific IgG4 levels (C), wheal sizes measured after the peanut-specific skin prick test (D), mean levels of basophil activation in response to 10 and 100 ng/mL peanut protein (measured as %CD63+ basophils corrected for spontaneous activation) (E) over the course of the study for placebo (orange triangles) and PnOIT (purple circles) participants. Data are shown as means with 95% confidence intervals. **p<0.01 between placebo and PnOIT; +p<0.05, ++p<0.01 change from pretreatment in placebo participants. PnOIT per-protocol participants were categorized as "desensitized, remission" (blue squares), "desensitized, no remission" (red diamonds), and "not desensitized, no remission" (black asterisks) based on the results of the week 134 and week 160 DBPCFC. Panels F through J show peanut-specific IgE levels (F, data also shown in Figure 4A), peanut IgE to total IgE ratios (G), peanut-specific IgG4 levels (H), wheal sizes of peanut-specific skin prick tests (I), mean levels of basophil activation in response to 10 and 100 ng/mL peanut protein (measured as %CD63+ basophils corrected for spontaneous activation) (J) over the course of the study for the PnOIT outcome groups. N=23 placebo (panel E, n=19), n=10 not desensitized, no remission (panel J, n=8), n=40 desensitized, no remission (panel G and J, n=38), and n=19 desensitized, remission (panel G, n=18 and panel J, n=15). Data are shown as means with 95% confidence intervals. #p<0.05, ##p<0.01 for desensitized, tolerant vs both not desensitized, not tolerant and desensitized, not tolerant.

Figure S3. IgE and IgG4 Antibody Responses to Peanut Component Proteins



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 95, week 134, and week 160 of the study. Panels A through D show the levels of IgE to peanut component proteins Ara h1 (A), Ara h 2 (B, placebo data also shown in Figure 4C), Ara h3 (C), and Ara h6 (D) for placebo (orange triangles) and PnOIT (purple circles) participants. Panels E through H show the levels of IgG4 to the same peanut component proteins Ara h1 (E), Ara h2 (F), Ara h3 (G), and Ara h6 (H) for placebo (orange triangles) and PnOIT (purple circles) participants. For panels A-H, n=23 placebo and n=68 PnOIT. Data are shown as means with 95% confidence intervals. *p<0.05, **p<0.01 between placebo and PnOIT; +p<0.05, ++p<0.01 change from pretreatment in placebo participants.

Figure S4. Epinephrine administration over time by OIT dose.



Data shown is for the PnOIT dose related to the epinephrine administration that occurred in participants during at-home build-up (A) and during maintenance (B) dosing (of note, 1 epinephrine dosing event in 1 PnOIT participant occurred during in-clinic, build-up PnOIT dosing and that dose is not reported in this figure). OIT dose is plotted on the y axis and the OIT dose week from the initial dose escalation (IDE) date is on the x axis. Graphs are broken down by age group during build-up and maintenance, respectively. Blue bubbles represent participants who are 12-23.9 months old, orange bubbles represent participants who are 24-35.9 months old, and green bubbles represent participants who are 36-47.9 months old. Bubbles without a label represent 1 participant.

Table S1. Disposition

	Peanut OIT n (%)	Placebo n (%)	Total n (%)
Number Enrolled [1]			209
Failed Screening Criteria			52 (25)
Serum IgE to peanut < 5 kUA/L			26 (12)
Skin prick test to peanut < 3 mm compared to negative control			2 (1)
No clinical reaction during 500 mg blinded OFC to peanut			15 (7)
Withdrew consent			1 (0)
Investigator/Physician decision			2 (1)
Allergy to oat			1 (0)
Refused to eat peanut			1 (0)
Screening DBPCFC not conducted			1 (0)
>= 4 years of age			1 (0)
Lost to follow-up			1 (0)
Unknown			1 (0)
Passed Screening and Not Randomized			11 (5)
Withdrew consent			7 (3)
Investigator/Physician decision			1 (0)
Adverse event - GI symptoms			1 (0)
Adverse event – Wheezing			1 (0)
Refused to eat peanut			1 (0)
Number Randomized [2]	96	50	146
Terminated During the IDE	2 (2)	0	2 (1)
Number Completing the IDE and Entering Build-Up Treatment	94 (98)	50 (100)	144 (99)
Terminated During Build-Up	4 (4)	6 (12)	10 (7)
Adverse event [3]	2 (2)	1 (2)	3 (2)
Non-compliance with study drug [4]	0	1 (2)	1 (1)
Withdrawn consent - Adverse events [5]	1 (1)	0	1 (1)
Withdrawn consent - Family health issues	0	1 (2)	1 (1)
Withdrawn consent - Family issues	0	2 (4)	2 (1)
Withdrawn consent - Other participant health issues	0	1 (2)	1 (1)
Withdrawn consent - Parents did not want to increase dose	1 (1)	0	1 (1)
Number Completing Build-Up and Entering Maintenance	90 (94)	44 (88)	134 (92)
Terminated During Maintenance	8 (8)	8 (16)	16 (11)
Adverse event [6]	3 (3)	1 (2)	4 (3)
Lost to Follow-Up	0	1 (2)	1 (1)
Non-compliance with study drug [7]	0	1 (2)	1 (1)
Withdrawn consent - Adverse events [8]	1 (1)	0	1 (1)
Withdrawn consent - Family health issues	1 (1)	1 (2)	2 (1)
Withdrawn consent - Family moved	0	1 (2)	1 (1)
Withdrawn consent - Other participant health issues	1 (1)	1 (2)	2 (1)
Withdrawn consent - Parent did not want to continue dosing	2 (2)	0	2 (1)
Withdrawn consent - Unspecified	0	2 (4)	2 (1)
Number Completing Maintenance and Entering Avoidance at Week 134	82 (85)	36 (72)	118 (81)
Terminated at Week 134 Without Completing the DBPCFC to Assess Desensitization	1 (1)	1 (2)	2 (1)

Table S1. Disposition

	Peanut OIT n (%)	Placebo n (%)	Total n (%)
Non-compliance with study drug [9]	1 (1)	0	1 (1)
Withdrawn consent - Parent believes child on placebo	0	1 (2)	1 (1)
Number Completing Week 134 and the DBPCFC to Assess Desensitization	81 (84)	35 (70)	116 (79)
Terminated at Week 134	9 (9)	3 (6)	12 (8)
Adverse event - Anaphylaxis	0	1 (2)	1 (1)
Withdrawn consent - Parent did not want to avoid peanut after passing blinded OFC to peanut at Week 134	7 (7)	0	7 (5)
Withdrawn consent - Parent did not want to continue after failing blinded OFC to peanut at Week 134	2 (2)	2 (4)	4 (3)
Terminated at Week 136	2 (2)	4 (8)	6 (4)
Adverse event [10]	0	1 (2)	1 (1)
Withdrawn consent - Adverse events [11]	0	1 (2)	1 (1)
Withdrawn consent - Parent did not want to avoid peanut after passing blinded OFC to peanut at Week 134	2 (2)	0	2 (1)
Withdrawn consent - Parent did not want to continue after failing blinded OFC to peanut at Week 134	0	2 (4)	2 (1)
Terminated at Week 160 Without Completing the DBPCFC to Assess Remission	0	5 (10)	5 (3)
Withdrawn consent - Parent did not want to continue after failing blinded OFC to peanut at Week 134	0	3 (6)	3 (2)
Withdrawn consent - Parent did not want to do further blood draws	0	2 (4)	2 (1)
Number Completing Avoidance at Week 160 and the DBPCFC to Assess Remission	70 (73)	23 (46)	93 (64)
Completed study participation due to positive blinded OFC to peanut	50 (52)	22 (44)	72 (49)
Negative blinded OFC to peanut and terminated without completing the open feeding	0	0	0
Number Completing the Open Feeding at Week 160	20 (21)	1 (2)	21 (14)
Completed study participation due to positive or indeterminate open feeding	3 (3)	0	3 (2)
Negative open feeding and withdrew consent prior to completing blood draw at Week 162	3 (3)	1 (2)	4 (3)
Number Completing the Blood Draw at Week 162 and Study Participation	14 (15)	0	14 (10)
Total Number Completing Study Participation	67 (70)	22 (44)	89 (61)

Note: This table includes all enrolled participants.
[1] The denominator used to calculate percentages is the number of participants enrolled.
[2] The denominator used to calculate all the percentages below is the number of participants randomized
[3] Peanut OIT: One participant had persistent vomiting with dosing and another participant had an allergic reaction. Placebo: One participant had constipation.
[4] Placebo: One participant reported circumstances (e.g., concurrent illness, such as gastroenteritis) requiring missed maintenance dosing of > 7 consecutive days.
[5] Peanut OIT: One participant withdrew from the study 5 days after experiencing a cough.
[6] Peanut OIT: Three participants were diagnosed with EoE. Placebo: One participant had stomach ache.
[7] Placebo: One participant reported non-adherence with home dosing protocol with excessive missed days as defined per protocol.
[8] Peanut OIT: One participant withdrew from the study 16 days after experiencing vomiting.
[9] Peanut OIT: One participant returned 115 doses of study drug at Visit 24 defined as non-adherence per protocol.
[10] Placebo: One participant had food aversion with weight loss.
[11] Placebo: One participant withdrew from the study 29 days after experiencing a reaction to the peanut OFC at week 134.

Table S2. Reasons for Withdrawal Within Each Age Group

	Peanut OIT (n=29)				Placebo (n=28)			
Reason for Withdrawal	12-23.9 mo (N=4) n (%)	24-35.9 mo (N=7) n (%)	36-47.9 mo (N=18) n (%)	Total (N=29) n (%)	12-23.9 mo (N=5) n (%)	24-35.9 mo (N=7) n (%)	36-47.9 mo (N=16) n (%)	Total (N=28) n (%)
Withdrew consent	4 (100)	5 (71)	10 (56)	19 (66)	4 (80)	5 (71)	11 (69)	20 (71)
Experienced an adverse event	0	1 (14)	6 (33)	7 (24)	1 (20)	2 (29)	2 (13)	5 (18)
Non-compliance with study drug	0	1 (14)	0	1 (3)	0	0	2 (13)	2 (7)
Failed IDE	0	0	2 (11)	2 (7)	0	0	0	0
Lost to follow-up	0	0	0	0	0	0	1 (6)	1 (4)

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

Table S3. Treatment Adherence

	Peanut OIT (N=96)	Placebo (N=50)
Number of Participants with completed Initial Dose Escalation	94	50
Number of Participants with at least One Instance of 3 or more consecutive doses missed during Build-up, n (%) [1]	9 (10)	4 (8)
Number of Instances of 3 or more consecutive doses missed during Build-up	9	4
Reasons for Instances of 3 or more consecutive doses missed during Build-up, n (%) [2]		
Concurrent Illness	6 (67)	3 (75)
Oit/Placebo Reaction During Home Dosing	1 (11)	0
Other: Left Doses At Home When Went Out Of Town For Vacation	1 (11)	0
Other: Parent Forgot To Administer Doses And Participant Was Wheezing When Coming In For A Dosing V	0	1 (25)
Other: Travel	1 (11)	0
Percentage of Doses Missed during Build-up		
Mean (SD)	3.1 (3.5)	3.1 (4.4)
Median	1.9	2.0
Q1, Q3	0.9, 3.8	0.9, 3.6
Number of Participants with completed Build-up	90	44
Number of Participants with at least One Instance of 3 or more consecutive doses missed during Maintenance, n (%) [3]	20 (22)	5 (10)
Number of Instances of 3 or more consecutive doses missed during Maintenance	31	8
Reasons for Instances of 3 or more consecutive doses missed during Maintenance, n (%) [4]		
Concurrent Illness	25 (81)	5 (63)
Oit/Placebo Reaction During Home Dosing	2 (6)	0
Other: Hospitalization For Kidney Infection	1 (3)	0
Other: Off Protocol Per Pi	1 (3)	0
Other: Ran Out Of Doses	0	1 (13)
Participant/Guardian Forgot	2 (6)	2 (25)
Percentage of Doses Missed during Maintenance		
Mean (SD)	3.7 (3.8)	2.6 (3.3)
Median	2.7	1.4
Q1, Q3	1.1, 4.4	0.6, 3.3

Note: This table includes all participants in the Intent-To-Treat sample.
[1] The denominator used to calculate percentages is the number of participants with completed Initial Dose Escalation.
[2] The denominator used to calculate percentages is the number of instances of 3 or more consecutive doses missed during Build-up.
[3] The denominator used to calculate percentages is the number of participants with completed Build-up.
[4] The denominator used to calculate percentages is the number of instances of 3 or more consecutive doses missed during Maintenance.

Table S4. Maximum Cumulative Tolerated OFC Dose at Week 160 Within Each Treatment Arm/Age Group

	Peanut OIT (n=70)				Placebo (n=23)			
	12-23.9mo (n=7) n (%)	24-35.9mo (n=20) n (%)	36-47.9mo (n=43) n (%)	Total (n=70) n (%)	12-23.9mo (n=3) n (%)	24-35.9mo (n=7) n (%)	36-47.9mo (n=13) n (%)	Total (n=23) n (%)
Maximum Cumulative Tolerated Dose								
0 mg	0	0	0	0	0	2 (29)	0	2 (9)
5 mg	0	0	0	0	1 (33)	3 (43)	4 (31)	8 (35)
55 mg	0	0	2 (5)	2 (3)	0	1 (14)	6 (46)	7 (30)
255 mg	1 (14)	3 (15)	6 (14)	10 (14)	1 (33)	0	2 (15)	3 (13)
755 mg	0	5 (25)	13 (30)	18 (26)	0	0	1 (8)	1 (4)
1755 mg	0	3 (15)	10 (23)	13 (19)	0	0	0	0
2755 mg	1 (14)	2 (10)	2 (5)	5 (7)	0	0	0	0
3755 mg	0	0	2 (5)	2 (3)	0	1 (14)	0	1 (4)
5005 mg	5 (71)	7 (35)	8 (19)	20 (29)	1 (33)	0	0	1 (4)

Note: This table includes all participants in the Per-Protocol sample for remission.
Note: Age is grouped by age at screening.

Table S5. Remission at Week 160 Within Each Treatment Arm/Age Group

Age Group	Peanut OIT	Placebo
Intent-To-Treat sample	(N=96)	(N=50)
12-23.9 months	5/10 (50)	1/7 (14)
24-35.9 months	7/26 (27)	0/14 (0)
36-47.9 months	8/60 (13)	0/29 (0)
Per-Protocol sample for remission	(N=70)	(N=23)
12-23.9 months	5/7 (71)	1/3 (33)
24-35.9 months	7/20 (35)	0/7 (0)
36-47.9 months	8/43 (19)	0/13 (0)

Note: Age group is defined as age at study enrollment.

Table S6. Moderate and Severe 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 Moderate dosing reaction	3 (3)	0	18 (19)	3 (6)	30 (33)	1 (2)	40 (42)	4 (8)	+^‡
System Organ Class Dosing Reaction									
Respiratory, thoracic and mediastinal disorders	2 (2)	0	14 (15)	1 (2)	27 (30)	0	34 (35)	1 (2)	+^‡
Cough	2 (2)	0	12 (13)	0	21 (23)	0	28 (29)	0	+^‡
Dyspnoea	0	0	1 (1)	0	0	0	1 (1)	0	
Laryngeal/throat symptoms	0	0	2 (2)	0	2 (2)	0	4 (4)	0	
Mouth/throat discomfort	0	0	0	0	1 (1)	0	1 (1)	0	
Wheezing	1 (1)	0	6 (6)	1 (2)	16 (18)	0	19 (20)	1 (2)	^‡
Skin and subcutaneous tissue disorders	1 (1)	0	8 (9)	2 (4)	13 (14)	1 (2)	18 (19)	3 (6)	^‡
Erythema/flushing/pruritus	0	0	1 (1)	0	0	0	1 (1)	0	
Rash	0	0	1 (1)	0	1 (1)	0	2 (2)	0	
Urticaria	1 (1)	0	7 (7)	2 (4)	12 (13)	1 (2)	17 (18)	3 (6)	
Gastrointestinal disorders	0	0	3 (3)	0	3 (3)	0	5 (5)	0	
Abdominal pain	0	0	2 (2)	0	3 (3)	0	4 (4)	0	
Diarrhoea	0	0	1 (1)	0	0	0	1 (1)	0	
Upper GI symptoms	0	0	3 (3)	0	3 (3)	0	5 (5)	0	
At least one Severe dosing reaction	0	0	2 (2)	0	3 (3)	0	5 (5)	0	
System Organ Class Dosing Reaction									
Respiratory, thoracic and mediastinal disorders	0	0	1 (1)	0	3 (3)	0	4 (4)	0	
Dyspnoea	0	0	0	0	1 (1)	0	1 (1)	0	
Laryngeal/throat symptoms	0	0	1 (1)	0	2 (2)	0	3 (3)	0	
Wheezing	0	0	0	0	1 (1)	0	1 (1)	0	
Skin and subcutaneous tissue disorders	0	0	1 (1)	0	0	0	1 (1)	0	
Facial swelling	0	0	1 (1)	0	0	0	1 (1)	0	

* 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.
‡ represents a statistically significant difference between the treatment groups overall using a Fisher's exact test.
Note: This table includes all participants in the safety sample for IDE, build-up, and maintenance.

Table S7. Epinephrine Administration - Detailed Information

Site / Participant ID	Age at enrollment (months)	Desensitization endpt at W134	Remission endpt at W160	Withdrawn from study	Wks from Random to withdrawal	N of Epi admin	Wks from Random to day of Epi admin	OIT dose at Epi admin (mg)	Grade of reaction	N of Epi doses
Arkansas										
Participant 1	32.6	Yes	No	Yes	153.1	1	32.3	2000	3	1
Participant 2	42.4	No	No	Yes	104.3	2	6	25	2	1
							99.1	1600	3	2
Participant 3	31.7	Yes	No	No		2	37.4	1600	2	1
							115.3	1600	2	1
Participant 4	39.6	Yes	Yes	No		1	85	2000	2	1
John Hopkins										
Participant 1	34.4	Yes	No	Yes	137.0	1	117.9	2000	2	1
Participant 2	39.2	Yes	No	No		2	30.3	1600	2	1
							32	2000	2	1
Mount Sinai										
Participant 1	45.1	No	No	No		1	60.7	2000	2	1
Participant 2	46.4	Yes	No	No		1	61.4	2000	2	1
Participant 3	38.8	Yes	No	No		1	55.1	2000	2	1
Participant 4	40.6	No	No	No		1	23.6	600	2	1
Participant 5	40.3	No	No	No		4	26.3	2000	2	1
							35.3	1200	1	1
							82.4	1200	2	1
							102.7	900	2	1
Participant 6	44.8	No	No	Yes	142.3	2	62.3	2000	2	1
							85.7	2000	2	1
Participant 7	42.4	No	No	No		1	28.4	900	2	1
Participant 8	22.8	Yes	No	Yes	162.9	1	130.1	1600	3	2
Participant 9	26.2	No	No	Yes	43.4	3	16.1	400	2	1
							26.3	1200	2	1
							32.3	1600	2	1
Stanford										
Participant 1	31.6	Yes	No	No		1	90.7	1600	2	1
Participant 2	42.5	Yes	No	No		1	48.1	1600	2	1
Participant 3	40.9	Yes	No	No		2	28.3	2000	2	1
							128.9	1600	2	1
Participant 4	35.6	Yes	No	No		3	61.4	2000	2	1
							87.6	2000	2	1
							115.7	2000	2	1
UNC										
Participant 1	34.3	No	No	No		1	62.3	2000	2	1
Participant 2	46.7	No	No	Yes	32.9	3	20.1	900	2	1
							25.3	1200	2	1
							30.7	1200	2	1

Note: This table includes all participants randomized to the peanut OIT arm who had at least one administration of epinephrine associated with study product dosing.

Table S8. Dosing Reactions During Oral Food Challenges

	Baseline OFC		OFC at Week 134		OFC at Week 160		Overall	
	Peanut OIT (N=96) n (%)	Placebo (N=50) n (%)	Peanut OIT (N=81) n (%)	Placebo (N=35) n (%)	Peanut OIT (N=70) n (%)	Placebo (N=23) n (%)	Peanut OIT (N=96) n (%)	Placebo (N=50) n (%)
At least one dosing reaction	96 (100)	50 (100)	18 (22)	34 (97)	52 (74)	22 (96)	96 (100)	50 (100)
At least one dosing reaction requiring Epi	36 (38)	23 (46)	4 (5)	21 (60)	22 (31)	10 (43)	48 (50)	34 (68)
At least one Minor dosing reaction	85 (89)	47 (94)	16 (20)	34 (97)	50 (71)	20 (87)	88 (92)	49 (98)
At least one Major dosing reaction	45 (47)	27 (54)	9 (11)	16 (46)	30 (43)	14 (61)	63 (66)	37 (74)
System Organ Class Dosing Reaction								
Skin and subcutaneous tissue disorders	71 (74)	38 (76)	9 (11)	21 (60)	33 (47)	13 (57)	79 (82)	40 (80)
Angioedema	20 (21)	11 (22)	2 (2)	6 (17)	5 (7)	4 (17)	22 (23)	16 (32)
Erythema/flushing/pruritus	15 (16)	14 (28)	4 (5)	5 (14)	3 (4)	2 (9)	19 (20)	16 (32)
Rash	3 (3)	1 (2)	0	2 (6)	4 (6)	0	7 (7)	3 (6)
Urticaria	57 (59)	28 (56)	7 (9)	16 (46)	28 (40)	10 (43)	68 (71)	32 (64)
Psychiatric disorders	66 (69)	35 (70)	2 (2)	26 (74)	25 (36)	16 (70)	70 (73)	44 (88)
Change in affect/lethargy	58 (60)	29 (58)	2 (2)	16 (46)	15 (21)	10 (43)	63 (66)	38 (76)
Emotional distress	33 (34)	18 (36)	0	24 (69)	21 (30)	13 (57)	44 (46)	34 (68)
Respiratory, thoracic and mediastinal disorders	32 (33)	12 (24)	12 (15)	18 (51)	33 (47)	13 (57)	52 (54)	29 (58)
Cough	22 (23)	6 (12)	9 (11)	11 (31)	22 (31)	2 (9)	37 (39)	18 (36)
Laryngeal/throat symptoms	2 (2)	4 (8)	2 (2)	2 (6)	11 (16)	5 (22)	14 (15)	10 (20)
Rhinitis/Nasal Symptoms	8 (8)	1 (2)	2 (2)	8 (23)	10 (14)	7 (30)	18 (19)	12 (24)
Wheezing	6 (6)	4 (8)	4 (5)	4 (11)	8 (11)	2 (9)	16 (17)	8 (16)
Gastrointestinal disorders	30 (31)	19 (38)	1 (1)	23 (66)	13 (19)	15 (65)	38 (40)	34 (68)
Abdominal pain	1 (1)	0	0	1 (3)	3 (4)	2 (9)	4 (4)	2 (4)
Diarrhoea	0	0	0	2 (6)	1 (1)	0	1 (1)	2 (4)
Upper GI symptoms	29 (30)	19 (38)	1 (1)	21 (60)	11 (16)	14 (61)	36 (38)	32 (64)
Immune system disorders	6 (6)	5 (10)	4 (5)	4 (11)	6 (9)	2 (9)	14 (15)	10 (20)
Hypersensitivity	6 (6)	5 (10)	4 (5)	4 (11)	6 (9)	2 (9)	14 (15)	10 (20)
Vascular disorders	0	0	0	1 (3)	0	0	0	1 (2)
Hypotension	0	0	0	1 (3)	0	0	0	1 (2)

Note: This table includes all participants in the Intent-To-Treat sample (baseline, total), Per-Protocol sample for desensitization (week 134), and Per-Protocol sample for remission (week 160).

Table S9. Adverse Events Related to OIT or OFC Dosing

	IDE Phase		Build-Up Phase		Maintenance Phase		Oral Food Challenges	
	Peanut OIT (N=5) n (%)	Placebo (N=1) n (%)	Peanut OIT (N=83) n (%)	Placebo (N=26) n (%)	Peanut OIT (N=59) n (%)	Placebo (N=12) n (%)	Peanut OIT (N=7) n (%)	Placebo (N=7) n (%)
Related adverse events	5 (100)	1 (100)	83 (100)	26 (100)	59 (100)	12 (100)	7 (100)	7 (100)
Life-threatening Related AE*	0	0	0	0	0	0	0	1 (14)
Severe Related AE	0	0	0	0	0	0	0	0
System Organ Class								
Preferred Term								
Immune system disorders	3 (60)	0	42 (51)	11 (42)	40 (68)	7 (58)	4 (57)	6 (86)
Anaphylactic reaction	0	0	0	0	0	0	0	1 (14)
Food allergy	0	0	0	0	0	1 (8)	4 (57)	5 (71)
Type I hypersensitivity	3 (60)	0	42 (51)	11 (42)	40 (68)	6 (50)	0	0
Gastrointestinal disorders	0	1 (100)	22 (27)	8 (31)	8 (14)	2 (17)	1 (14)	0
Abdominal pain	0	1 (100)	17 (20)	0	2 (3)	1 (8)	1 (14)	0
Constipation	0	0	0	1 (4)	0	0	0	0
Diarrhoea	0	0	0	5 (19)	0	0	0	0
Dysphagia	0	0	0	0	0	1 (8)	0	0
Eosinophilic oesophagitis	0	0	0	0	3 (5)	0	0	0
Eructation	0	0	0	0	2 (3)	0	0	0
Faeces discoloured	0	0	0	2 (8)	0	0	0	0
Flatulence	0	0	1 (1)	0	0	0	0	0
Gastritis	0	0	0	0	1 (2)	0	0	0
Glossodynia	0	0	1 (1)	0	0	0	0	0
Oral pruritus	0	0	1 (1)	0	0	0	0	0
Regurgitation	0	0	1 (1)	0	0	0	0	0
Vomiting	0	0	1 (1)	0	0	0	0	0
Skin and subcutaneous tissue disorders	2 (40)	0	12 (14)	6 (23)	6 (10)	2 (17)	1 (14)	0
Chronic spontaneous urticaria	0	0	0	0	1 (2)	0	0	0
Dermatitis atopic	0	0	1 (1)	0	3 (5)	1 (8)	0	0
Dermatitis diaper	0	0	1 (1)	0	0	0	0	0
Eczema	0	0	6 (7)	3 (12)	1 (2)	1 (8)	0	0
Pruritus	1 (20)	0	4 (5)	2 (8)	1 (2)	0	1 (14)	0
Rash	1 (20)	0	0	1 (4)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	6 (7)	1 (4)	4 (7)	0	1 (14)	0
Choking	0	0	0	0	1 (2)	0	0	0
Cough	0	0	3 (4)	1 (4)	3 (5)	0	1 (14)	0
Nasal congestion	0	0	1 (1)	0	0	0	0	0
Oropharyngeal pain	0	0	1 (1)	0	0	0	0	0
Throat irritation	0	0	1 (1)	0	0	0	0	0
Blood and lymphatic system disorders	0	0	1 (1)	0	0	0	0	0
Eosinophilia	0	0	1 (1)	0	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0	1 (2)	0	0	0
Weight gain poor	0	0	0	0	1 (2)	0	0	0
General disorders and admin. site conditions	0	0	0	0	0	1 (8)	0	0
Chest pain	0	0	0	0	0	1 (8)	0	0
Psychiatric disorders	0	0	0	0	0	0	0	1 (14)
Food aversion	0	0	0	0	0	0	0	1 (14)

Table S9. Adverse Events Related to OIT or OFC Dosing

	IDE Phase		Build-Up Phase		Maintenance Phase		Oral Food Challenges	
	Peanut OIT (N=5) n (%)	Placebo (N=1) n (%)	Peanut OIT (N=83) n (%)	Placebo (N=26) n (%)	Peanut OIT (N=59) n (%)	Placebo (N=12) n (%)	Peanut OIT (N=7) n (%)	Placebo (N=7) n (%)

Note: This table includes participants in the safety sample that had at least one related adverse event in IDE, build-up, maintenance, or during OFCs
Note: Adverse events (such as anaphylactic reaction) are coded according to MedDRA version 16.0 by system organ class and preferred term. Severity is determined based on the CTCAE version 4.0.
Note: This table only includes a symptom or event that was related to a blinded OFC, IDE, clinic OIT dosing, or daily home OIT dosing and that met any of the following criteria, as defined per protocol: 1) Hypotension, cyanosis, SpO2 < 92%, confusion, collapse, loss of consciousness, incontinence, or more than two injections of epinephrine that occurred at any time; 2) Any symptom or event that occurred more than two hours after dosing; or 3) Any symptom or event not expected according to the General Investigational Plan.
Note: A Type 1 hypersensitivity adverse event is defined as an allergic reaction that occurred as a result of IDE, clinic OIT dosing, or daily home OIT dosing.
*This event was also recorded as SAE and is also included in Table S9.

Table S10. Serious Adverse Events

Treatment	Preferred Term	Outcome	Grade	Action Taken	Relationship to Study Therapy
Placebo	Anaphylactic reaction	Resolved	4	None	Definite
Patient Is A 6 Yo M Who Presented In Clinic For Day 2 Of The Visit 24 DBPCFC. At 10:10 A.M. Participant Ingested A 5 Mg Dose With No Reaction. At 10:25 A.M. Participant Ingested A 50 Mg Dose With No Reaction. At 10:55 A.M. Participant Ingested A 200 Mg Dose With No Reaction. At 11:25 A.M. Participant Ingested A 500 Mg Dose With No Reaction. Patient Was Doing Well Until Shortly After Receiving The 1000mg Dose At 11:55 Am, When Patient Reported Abdominal Pain Which Progressively Worsened. At 12:15pm The Patient Was Also Noted To Have Facial Flushing, Conjunctival Injections, And Nasal Congestion. He Was Given Cetirizine (5mg) Po And Famotidine (10mg) Po At 12:15pm. At 12:25 Pm, He Was Noted To Have Wheezing And Was Given Epinephrine (0.15mg) Im In The Right Thigh And Nebulized Albuterol. Wheezing Resolved, But Facial Flushing, Conjunctival Injections, And Nasal Congestion Persisted And He Had Urticaria (<10% Bsa). At 12:30 Pm He Was Given Another Dose Of Cetirizine (5 Mg) Po, Azelastine Nasal Spray And Topical Triamcinolone For Persistent Symptoms. Urticaria Progressed To Affect >50% Bsa At 12:50pm, And The Patient Was Treated With Epinephrine (0.15mg) In The Left Thigh At 12:50 Pm. At 13:30, Pt Had Increased Pruritis With Urticaria And Was Treated With Diphenhydramine 12.5mg Po, Ketotifen Eye Drop And Oxymetazoline Nasal Spray Was Given Still Affording Only Partial Relief. At 14:30, The Patient Complained Of Worsening Abdominal Pain And Vomited, And Then At 14:35, His Vitals Were Remarkable For A Manual Bp Of 53/40 And Associated Lethargy. A 3rd Epinephrine Dose (0.15mg) Was Given In The Right Thigh At 14:36. A Code Was Called. IV Decadron (10 Mg) And IV Fluid Bolus (400cc) Was Given Resulting In Improvement In Blood Pressure (90-110s/40-60s). He Was Also Given IV Diphenhydramine (9 Mg) And IV Zofran (4 Mg) And Continued IV Fluids.					
Placebo	Vaccination complication	Resolved	2	None	Unrelated
Placebo	Vomiting	Resolved	2	Study Treatment Interrupted	Unrelated
Placebo	Asthma	Resolved	3	Study Treatment Interrupted	Unrelated
Placebo	Vomiting	Resolved	3	Study Treatment Interrupted	Unrelated
Peanut OIT	Asthma	Resolved	3	Study Treatment Interrupted	Unrelated
	Asthma	Resolved	3	None	Unrelated
Peanut OIT	Respiratory tract infection	Resolved	3	Study Treatment Interrupted	Unrelated
Peanut OIT	Pyelonephritis	Resolved	3	Study Treatment Interrupted	Unrelated

Note: Adverse events are coded according to MedDRA version 16.0 by system organ class and preferred term. Severity is determined based on the CTCAE version 4.0.

Note: Days are calculated by subtracting the date informed consent was signed.

4. REFERENCES

1. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-7.
2. Burks AW, Jones SM, Wood RA, et al. Oral immunotherapy for treatment of egg allergy in children. NEnglJMed 2012;367:233-43.
3. Aceves SS, Newbury RO, Dohil MA, Bastian JF, Dohil R. A symptom scoring tool for identifying pediatric patients with eosinophilic esophagitis and correlating symptoms with inflammation. Ann Allergy Asthma Immunol 2009;103:401-6.
4. Gupta RS, Lau CH, Hamilton RG, Donnell A, Newhall KK. Predicting outcomes of oral food challenges by using the allergen-specific IgE-total IgE ratio. The journal of allergy and clinical immunology In practice 2014;2:300-5.
5. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 2015;372:803-13.
6. Santos AF, Du Toit G, O'Rourke C, et al. Biomarkers of severity and threshold of allergic reactions during oral peanut challenges. J Allergy Clin Immunol 2020;146:344-55.