Single Center, Placebo Controlled Clinical Study in Desensitization vs Tolerance Induction in Peanut Allergy Subjects

Study Protocol

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National Institute of Allergy and Infectious Diseases

PROTOCOL NUMBER

AADCRC-STAN-001

LONG TITLE: Single Center, Placebo Controlled Clinical Study in Desensitization vs. Tolerance Induction in Peanut Allergy Subjects

SHORT TITLE: Tolerance vs. Desensitization in Peanut-Allergic Individuals

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INVESTIGATOR SIGNATURE PAGE	
Protocol: AADCRC-STAN-001	**Version/Date: 7/January 24, 2018**
Site Principal Investigator: R. Sharon Chinthrajah, MD	
Title: Single Center, Placebo Controlled Clinical Study in Desensitization vs. Tolerance Induction in Peanut Allergy Subjects	
Study Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	
INSTRUCTIONS: *The site Principal Investigator should print, sign, and date at the indicated location below. A copy should be kept for your records and the original signature page sent. After signature, please return the original of this form by surface mail to:* [redacted], RN	
I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the International Conference on Harmonization (ICH) document *Guidance for Industry: E6 Good clinical Practice: Consolidated Guidance* dated April 1996. Further, I will conduct the study in keeping with local legal and regulatory requirements. As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID. _____ **Site Principal Investigator (Print)** _____ _____ **Site Principal Investigator (Signature)** **Date**	

National Institute of Allergy and Infectious Diseases

Protocol Synopsis

Title	Single Center, Placebo Controlled Clinical Study in Desensitization vs. Tolerance Induction in Peanut Allergy Subjects
Short Title	Tolerance vs. Desensitization in Peanut-Allergic Individuals
Clinical Phase	Phase II
Number of Sites	1
IND Sponsor/Number	Kari C. Nadeau, MD, PhD/[redacted]
Investigational Product(s)/Intervention(s)	Investigational Product: Peanut Flour Interventions: • Medical and allergy history (including dietary history) • Physical assessment • Spirometry • Serum or urine pregnancy tests • Plasma analysis for IgE and IgG4 to peanut (UniCAP™) • Oral food challenge to peanut • Skin prick test • Study product administration • Initial Dose Escalation Day Oral Immunotherapy (OIT) • Build up and maintenance OIT
Study Objectives	**Primary Objective:** Determine whether peanut oral immunotherapy induces clinical tolerance as assessed after the initial 3 month avoidance period **Secondary Objectives:** • Identify the basic immune mechanisms which can explain the differences in the effects of OIT in desensitized vs. tolerant individuals. • Determine whether immune monitoring measurements reflecting underlying mechanisms during OIT can be used to predict responses to OIT in individual subjects and, ultimately, to improve the safety and efficacy outcomes in peanut OIT protocols.
Study Design	A Phase 2, single-center, randomized, double blind, placebo controlled study of the induction of peanut tolerance by oral immunotherapy (OIT). Our intent to treat population will be 120 subjects, ages 7-55 years, with an allergy to peanut, as determined by DBPCFC, history, clinical

	symptoms, and positive skin prick test (SPT). The 120 enrolled subjects will be randomized 2.4:1.4:1. Thus, there will be three arms: (1) Arm A on peanut OIT until week 104 and once meeting criteria *[i.e. 1) assigned to OIT treatment for minimum 104 weeks, 2) reaching maintenance 13 weeks prior to DBPCFC at week 104, 3) no severe reactions (Grade 3, APPENDIX 4) to home dosing from Week 92-Week 104, and/or 4) no objective reactions, (Appendix 4) at the Week 104 DBPCFC]* has been assigned to avoid peanut (i.e. 600 mg oat flour). (2) Arm B on peanut OIT until week 104 and once meeting criteria, has been assigned to be maintained on 300 mg peanut protein (i.e. 600 mg peanut flour). (3) Arm C that is maintained on placebo (oat flour) and once meeting criteria, will receive 600 mg oat flour beginning on week 104. This will be true even if a subject in the placebo group meets criteria at week 104. This way all participants will receive approximately the same volume of flour so that the subject blinding will be easier to maintain. The decision to maintain subjects on only 300 mg peanut protein after week 104 is for ease of eating peanut and to test if a lower amount of protein can still maintain desensitization. After week 104, subjects will then be rechallenged every 3 months for a year. Individuals will be defined as "clinically tolerant" if there is no clinical reactivity upon rechallenge. Clinical reactivity is defined as any objective reaction based on the Bock's Criteria (**Appendix 4**). We plan to identify the basic immune mechanisms which can explain the differences in the effects of OIT in individuals who do or do not become tolerant and to determine whether immune monitoring can predict the safety and efficacy outcomes in peanut OIT protocols. Subjects will also be asked via a separate sub-study and consent which will look at biopsies from the gastrointestinal tract to show different markers at week 52, 104 and week 117 (or equivalent, with "or equivalent" meaning in this context that the visit may not be scheduled exactly in week 117, given such factors as the subject's schedule, etc…) compared to baseline. In addition, we will determine whether there are trends for differences in the markers detected in GI tissues in placebo vs avoidance vs treatment arms.
Primary Endpoint(s)	Proportion of peanut allergic subjects who pass a DBPCFC after the 3 month avoidance period (Week 117 or equivalent) following the end of active treatment phase
Secondary Endpoint(s)	1. Proportion of PA subjects who pass a DBPCFC after a 6 month avoidance period. 2. Proportion of PA subjects who pass a DBPCFC after a 9 month avoidance period. 3. Proportion of PA subjects who pass a DBPCFC after a 12 month avoidance period.

	4.Proportion of PA subjects who can successfully complete the build-up phase of peanut OIT to the highest dose (4,000 mg of peanut protein) with only mild (objective, **APPENDIX 4**) symptoms related to dosing. 5. Proportion of PA subjects who can successfully undergo the build-up and maintenance phases of peanut OIT with only mild symptoms. 6. Comparison of the proportion of subjects in placebo, avoidance, and 300 mg peanut protein groups who are able to undergo OFCs with no clinical reactivity after initiating OIT. *Sub Study GI Endpoint* *Proportion of PA subjects who show increased immune cells consistent with immune tolerance (i.e. regulatory T cells) vs. inflammatory allergy (i.e. eosinophils, mast cells) over time points obtained with GI biopsy tissues.*
Accrual Objective	120
Study Duration	This is a 5 year study. Participants will be in an active phase of the protocol for 3 years (see **Appendix 1** for individual subject timeline); long term follow-up will be conducted but not beyond the 5 years of the grant.
Treatment Description	Subjects will undergo an Initial Dose Escalation Day to consumption of maximum single dose of 6 mg peanut/placebo protein. They will consume this dose at home for two weeks and document reactions. Upon returning to the CFRU (Clinical Food Research Unit) two weeks later, a dose escalation will be attempted. This cycle will continue until the subject reaches a maximum dose of 4,000 mg peanut/placebo protein daily. There will be three arms: (1) Arm A on peanut OIT until week 104 and once meeting criteria *[i.e. 1) assigned to OIT treatment for minimum 104 weeks, 2) reaching maintenance 13 weeks prior to DBPCFC at week 104 3) no severe reactions (Grade 3, APPENDIX 4) to home dosing from Week 92-Week 104, and/or 4) no objective reactions, (Appendix 4) at the Week 104 DBPCFC]* has been assigned to avoid peanut (i.e. 600 mg oat flour). (2) Arm B on peanut OIT until week 104 and once meeting criteria, has been assigned to be maintained on 300 mg peanut protein (i.e. 600 mg peanut flour). (3) Arm C that is maintained on placebo (oat flour) and once meeting criteria, will receive 600 mg oat flour beginning on week 104. This will be true even if a subject in the placebo group meets criteria at week 104.This way all participants will receive approximately the same volume of flour so that the subject blinding will be easier to maintain. The decision to maintain subjects on only 300 mg peanut protein after week 104 is for ease of eating peanut and to test if a lower amount of protein can still maintain desensitization.
Inclusion Criteria	• Subject and/or parent guardian must be able to understand and provide informed consent and/or assent as applicable.

	• Peanut-allergic subjects between the ages of 7-55 years old. • Weight equal or greater than 17 kg. • Sensitivity to peanut allergen as documented by a positive skin prick test result (5 mm or greater diameter wheal relative to negative control) within 10 months preceding enrollment. • Allergy to peanut based on a double-blind placebo-controlled oral food challenge (DBPCFC) (see **Appendix 4** for scoring details) failed at a cumulative dose ≤500 mg with peanut protein within 10 months preceding enrollment. • All female subjects of child-bearing potential will be required to provide a blood or urine sample for pregnancy testing that must be negative one week before being allowed to participate in the study. • Subjects must plan to remain in the study area during the trial. • Subjects must be trained on the proper use of the EpiPen (see **Appendix 5)** to be allowed to enroll in the study. • Subjects with other food allergies must agree to eliminate these other food items from their diet so as not to confound the safety and efficacy data from the study. • Use of birth control by female subjects of child-bearing potential
Exclusion Criteria	• Inability or unwillingness of a participant to give written informed consent or comply with study protocol • History of uncontrolled cardiovascular disease • History of other chronic disease (other than asthma, atopic dermatitis, or rhinitis) requiring therapy (e.g., heart disease, diabetes) that, in the opinion of the Principal Investigator, would represent a risk to the subject's health or safety in this study or the subject's ability to comply with the study protocol • History of eosinophilic gastrointestinal disease • Current participation in any other interventional study • Subject is on 'build-up phase" of immunotherapy to another allergen (i.e., has not reached maintenance dosing) • Severe asthma (2007 NHLBI Criteria Steps 5 or 6) at time of enrollment • Mild or moderate (2007 NHLBI Criteria Steps 1-4) asthma at time of enrollment with any of the following criteria met: - FEV1 < 80% of predicted, or FEV1/FVC < 75%, with or without controller medications (only for age 6 or greater and able to do spirometry) *or* - ICS dosing of > 220 mcg daily fluticasone (or equivalent inhaled corticosteroids based on NHLBI dosing chart) *or*

	- 1 hospitalization in the past year for asthma *or* - ER visit for asthma within the past six months • Use of steroid medications (IV, IM or oral) in the following manners for asthma - history of daily oral steroid dosing for >1 month during the past year *or* - steroid burst (5 days or more of 1 mg/kg prednisone) course in the past 3 months *or* - >2 steroid burst courses in the past year • Use of complementary and alternative medicine (CAM) treatment modalities (e.g., herbal remedies) for atopic and/or non-atopic disease within 90 days preceding Initial Dose Escalation Day (IDED) or at any time after the IDED • Inability to discontinue antihistamines for the initial day of escalation, skin testing or OFCs • Use of omalizumab within the past six months, or immunomodulator therapy (not including corticosteroids) • Use of β-blockers (oral) • Pregnancy or lactation • History of sensitivity to oat • History of severe anaphylaxis to peanut with symptoms including hypotension requiring fluid resuscitation and/or the need for mechanical ventilation • Use of investigational drugs within 24 weeks of participation • Past or current medical problems or findings from physical assessment or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.
Study Stopping Rules	During the course of the study, if the investigator or the NIAID Medical Officer discovers conditions that indicate that the study should be discontinued, an appropriate procedure for stopping the study pending DSMB review will be instituted. If any of the stopping rules listed below are met, study enrollment will be suspended, the Initial Dose Escalation days will be suspended, dose escalation during Build-up will be stopped, and all enrolled participants will remain on their current dose pending expedited review of all pertinent data by the Data Safety Monitoring Board: • Any death related to peanut OIT dosing • One case of severe and prolonged anaphylaxis that does not respond to 3 doses of epinephrine, or that includes intubation and that is related to peanut dosing or to oral food challenge.

	• More than 2 cases of hypotension related to peanut dosing or to oral food challenge.
	• More than 3 participants require more than 2 injections of epinephrine for anaphylaxis during a single dosing event of the peanut product due to study dosing
	• More than 3 of either of the following events:
	  ○ Severe adverse event, other than anaphylaxis, related to investigational product or
	  ○ Eosinophilic esophagitis with clinical symptoms and confirmatory biopsy findings

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Glossary of Abbreviations

CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
CFRU	Clinical Food Research Unit
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IDED	Initial Dose Escalation
IEC	Institutional Ethics Committee
IMM	Independent Medical Monitor
IND	Investigational New Drug
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
PC	Protocol Chair
PI	[Site] Principal Investigator
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Suspected Adverse Reaction

1. Background and Rationale

1.1. Background and Scientific Rationale

Few studies have been conducted to optimize safety and to identify the immunological mechanism(s) underlying any long-lasting effects of oral immunotherapy (OIT). Specifically, it is not yet clear what factors will determine, in an individual subject, whether OIT has induced tolerance (in which he or she can safely ingest peanut ad lib without the need for daily consumption of peanut).[1, 2] To address these challenges in the field of food allergy research, the Stanford Alliance for Food Allergy Research (SAFAR) proposes to link the findings of this current clinical study to mechanistic studies (proposed as distinct projects under the same AADCRC study). This current clinical study (n=95 OIT and n=25 placebo conducted over 5 years in subjects 7-55 years of age with peanut allergies), together with the three mechanistic-based research projects (Section 9), presents a unique opportunity to create a comprehensive dataset combining the clinical outcomes of the OIT protocol with the results of innovative studies of tolerance in order to better understand mechanisms of OIT and to improve the safety and efficacy of oral immunotherapy of peanut allergy (PA).

There have been reports of success in a small number of mostly pediatric (under 18 years) patients in which oral food allergen immunotherapy has achieved desensitization (i.e. clinical non-reactivity to ingestion of a known allergen that must be maintained by daily consumption of that allergen) for milk[1,4,5], egg[6,7], and peanut[8-25]. The protocols for such trials are varied, involving rush therapy phases, weekly increases in doses, or both. In our first Phase 1 peanut oral immunotherapy (OIT) study conducted at Stanford from July 2009 to present, we focused on the safety parameters of peanut OIT in children and adults. Since the incidence and prevalence of food allergies in adults and children are rising (http://www.foodallergy.org/files/FoodAllergyFactsandStatistics.pdf) it is important to be able to understand the therapeutic and mechanistic effects of food allergy oral immunotherapy in both populations. We recently published our safety findings on some subjects in the Phase 1 peanut OIT study[3]. All subjects are tolerating peanut at increasing doses. Twenty (20) subjects were given placebo OIT in our study, which is important to evaluate the rate of spontaneous remission of peanut allergy and to compare safety profiles between the OIT and placebo groups. In addition, 16 of the current peanut OIT subjects have been tested for tolerance; 6 have become “immune tolerant” (referred to herein as “tolerant”) (i.e., they can eat peanut with no clinical reaction after a period of avoidance from peanut OIT—in the case of our subjects to date, 3 months); by contrast, 10 have not become tolerant to peanut (i.e., they developed a clinical reaction to peanut challenge after a period of avoidance from peanut OIT).

Our proposal, representing a new clinical study of OIT in adult and pediatric subjects with PA, is designed to provide data that can help identify mechanisms in the development of immune tolerance and improve the safety of future OIT studies. The new protocol proposed here will enroll different patients from those already studied at Stanford and will differ from our Phase 1 study (Syed, American Academy of Asthma, Allergy and Immunology Conference, San Antonio, TX, 2013) and from that of others since: 1) the patients will include both adults and children; 2) subjects will have the opportunity to be tested for immune tolerance during longer intervals of peanut avoidance; 3) we will perform sophisticated tests to discriminate clinically between tolerance and lack of tolerance; and 4) we will perform basic science studies on immune indicators in an attempt to identify those tests that are useful for allowing the safe and efficacious dosing of individual PA subjects during OIT and/or for discriminating between those patients who do or do not develop tolerance as a result of OIT.

In a separate substudy of 20 subjects, we will look at biopsy samples from the gastrointestinal tract of participants who have enrolled in the main study. Allergic disorders of the gastrointestinal tract are characterized by infiltration of the mucosal lining with inflammatory cells, such as eosinophils. These disorders include eosinophilic gastroenteritis, esophagitis and colitis. Patients with these disorders often have a history of allergy, including a high IgE level, peripheral eosinophils and allergic disease (such as food allergies or allergic rhinitis). This will help with our understanding of possible associations with eosinophilic disease and oral immunotherapy, with tolerance markers in the local organ vs peripheral blood and how it affects the local tissue in the GI tract over time. We will explore whether the 20 participants with GI biopsies show different markers at week 52 vs. week 104 vs. week 117 (or equivalent) vs. baseline. In addition, we will determine whether there are trends for differences in the markers detected in GI tissues in placebo vs avoidance vs treatment arms. The procedures to find these markers include immunohistochemistry to identify cells-inflammatory and regulatory (mast cells, basophils, eosinophils, T cells, B cells, dendritic cells, and epithelial cells and associated markers –

for example TSLP, IL-33, IL-18, IL-10 , CD103, IL-4, IL-13, histamine, STAT6, GATA3, T-bet, IFN-g, TGF-b), single cell sorting with RNA Seq, and cryopreservation for future analysis outside the scope of the proposal.

At the biopsy level, we anticipate that subjects will have increased IL-4/IL-13/IL-5 in T cells, and increased mast cells and eosinophils at baseline, and that, over time, they will have **decreases** in IL-4/IL-13/IL-5 in T cells, mast cells, eosinophils and **increases** in Treg and interferon gamma secreting T effector cells at the local tissue level over time at week 52, week 104 and week 117 (or equivalent). Samples will be read by a trained Pathologist and results will be available within one week. If changes indicate EoE, participants will be referred to our gastroenterology clinics and will discontinue the study.

We also expect increases in tolerogenic DCs overtime (i.e. increases in CD103). Overall, we think that this study will be the first of its kind to examine the local tissue of the GI tract during immunotherapy in food allergy and this is an exploratory study to be able to move forward with further hypothesis testing on future trials.

1.2. Rationale for Selection of Investigational Product or Intervention

The rationale for dosing builds on the work of the Consortium of Food Allergy Research (CoFAR), a Stanford Phase 1 study, and other studies by Dr. Burks (University of North Carolina) and Dr. Jones (University of Arkansas). The dosing consists of a single-day initial escalation at very low doses, followed by a build-up phase of increasing doses, occurring every 2 weeks. This has been demonstrated to be well tolerated and efficacious in previous studies and will be used in this current trial.

1.3. Preclinical Experience

n/a

1.4. Clinical Studies

Recently, Dr. Wesley Burks presented work showing that 10 children with PA completed an OIT protocol and underwent an oral food challenge (OFC) 4 weeks after cessation of oral intake of peanut to evaluate for the possibility of clinical tolerance (Vickery, et al., American Academy of Allergy, Asthma, and Immunology National Conference. Orlando, Florida, March 6, 2012). Three (3) out of 10 subjects passed the OFC; the authors considered these subjects clinically tolerant. Over the course of treatment, peanut IgE levels lower than 85 kU/L at a time point of 3 months into OIT was predictive of subjects who became immune tolerant. These initial findings, along with our preliminary data, are provocative and require further studies to be conducted to evaluate the reproducibility of the results obtained in this small group of children, to extend the work to adults with PA, and also to document the duration of the clinical lack of reactivity to peanut achieved in such subjects. A recent review by Byrne, et al. succinctly asks a key question: "How do we know when peanut and tree nut allergy have resolved, and how do we keep it resolved?"[26]

2. Study Hypotheses/Objectives

2.1. Hypotheses

Our hypothesis is that peanut immunotherapy will induce changes in subject's cellular and humoral immune system and thus make them less allergic to peanut allergens.

2.2. Primary Objective(s) of the overall research program

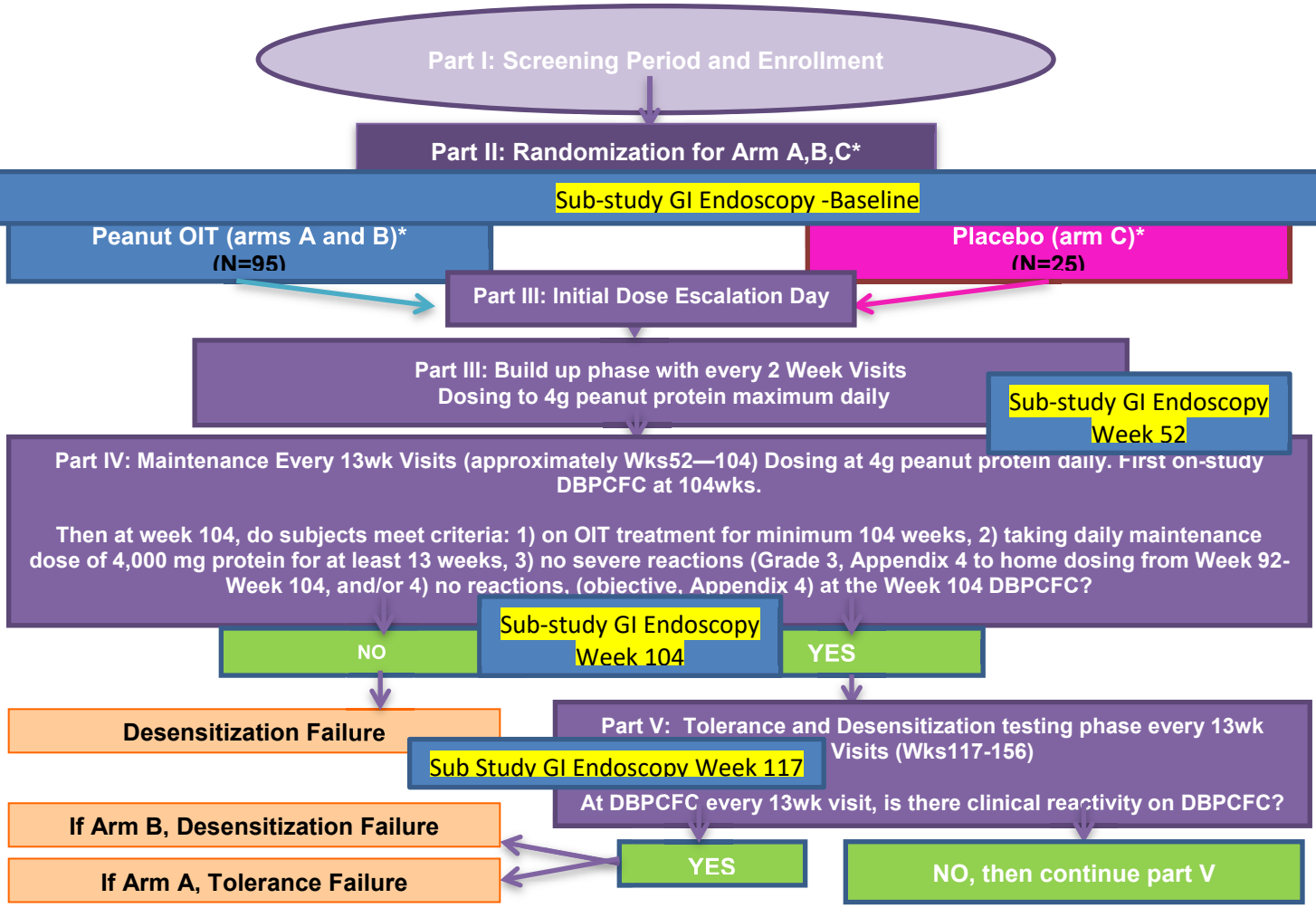
Determine whether peanut oral immunotherapy induces clinical tolerance as assessed after the initial 3 month peanut avoidance period

2.3. Secondary Objective(s) of the overall research program

- Identify the basic immune mechanisms which can explain the differences in the effects of OIT in desensitized vs. tolerant individuals.

- Determine whether immune monitoring measurements reflecting underlying mechanisms during OIT can be used to predict responses to OIT in individual subjects and, ultimately, to improve the safety and efficacy outcomes in peanut OIT protocols.

Figure 1: Study Design



* The 120 enrolled subjects will be randomized 2.4:1.4:1 (please see section 13). Thus, there will be three arms: (1) Arm A on peanut OIT until week 104 and once meeting criteria *[i.e. 1) on OIT treatment for minimum 104 weeks, 2) taking daily maintenance dose of 4,000 mg protein for at least 13 weeks, 3) no severe reactions (Grade 3, APPENDIX 4) to home dosing from Week 92-Week 104, and/or 4) no objective reactions, (Appendix 4) at the Week 104 DBPCFC]* has been assigned to avoid peanut (i.e. 600 mg oat flour). (2) Arm B on peanut OIT until week 104 and once meeting criteria, has been assigned to be maintained on 300 mg peanut protein (i.e. 600 mg peanut flour). (3) Arm C that is maintained on placebo (oat flour) and once meeting criteria, this arm will receive 600 mg oat flour beginning on week 104. This will be true even if a subject in the placebo group meets criteria at week 104. This way all participants will receive approximately the same volume of flour so that the subject blinding will be easier to maintain. The decision to maintain subjects on only 300 mg peanut protein after week 104 is for ease of eating peanut and to test if a lower amount of protein can still maintain desensitization.

3. Study Design

3.1. Description of Study Design

A Phase 2, single-center, randomized double blind, placebo controlled study of the induction of peanut tolerance by oral immunotherapy (OIT). Our intent to treat population will be 120 subjects, ages 7-55 years, with an allergy to peanut, as determined by DBPCFC, history, clinical symptoms, and positive skin prick test (SPT). Please see Figure 1.

First, subjects will be screened (Part I, Figure 1). The 120 enrolled subjects will be randomized 2.4:1.4:1 (please see section 13). Thus, there will be three arms: (1) Arm A on peanut OIT until week 104 and once meeting criteria *[i.e. 1) on OIT treatment for minimum 104 weeks, 2) taking daily maintenance dose of 4,000 mg protein for at least 13 weeks, 3) no severe reactions (Grade 3, APPENDIX 4) to home dosing from Week 92-Week 104, and/or 4) no objective reactions, (Appendix 4) at the Week 104 DBPCFC]* has been assigned to avoid peanut (i.e. 600 mg oat flour). (2) Arm B on peanut OIT until week 104 and once meeting criteria, has been assigned to be maintained on 300 mg peanut protein (i.e. 600 mg peanut flour). (3) Arm C that is maintained on placebo (oat flour) and once meeting criteria, will receive 600 mg oat flour beginning on week 104. This will be true even if a subject in the placebo group meets criteria at week 104. This way all participants will receive approximately the same volume of flour so that the subject blinding will be easier to maintain. The decision to maintain subjects on only 300 mg peanut protein after week 104 is for ease of eating peanut and to test if a lower amount of protein can still maintain desensitization. This upfront randomization is performed because our statistical analysis plan is focused on an intent to treat analysis.

All arms will undergo an Initial Dose Escalation (IDE) Day and updosing regimen with a maintenance phase of OIT or placebo to a maximum of 4,000 mg protein daily, as peanut flour, in the OIT groups, and to a maximum of an equivalent amount of oat flour for the placebo group). (Part III, Figure 1). After maintenance is achieved, all subjects will begin performing DBPCFCs (staged so as to ensure safety) at Week 104 and every 13 weeks thereafter (Part IV, Figure 1). At Week 104, individuals that reach criteria (Part IV, Figure 1) will, based on the randomization that was done at the start of the study, either stop therapy with peanut and be switched to oat flour, or will be maintained on 300 mg peanut protein per day (Parts V, Figure 1). If subjects fail the week 104 DBPCFC they will not be given home doses. Those that fail the week 104 FC will remain in the study and return for a study completion visit at week 117 to meet the primary endpoint (will be analyzed in the intent to treat comparisons). All subjects will be evaluated every 13 weeks thereafter until the end of study.

Individuals in Arm A will be defined as “clinically tolerant” if there is no clinical reactivity at the Week 104 and Week 117 (or equivalent) DBPCFC. Clinical reactivity is defined as any objective reaction based on the Bock’s Criteria (**Appendix 4**). Individuals in Arm A who meet the definition of “clinically tolerant” will continue to avoid peanut protein (i.e. continue on 600 mg per day of oat flour) as long as each subsequent DBPCFC (performed every 13 weeks until end of study) shows no clinical reactivity.

Individuals in Arm B will be defined as “desensitized” to a minimum of 300 mg per day of peanut protein if they show no clinical reactivity at DBPCFCs (week 117 (or equivalent) to end of study).

Individuals in Arm C will be defined as “natural loss of responsiveness” if they show no clinical reactivity at DBPCFCs (week 117 (or equivalent) to end of study).

We plan to identify the basic immune mechanisms which can explain the differences in the effects of OIT in individuals who do or do not become clinically tolerant and to determine whether immune monitoring can predict the safety and efficacy outcomes in peanut OIT protocols. After initial screening and enrollment, there are three phases of the study:

- Dose escalation and Build up Phase (Part III, Figure 1)
- Maintenance phase (Part IV, Figure 1)
- Tolerance and Desensitization Testing phase (Part V, Figure 1)

Overall, 120 subjects who are eligible will undergo the Initial Dose Escalation Day. Subsequent updosing visits will occur every 2 weeks as a part of the build-up phase. They will continue to updose until they reach 4,000 mg protein daily, which is the maximum maintenance amount of protein. We expect active OIT treatment subjects to reach 4,000 mg of peanut protein between 44-78 weeks.

GI Sub Study.

Subjects will also have the opportunity to participate in this study via a separate consent after they have enrolled in the study and prior to starting IDED at week 0.

Treatment and Desensitization Failures:

A treatment failure will be defined as a) failure to reach 1.5 mg peanut protein (single dose) during the Initial Dose Escalation Day or b) failure to reach 1,000 mg peanut protein by week 104.

Subjects who do not meet the criteria (Part IV, Figure 1) at Week 104 and who demonstrate clinical reactivity (objective, Appendix 4) will be considered desensitization failures.

If Arm B subjects demonstrate clinical reactivity (objective, Appendix 4) in any DBPCFC from Week 117 (or equivalent) to end of study, they will be considered desensitization failures.

If Arm A subjects demonstrate clinical reactivity (objective, Appendix 4) in any DBPCFC from Week 117 (or equivalent) to end of study, they will be considered tolerance failures.

Research staff may be unblinded when the primary endpoint (at the completion of the week 117 visit) is reached for the study. Treatment failures, desensitization failures, and tolerance failures may be unblinded (both participant and research staff) at week 117 and/or may be followed until the end of the study at the specified study visits (Appendix 1, Schedule of Events, early completion visit). They will be considered in statistical analyses of the intent-to-treat population.

Integration with mechanistic science program: We will use blood samples and clinical outcome measurements from this study to identify specific features of the immune response that are associated with ”clinical tolerance” at week 104, 117 (or equivalent), 130, 143, and 156. . We will also determine special immune features associated with subjects who are desensitized at week 104, 117 (or equivalent), 130, 143, and 156. It will be important to compare any of the immune features to those of the placebo arm, treatment failures, and desensitization failures. Treatment groups A, B, and C are key cohorts to be able to identify possible quantitative and/or qualitative differences in immune phenotypic features among subjects in the tolerance, desensitization, and placebo groups, since such information is critical to our efforts to identify possible differences in the mechanisms that underlie immune tolerance vs. desensitization.

Study Design Safety Considerations

The design considers important safety issues:

- All updosing visits will be supervised in a hospital setting where trained study physicians are available within 60 seconds
- Standing orders from an MD are provided for all clinical study personnel (RN, NP, PA, etc.) to initiate treatment of reactions immediately (i.e., prior to MD notification), including IM administration of epinephrine, based on their own clinical judgment.
- A crash cart with pediatric and adult equipment is available in close proximity (within 50 feet) of all patient hospital rooms
- A code team is available for pediatric and adult patients
- The peanut OIT will only escalate to a maximum 6 mg single dose during the initial dose escalation Day
- Dosing symptoms and adverse events will be captured throughout the study
- Subjects will be prescribed an epinephrine auto-injector (if not prescribed by a treating clinician previous to study entry) and all subjects will be trained in its use

Subjects will be cautioned against consuming any peanuts or peanut-containing foods other than study-supplied food allergen while on study.

3.2. Primary Endpoint

Proportion of peanut allergic subjects who pass a DBPCFC after the 3-month avoidance period (Week 117 or equivalent) following the end of active treatment phase

3.3. Secondary Endpoints

- Proportion of PA subjects who pass a DBPCFC after a 6-month avoidance period.
- Proportion of PA subjects who pass a DBPCFC after a 9-month avoidance period.
- Proportion of PA subjects who pass a DBPCFC after a 12-month avoidance period.
- Proportion of PA subjects who can successfully complete the build-up phase of peanut OIT to the highest dose (4,000 mg of peanut protein) with only mild Objective **APPENDIX 4**symptoms
- Proportion of PA subjects who can successfully undergo the build-up and maintenance phases of peanut OIT with only mild symptoms.
- Comparison of the proportion of subjects in placebo, avoidance, and 300 mg peanut protein/day groups who are able to undergo OFCs with no clinical reactivity after initiating OIT.

Sub Study GI Endpoint

- *Proportion of PA subjects who show increased immune cells consistent with immune tolerance (i.e. regulatory T cells) vs inflammatory allergy (i.e. eosinophils, mast cells) over time points obtained with GI biopsy tissues.*

3.4. Stratification, Randomization, and Blinding/Masking

Randomization will occur in a 2 by 2 block design performed by Dr. Turnbull using a computerized system.

3.4.1. Procedure for Unblinding/Unmasking

Unblinding must be approved by the study NIAID Medical Monitor unless an immediate life-threatening condition has developed and the NIAID Medical Monitor is not accessible. In all cases of unblinding, the site investigator will notify the NIAID Medical Monitor within 24 hours. The emergency unblinding will also be reported to the Data and Safety Monitoring Board (DSMB).

A full account of the event will be recorded, including the date and time of the unblinding, the reason for the decision to unblind, and the name of the individual who made the decision and the names of the Medical Monitor and others who were notified.

Unblinding the study due to an approved interim analysis, final analysis, or study termination will require written approval from NIAID.

3.5.2 Securing Blinding and Randomization Information

Randomization lists are maintained in a secured area, the pharmacy, by the individuals responsible for maintaining the blind, the unblinded pharmacists. The PPD site monitor (Clinical Research Associate) inspects the lists at each site visit to ensure they remain in the secured pharmacy, only accessible by the unblinded pharmacists. In the case of unscheduled unblinding or the removal of the randomization lists from the secured pharmacy binder, the Clinical Research Associate will verify that the site Principal Investigator and the NIAID Medical Monitor have been notified and that a written account has been completed and forwarded to these individuals.

4. Selection of Participants and Clinical Sites/Laboratories

4.1. Rationale for Study Population

The lower cutoff of 7 years of age was selected to include only subjects with sufficient blood volumes (to perform the mechanistic studies we need blood every 3 months or per schedule of events (+ or - 1 clinic visit). We have included a weight cut off of 17 kg so that we are compliant with IRB and NIH guideline—i.e. (for children: 5 ml/kg at any single draw, no more than 9.5 ml/kg over an 8-week period; adults: the smaller of 10.5 ml/kg or 550 ml total at any single draw). The upper age limit of 55 years was selected to ensure that the patients do not have underlying cardiovascular conditions that could preclude the use of epinephrine in subjects exposed to the risk of anaphylaxis.

Cross-reactivity between peanut and grass pollen may affect the SPTs performed to peanut. All subjects will be screened for appropriate environmental allergen sensitivity by SPT.

4.2. Inclusion Criteria

Individuals who meet all of the following criteria are eligible for enrollment as study participants:

1. Subject and/or parent guardian must be able to understand and provide informed consent and/or assent as applicable.
2. Peanut-allergic subjects between the ages of 7-55 years old.
3. Weight equal or greater than 17 kg.
4. Sensitivity to peanut allergen as documented by a positive skin prick test result (5 mm or greater diameter wheal relative to negative control) within 6 months preceding enrollment.
5. Allergy to peanut based on a double-blind placebo-controlled oral food challenge (DBPCFC) (see **Appendix 4** for scoring details) failed at a cumulative dose ≤500 mg peanut protein within 6 months preceding enrollment.
6. All female subjects of child-bearing potential will be required to provide a blood sample for pregnancy testing that must be negative one week before being allowed to participate in the study.
7. Subjects must agree to remain in the study area during the trial.
8. Subjects must be trained on the proper use of the EpiPen and patient comprehension should be confirmed (see **Appendix 5)** to be allowed to enroll in the study.
9. Subjects with other food allergies must agree to eliminate these other food items from their diet so as not to confound the safety and efficacy data from the study.
10. Female subjects of child bearing potential must agree to use birth control for the duration of the study.

4.3. Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants:

1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol
2. History of uncontrolled cardiovascular disease
3. History of other chronic disease (other than asthma, atopic dermatitis, or rhinitis) requiring therapy (e.g., heart disease, diabetes) that, in the opinion of the Principal Investigator, would represent a risk to the subject's health or safety in this study or the subject's ability to comply with the study protocol
4. History of eosinophilic gastrointestinal disease
5. Current participation or participation within the last 6 months in any other interventional study.
6. Subject is on 'build-up phase" of immunotherapy to another allergen (i.e., has not reached maintenance dosing)
7. Severe asthma (2007 NHLBI Criteria Steps 5 or 6) at time of enrollment
8. Mild or moderate (2007 NHLBI Criteria Steps 1-4) asthma at time of enrollment with any of the following criteria met:
    a. FEV1 < 80% of predicted, or FEV1/FVC < 75%, with or without controller medications (only for age 6 or greater and able to do spirometry) *or*
    b. ICS dosing of > 220 mcg daily fluticasone (or equivalent inhaled corticosteroids based on NHLBI dosing chart) *or*
    c. 1 hospitalization in the past year for asthma *or*
    d. ER visit for asthma within the past six months
9. Use of steroid medications (IV, IM or oral) in the following manners for asthma
    a. history of daily oral steroid dosing for >1 month during the past year *or*

b. burst or steroid course in the past 3 months *or*
c. >2 burst steroid courses in the past year

10. Use of complementary and alternative medicine (CAM) treatment modalities (e.g., herbal remedies) for atopic and/or non-atopic disease within 90 days preceding Initial Dose Escalation Day (IDED) or at any time after the IDED
11. Inability to discontinue antihistamines for the Initial Dose Escalation Day, skin testing or OFCs
12. Use of omalizumab within the past six months, or immunomodulator therapy (not including corticosteroids)
13. Use of β-blockers (oral)
14. Pregnancy or lactation
15. History of sensitivity to oat
16. History of severe anaphylaxis to peanut with symptoms including hypotension requiring fluid resuscitation and/or the need for mechanical ventilation
17. Use of investigational drugs within 24 weeks of participation
18. Past or current medical problems or findings from physical assessment or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.

5. Known and Potential Risks and Benefits to Participants

5.1. Risks of Investigational Product or Intervention as cited in Investigator Brochure or Package Insert

There is no IB or Package Insert for the peanut flour.

5.2. Risks of Investigational Product or Intervention cited in Medical Literature and/or those based on the Investigators' experience

In patients with peanut allergy, there have been many oral immunotherapy studies performed using procedures and dosing similar to those proposed in this Phase 2 study. In general, safety profile has been very good across the studies, and based on those studies approximately 80%, 15% and <1% of the subjects are expected to have a mild, moderate or severe symptoms, respectively, during some point in their dosing with the peanut immunotherapy. It is important to note that essentially all adverse events have been allergy-related, predictable, and reversible. The only major atypical adverse event has been several reported cases of eosinophilic esophagitis, reversible upon cessation of dosing.

Specifically, the buildup and daily maintenance doses of peanut OIT may cause allergic symptoms including sneezing, rhinorrhea, urticaria, angioedema, flushing, flares of eczema, ocular, nasal, oral and/or throat pruritus, nausea, vomiting, abdominal discomfort, cough, wheezing and/or shortness of breath in addition to severe anaphylaxis. Although no subject will be allowed to enroll who carries the diagnosis of eosinophilic disorder, the risk of eosinophilic esophagitis during OIT will be evaluated during the study[37-38]. The likelihood of a subject experiencing any allergic symptoms is expected to be lessened by initiating dosing at extremely small amounts of characterized peanut allergen and by buildup dosing under observation in a clinical setting until the maintenance dose is achieved.

Oral food challenges may induce an allergic response. Allergic reactions can be severe including life-threatening allergic reactions; however, the risk of an allergic reaction is reduced by initiating the challenge with a very small amount of the food, gradually increasing the dose, and stopping the challenge at the first sign of a reaction. If subjects have an allergic reaction during the challenges, they may need oral, intramuscular, or intravenous medications. Subjects will have an IV catheter placed before the OFCs if they have a history of anaphylaxis with hypotension requiring IV fluid resuscitation. Additionally, IV catheters may be placed, at physician discretion for any visit, based on factors such as previous reactions, recent clinical history, and clinical status observed at the visit. Trained personnel, including a study physician,

as well as medications and equipment, will be immediately available to treat any reaction. The anticipated rate of life threatening anaphylactic reactions would be < 0.1%.

There may be a risk that during participation in the trial the subjects may decrease their vigilance against accidental peanut ingestion because they believe they are protected from it. This phenomenon has been reported in previous trials, and subjects in the trial will be warned that they should continue to practice their usual vigilance against accidental ingestion of peanuts or peanut-containing foods.

5.3. Risks of Other Protocol Specified Medications

Anti H-1 blockers (e.g., cetirizine, loratadine, fexofenadine) will be used orally according to manufacturer's instructions approximately one hour prior to each food allergen dose at home. The risks of these medications include:

- Central nervous system: Headache, fatigue, somnolence, drowsiness, insomnia, sleep disorders, dizziness, muscle pain
- Gastrointestinal: Diarrhea, nausea, vomiting, dyspepsia, abdominal pain, dry mouth
- Neuromuscular & skeletal: Myalgia, back pain, pain in extremities
- Hypersensitivity reactions (anaphylaxis, angioedema, chest tightness, dyspnea, flushing, pruritus, rash, urticaria)

5.4. Risks of Study Procedures

A potential risk associated with the Initial Dose Escalation Day procedure, updosing procedure, and oral food challenges is the risk of anaphylaxis. Symptoms of anaphylaxis may include pruritus, urticaria, angioedema, wheezing, cough, dyspnea, emesis, diarrhea, and hypotension that may progress to hypotensive shock.

The potential discomforts with the Initial Dose Escalation Day procedure, updosing procedure, and oral food challenges are no more than when eating the suspected food in the past. Symptoms are usually transient lasting less than 2 hours and include pruritus, urticaria, nausea, abdominal discomfort, emesis and/or diarrhea, rhinitis, and sneezing and/or wheezing. The major risks involved include respiratory distress and rarely anaphylactic shock. Medication, personnel, and equipment are immediately available in the CFRU to treat allergic reactions. Subjects will be provided a prescription for an EpiPen® or EpiPen, Jr.® or equivalent to have with them at all times and to use in case of an allergic reaction.

Risks associated with phlebotomy or insertion of an intravenous catheter include infection, syncope, and localized pain, stinging, bleeding, or contusions at the phlebotomy site where the needle is inserted into the vein.

The risk involved with skin testing includes discomfort from the needle prick, along with pruritus and swelling at the skin test site in positive responses. Less common side effects include severe allergic reactions.

There may be an increased risk of developing Eosinophilic esophagitis (EoE), which is an immune-mediated disease as a result of inflammation of the esophagus. Symptoms range by age, with children potentially presenting with feeding difficulties, abdominal pain, and/or vomiting and adults may experience chest pain, food getting "stuck", and/or abdominal pain. If these symptoms are present, an endoscopy will be needed to confirm diagnosis, which may be performed by a gastroenterologist.

The risks involved with the GI Sub-study endoscopy are rare and include bleeding, perforation of the esophagus, stomach or duodenum, sepsis and pneumonia. The risks associated with the biopsy procedure include bleeding and perforation of the esophagus, stomach and duodenum. The risks associated with the use of the FDA approved medications routinely used for standard of care endoscopies (fentanyl, midazolam and Benadryl) include respiratory depression, constipation, dry mouth, dizziness, blurred vision, sleepiness and agitation.

5.5. Potential Benefits

There are no benefits to participating in this study. A potential benefit for the subjects randomized to the active (peanut) oral immunotherapy is the potential decrease in the subject's reactivity to peanuts after an accidental exposure/ ingestion of peanut. The likelihood of this is unknown.

6. Investigational Agent

6.1. Investigational Agent

6.1.1. Study Drug (Peanut Flour)

The investigational product in this trial is partially defatted peanut flour, 12% fat, light roast. This material is purchased from:

Byrd Mill Company
P.O. Box 1775
Ashland, VA 23005

Byrd Mill has stated that the peanut flour is manufactured under GMP for food products, no other nuts are processed at this peanut processing facility, and the peanut flour is not stored with material derived from other nuts. Analysis conducted to determine the peanut protein content in the bulk peanut flour has been done and a sample copy of the result is presented in the **Appendix 8**.

6.1.1.1. Formulation, Packaging, and Labeling

The raw material used in the manufacture of investigational product is peanut protein, manufactured by Byrd Mill Company. Raw material is accepted based upon review of the Certificate of Analysis, reproduced below.

The labels on Soufflé portion cups of investigational product and placebo are white, with dimensions 1 x 2.625 inches and the text is Arial font. The text that will appear on the labels is provided below:

Peanut Powder or Placebo

SUMC (Stanford University Medical Center)

Kari Nadeau, MD, PhD, IND #: _____

Lot #: _____ Protocol #: 0001

Dose: _____

Keep refrigerated (2-8°C)

Caution: New Drug – Limited by Federal Law to Investigational Use

6.1.1.2. Dosage, Preparation, and Administration

The drug product consists of 27 different amounts of peanut protein, which are listed in **Table 1** and **Table 2** below. Each dosage of investigational product will be supplied in a 1oz (or other appropriately sized) Soufflé Portion Cup manufactured by Solo Cup Company (Highland Park, IL). The Soufflé Portions Cups are closed with plastic lids obtained from the same manufacturer. No other excipients are added to the peanut flour. The investigational product is supplied as a dry, tan powder, which should be stored in a cool, dry place at 2 - 8 °C.

Measuring, packaging and labeling will be done by:

Stanford University Medical Center

Clinical Food Research Unit (CFRU) cGMP

Stanford Packard El Camino Hospital, PEC, 1st Floor

2500 Grant Road

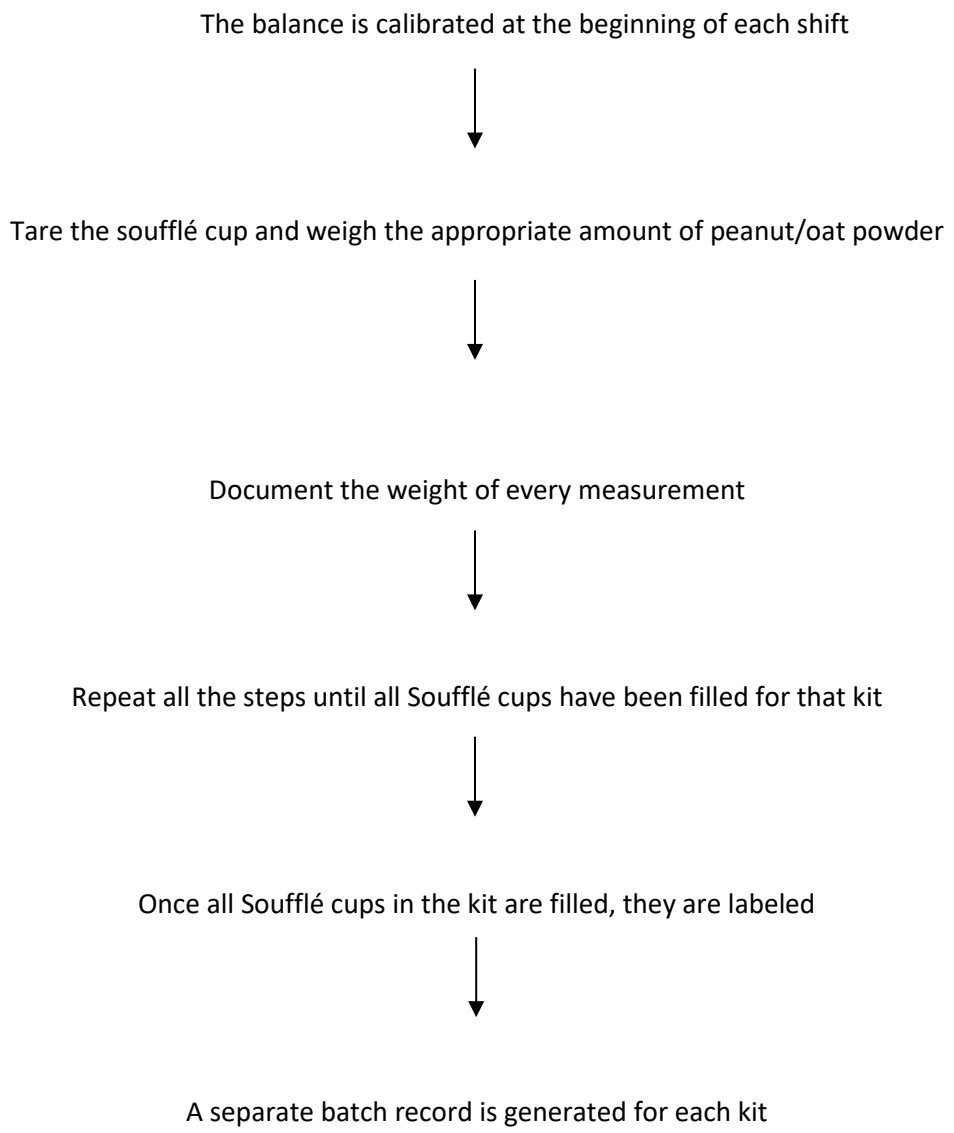
Mountain View, CA

Distinct peanut protein products will be measured and packaged using batch records for each dose. Each dose is filled at a ±5% tolerance by weight. Copies of completed batch records are available upon request. Each Soufflé portion cup containing the dose will be labeled and identified by a unique random

assignment number and the dose number. A flow diagram describing the filling of Soufflé portion cups for each dose is presented below.

The CFRU cGMP unit complies with relevant sections of the Food Drug and Cosmetic Act (21 U.S.C. 351) for early phase products appropriate for a university-based clinical research program. Specifically, drug candidates are produced in compliance with current Good Manufacturing Practices (cGMP) as defined in 21 CFR 210 and 211. In addition, the cGMP unit adheres to pertinent sections of the July 2008 Guidance for Industry cGMP for Phase 1 Investigational Drugs. This document is intended to assist innovators involved with the manufacture of investigational drugs in early stage clinical trials. In order to manage the documentation requirements, Standard Operating Procedures (SOPs) and standards set forth in the aforementioned FDA Guidances and Regulations, the CFRU cGMP unit uses an electronic document control system and will be reviewed and supported from trained research and regulatory personnel.

Figure 2: Manufacturing Flow Diagram



6.1.2. Placebo (Oat Flour)

The placebo, oat flour, will be purchased commercially from the following manufacturer:

Arrowhead Mills, Inc.

A Division of the Hain Celestial Group. Inc.

Melville, NY 11747

Toasted oat flour, prepared as described in IND [redacted] is acceptable based upon being approved and used previously for IND [redacted].

6.1.2.1. Formulation, Packaging, and Labeling

Packaging and labeling will be identical to that used for peanut flour as described under Section 6.1.1.1.

6.1.2.2. Dosage, Preparation, and Administration

Dosage, preparation, and administration will be identical to that used for peanut flour as described under Section 6.1.1.2.

6.2. Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of the investigational agent, including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed.

Original records for receipt, storage, use, and disposition will be maintained by the study site. An original drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed.

All records regarding the disposition of the investigational product will be available for inspection.

Following study drug/placebo administration, the site personnel will retain all empty or partially used vials. All drug material will be released and recorded by the nutrition personnel.

6.3. Assessment of Participant Compliance with Investigational Agent

Families will document daily dosing and any reaction from at-home dosing on diary logs. Monitoring of compliance will be performed by reviewing the participant's diary and monitoring and counting their returned study medication. Unused study medication will be brought back to the CFRU with each visit and collected by study staff for reconciliation of remaining peanut/oat flour.

6.4. Toxicity Prevention and Management

Reactions to Peanut OIT During Initial Dose Escalation Day

Participants may develop symptoms during the initial escalation. The investigator's judgment will be required to determine the best course of action with possible actions being:

1. Extend time interval between dosing (up to an additional 30 minutes).
2. Return to previously tolerated dose (i.e., repeat of last tolerated dose) then advance forward.
3. Discontinue protocol.

For *oral or pharyngeal pruritus*, the action should be to continue the normal dosing in 30 minutes.

For *mild symptoms*, defined as:

- skin — limited or localized hives or swelling, skin flushing or pruritus
- respiratory — rhinorrhea or sneezing, nasal congestion, occasional cough, throat discomfort
- GI — mild abdominal discomfort or minor episode of vomiting

the action should be either to repeat the last dose in 30-60 minutes or to advance in 30-60 minutes depending on the physician's discretion.

For *moderate symptoms*, defined as:

- skin — systemic hives or swelling
- respiratory — throat tightness without hoarseness, persistent cough, wheezing without
- dyspnea
- GI — persistent moderate abdominal pain/cramping/nausea, increased vomiting

the action should be to implement a 30-60 minute observation period and if symptoms resolve, reduce the dose by one step, repeat the same dose, or increase the dose by one step; if symptoms continue or worsen, the participant can be treated with antihistamines: if symptoms resolve, reduce the dose by one step, repeat the same dose, or increase the dose by one step; if symptoms require additional treatment, then consultation with the Principal Investigator is warranted to determine the next course of action.

For *severe symptoms*, defined as:

- respiratory — laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea

- GI — significant severe abdominal pain/cramping/repetitive vomiting
- neurological — change in mental status
- circulatory — hypotension

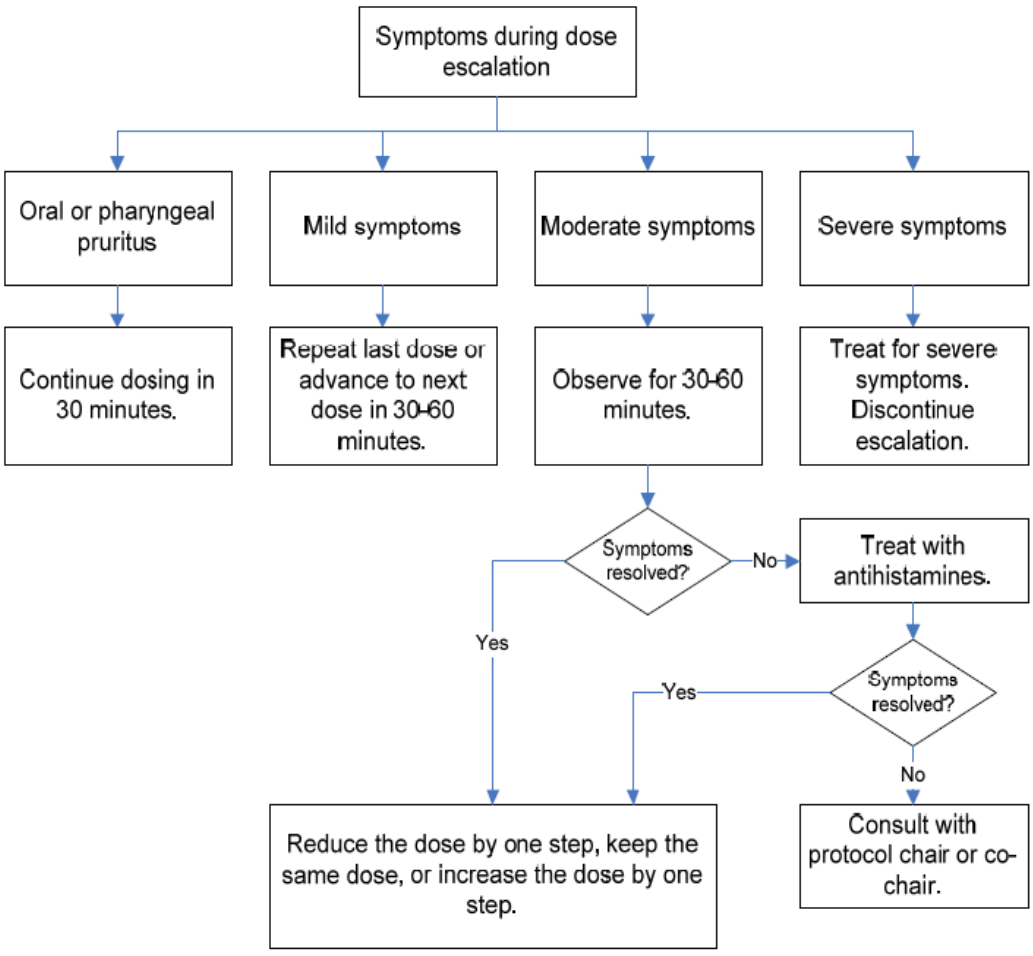
The initial escalation dose should be discontinued and the appropriate rescue medications administered.

If the subject requires treatment for symptoms with antihistamines on one occasion during the initial escalation protocol, then the rest of the protocol may be followed. If the subject requires more than one medication (e.g., albuterol, diphenhydramine, epinephrine, or others) or multiple doses of antihistamines, the initial escalation protocol should be terminated.

The PI will be available for questions and decision making for any questions related to the study protocol at all times.

All subjects will be observed for a minimum of 2 hours following administration of the final dose and will be discharged only when deemed clinically stable by a study physician.

Figure 3: Management of Symptoms During Initial Dose Escalation Day



Reactions to Peanut OIT During Build-up or Maintenance Phase

To be able to be eligible for an updosing or maintenance dose visit, subjects cannot have active wheezing, spirometry (as per manual of procedures) demonstrating FEV1 <80% predicted, or a current flare of atopic dermatitis that contraindicates updosing in the clinical judgment of the study physician. As needed, subjects will be maintained on their current dose of study product until their flare of asthma or atopic dermatitis is resolved.

If a subject has an updosing in the CFRU without symptoms, the action should be to continue per protocol with daily home dosing of the tolerated dose with the next updosing visit 2 weeks later.

If the subject only experiences oral/pharyngeal pruritus during the administration of the daily dose, then the same dose can be repeated the next day at home and continued throughout the interval unless other symptoms begin to develop.

For other mild symptoms (Objective, **APPENDIX 4**), the action should be either to repeat the dose the next day (day 2) at home or to have the subject return to the CFRU the next day (day 2) for a repeat of the previous day's dose or the last tolerated dose (at the study physician's discretion). If the dose is tolerated, then the subject will continue on that dose and return at the normal interval. If the dose causes mild symptoms again, then the subject may return to the CFRU the next day (day 3) and be given the last tolerated dose or a 1-2 step dose reduction. If tolerated, the subject will continue on this dose for the normal time interval. If mild symptoms recur, a 1-2 step reduction should be administered the next day (day 4). If tolerated then that dose should be continued for 2 weeks. If not tolerated, consultation with the PI is indicated.

If moderate symptoms (Grade 2, **APPENDIX 4**) occur, the action should be to have the subject return to the CFRU the next day (day 2) for dosing with the previous days dose or the last tolerated dose, at study physician discretion, under observation. If the dose is tolerated, the subject will continue on that daily home dose for the normal time interval per protocol. If the subject does not tolerate this dose, the subject should receive the last tolerated dose or a 1-2 step dose reduction the next day (day 3) in the CFRU or at home if the planned dose was previously tolerated. If this dose is tolerated, it will be continued as the daily home dose for the normal time interval, then escalation attempted in the CFRU as noted below. If this dose is not tolerated, then the next dose will be a 1-2-step reduction in dosing, and the dose will be given on the CFRU the next day (day 4). If this next dose is not tolerated, then a discussion with the PI will ensue to make a decision about whether to continue the subject on active treatment in the study.

If severe symptoms (Grade 3, **APPENDIX 4**) occur the action should be to treat the subject, and at the study physician's discretion either 1) have them return to the CFRU the next day (day 2) for dosing with a 2-step reduction in dose under observation or 2) discontinue them from the active treatment. If the subject tolerates the dose reduction, then they will remain on that dose for 2 weeks and then return to the CFRU for the dose escalation. A discussion with the PI may ensue to make a decision about whether to continue the subject on active treatment in the study.

If a subject fails dose escalation after three consecutive (with 2-4 weeks between) attempts, he/she will be considered a dose escalation failure and the last tolerated dose will be accepted as the maintenance dose.

For a completed dose escalation with no symptoms, subjects should be observed for 30 minutes. For mild symptoms, subjects should have a 1-2 hours post-protocol observation period. For moderate to severe symptoms, the observation period should be at least 4 hours and up to 24 hours based on symptoms and treatment regimen needed to stabilize the subject.

Any subject deemed to have severe allergic reactions to OIT, including hypoxia, hypotension or change in mental status and receives aggressive therapy (e.g., IV fluid resuscitation, mechanical ventilation, repeated doses of epinephrine for a life threatening reaction) at any time should be discussed with the PI and discontinued from active therapy.

For specific questions related to dosing escalation or continuation of the same dose that are not answered in the above protocol, the PI will be available for questions and decision-making.

Any subject who discontinues build-up dosing due to repeated allergic reactions to the characterized peanut allergen will have his/her blood drawn for mechanistic studies within approximately 1 week of discontinuation of therapy.

6.5. Premature Discontinuation of Investigational Agent

Study therapy may be prematurely discontinued for any participant for any of the following reasons:

- Anaphylaxis resulting in hypotension, neurological compromise or mechanical ventilation secondary to peanut OIT dosing or any peanut food challenge

Any subject deemed to have severe allergic reactions to OIT and who receives aggressive therapy (e.g., IV fluid resuscitation, mechanical ventilation, repeated doses of epinephrine for a life threatening reaction) at any time should be discontinued from further therapy. The circumstances include, but may not be limited to, the following:

- Poor control or persistent activation of secondary atopic disease (e.g., AD, asthma)
- Started on beta-blockers, or other prohibited medications, with no alternative medications available per the prescribing physician
- Pregnancy
- Circumstances (e.g., concurrent illness, such as gastroenteritis) requiring missed peanut OIT maintenance dosing of > 7 consecutive days
- Non-adherence with home peanut OIT dosing protocol (excessive missed days; i.e., > 3 consecutive days missed on 3 or more occasions) without consulting with study staff would be a safety issue warranting discontinuation

Any subject may be prematurely terminated from the study if:

- The subject elects to avoid consent from all future study activities, including follow-up
- The subject is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the subject have failed)
- The subject develops biopsy-documented eosinophilic esophagitis (EoE) with clinical symptoms or other eosinophilic gastrointestinal disease
- The subject dies
- Study therapy may also be prematurely discontinued for any participant if the investigator believes that the study treatment is no longer in the best interest of the participant

Follow-up of Subjects Who Discontinue Treatment Only

Subjects who prematurely discontinue treatment with peanut OIT may remain in the study until the end of study visit at Week 156. All willing subjects will be followed every 13 weeks for the duration of the study to monitor safety and efficacy parameters.

Subjects who initiate therapy (i.e., who do not fail the Initial Dose Escalation Day AND also initiate home dosing) in this trial will not be replaced.

7. Other Medications

7.1. Concomitant Medications

7.1.1. Protocol-mandated

There are no protocol-mandated concomitant medications.

7.1.2. Other permitted concomitant medications

All subjects may continue their usual medications, including those taken for asthma, allergic rhinitis and atopic dermatitis, during the study. However, they must be able to discontinue antihistamines prior to the initial day of escalation, skin testing and all oral food challenges. Usual topical steroid use is permitted at the time of skin testing. Systemic (oral, IV, IM) steroid use longer than 5 days at one time or longer than 3 weeks (21 days) duration each year is not allowed. Up-dosing will not occur within 3 days of systemic steroid use.

7.2. Prophylactic Medications

There will be no prophylactic medications required in this protocol.

7.3. Prohibited Medications

- Omalizumab (Xolair)
- Systemic (oral, IV, IM) corticosteroids used for any greater than 5 days at one time or longer than a total of 3 weeks (21 days) duration each year for asthma. If used, subjects must not be up-dosed until at least 3 days after ceasing the administration of oral steroids
- Oral β-blockers

7.4. Rescue Medications

Treatment of individual allergic reactions during peanut OIT therapy should be with either an antihistamine and/or epinephrine, along with IV fluids, albuterol and steroids as indicated. Subjects and parents are likely to already have EpiPens®, but for those who do not, a prescription for EpiPens® (or equivalent device) will be provided. Subjects and parents will be trained in proper use and will be able to demonstrate proper technique with the EpiPen® (or equivalent device).

Generally, for mild and moderate symptoms, the subject should receive antihistamines, and for more severe symptoms, the subjects should receive epinephrine, antihistamines, and then the other medications as indicated. If severe anaphylaxis occurs at any time, dose escalation will stop and the dose will be reduced to the last tolerated dose and the subject continued on that dose as long-term maintenance without further escalation.

Antihistamines

If a subject requires only antihistamines for treatment of allergic symptoms, the dose escalation can be continued. If symptoms during a build-up day require antihistamines in multiple doses or in combination with other medications (except epinephrine), there should be a dose reduction by 1-2 doses with the next dose given in CFRU. If dose escalation fails or requires treatment after two more escalation attempts each spaced 2 to 4 weeks apart, the dose should be reduced to the last tolerated dose and continued long term without further escalation.

Epinephrine

Any reaction (in CFRU or at home) that requires two or more doses of epinephrine will halt further dose escalation for this individual. Maintenance on the last tolerated dose would be continued.

CFRU

If a single administration of epinephrine is required during in CFRU escalation, the dose should be reduced by two doses, and the subject continued on that dose for four weeks. After 4 weeks at the reduced dose, an escalation attempt may be tried in CFRU.

If a single administration of epinephrine is required a second consecutive time during this escalation attempt, the dose should be reduced by two doses, and the subject continues on that dose for 6-8 weeks. After 6-8 weeks at the reduced dose, an escalation attempt may be tried in CFRU.

If a single administration of epinephrine is required a third consecutive time during this escalation attempt, the dose should be reduced by two doses and the subject continued on that dose as long-term maintenance without further escalation.

Home

If a single administration of epinephrine use occurs during dosing at home, this epinephrine use is not counted as one of the uses described above, unless severe anaphylaxis occurs at home. The subject should return to CFRU for an observed dose prior to resuming any dosing at home.

8. Study Procedures

8.1. Enrollment

The research study will be explained in lay terms to each potential research participant. The potential participant will sign an informed consent form before undergoing any study procedures. Participants will be considered enrolled into the study and assigned a unique study identification number after signing the informed consent/assent document(s).

8.2. Screening/Baseline Visit(s)

The purpose of the screening period is to confirm eligibility to continue in the study. The Screening/Baseline assessments may take place over several visits. All assessments must be completed no more than 10 months (Appendix 1) preceding initiation of peanut/placebo treatment. Baseline/screening visits following requirements below, conducted under a different protocol within the past 10 months prior to IDED, can be used towards this study.

The following procedures, assessments, and laboratory measures will be conducted to determine participant eligibility:

- Consent and assent
- Medical history, including review of all food allergies
- Physical assessment
- Blood draw for peanut-specific IgE and IgG4 measurement
- Skin prick test to peanut extract (neat extract with no dilution, Greer Laboratories, Lenoir, NC)
- Spirometry
- DBPCFC to a 500 mg cumulative total peanut protein
- Pregnancy test, if subject is a female who has undergone menarche and is of childbearing potential (i.e., not otherwise incapable of having children from a previous medical condition, surgery, or other circumstance)

Any of the above items may be repeated within the 10 months preceding initiation of study treatment if warranted, in the opinion of the investigator, by changes in the subject's clinical status.

Double-Blind Placebo-Controlled Food Challenge (DBPCFC) at Screening

Randomization and preparation of the challenge materials will be performed by trained study personnel in the GMP facility at Stanford. Prior to the food challenge, subjects will be asked to restrict the use of oral antihistamines (five half-lives), beta-agonists (12 hours), theophylline (12 hours), and cromolyn (12 hours).

The screening DBPCFC will consist of 7 doses of peanut given every 15-30 minutes in increasing amounts up to a cumulative total of 500 mg of peanut protein. If the study team suspects a reaction may be developing, they may exercise their clinical judgment to separate doses by up to an additional 30 minutes (one hour maximum between doses). The other challenge will consist of placebo material given also in 7 doses. The doses will be 5 mg, 20 mg, 50 mg, 100 mg, 100 mg, 100 mg, and 125 mg. Before each challenge, the subject will have a physical assessment administered by a trained physician's assistant, registered nurse, nurse practitioner, and/or physician of the study team who is blinded to the testing material. The supervising investigator will also be blinded to testing material.

Reactions will be scored using a Food Challenge Symptom Score sheet (see criteria in **Appendix 4**). If the subject begins to have any objective symptoms or subjective symptoms deemed clinically significant, the food challenge will be terminated and the subject will be given appropriate treatment. The subject will be observed for a minimum of two hours after the final administered dose and discharged only when deemed clinically stable by a study physician. All food challenges will be performed under physician supervision. If the subject has no symptoms related to allergic reactions to the peanut ingestion with the DBPCFC, they will not be enrolled in the study.

Separate GI Substudy.

After enrollment into the study, participants who are 18 y.o. or over will be asked, via a separate consent, if they are interested in participating in a study in which biopsies are obtained of the gastrointestinal track to test for safety and efficacy markers. There will be an upper GI endoscopy scheduled at baseline and then again at week 52, 104, and week 117 (or equivalent) of the protocol. We expect to enroll approximately 20 adult subjects in this subset.

Subjects will undergo an endoscopy prior to their IDED. This will be performed by a board certified gastroenterologist at Stanford Endoscopy suite. This will be performed under mild anesthesia using fentanyl, versed and midazolam and

subjects will be observed in the endoscopy recovery room per standard of care. Biopsies will be taken from the esophagus, stomach and duodenum.

8.3. Study Visits

Peanut OIT Treatment Overview

Peanut OIT administration will include an Initial Dose Escalation Day (IDED) with peanut oral immunotherapy dosing beginning at 0.5 mg with graduated doses up to 6 mg (if tolerated) occurring in the Stanford CFRU. Subjects tolerating less than 1.5 mg single dose will be considered an Initial Dose Escalation Day failure and will be discontinued from the study.

A targeted history and physical assessment will be performed at each in person visit. Physical assessments performed in this protocol will be allergy focused and include the following systems: head and neck, including thyroid; eyes, ears, nose, and throat; lungs; heart; abdomen; and skin. Subjects will be assessed for exacerbation of atopic dermatitis or asthma (as determined by active wheezing) prior to each in-CFRU dosing. In the presence of an exacerbation of atopic dermatitis, the study physician will use their professional judgment in deciding whether the exacerbation should preclude an attempt at updosing. In the presence of wheezing in any child, regardless of asthma history, spirometry (per manual of procedures) will be performed to assess FEV1. If FEV1<80% predicted value, bronchodilators will be administered and spirometry will be repeated. If FEV1 ≥80% predicted value (with or without bronchodilator administration) the updose will be attempted in CFRU. If FEV1 <80% predicted value after bronchodilator administration, the participant will remain at their current dose for two additional weeks. That day's dose may be administered either in CFRU and monitored as an updose.

In addition to dosing visits, subjects will return to the CFRU at designated visits (**see Appendix 1**) for their OFC or other assessments/blood draws. A medical and diary review, and targeted physical assessment will also be performed at these visits. OFCs will occur every 3 months (approximately every 13 weeks) beginning with week 104.

After subjects have met the criteria outlined above (Section 3.1), medical history, diet history, spirometry, SPT, and a physical assessment will be performed. These subjects will be randomized 1:1 either to avoid OIT therapy (**see Figure 1**), and begin the avoidance phase, or they will be randomized to decrease their daily dose to 300 mg of peanut protein. After 3 months both arms will be re-challenged with 4,000 mg peanut protein, and then every 13 weeks for up to 4 additional OFCs. The placebo group may be unblinded to the research staff at week 117.

Peanut OIT:

Initial Dose Escalation Day (Day 0) – The Initial Dose Escalation (IDE) Day will be done at the CFRU and consist of peanut OIT dosing, beginning at 0.5 mg of peanut protein with graduated doses every 30 minutes up to 6 mg (see schedule for initial day dose escalation, **Table 1**). Subjects will not have active wheezing, spirometry demonstrating FEV1 <80% predicted, or a current flare of atopic dermatitis that contraindicates dosing in the clinical judgment of the study physician. A physician will be present at all times during any of the CFRU peanut OIT dosing visits and will be available to respond within 60 seconds to any allergic reaction. Subjects tolerating the 6 mg single dose will remain on that daily dose for 2 weeks. They will then return every 2 weeks to the CFRU for single updose. Subjects who do not tolerate the 1.5 mg dose will be considered treatment failures and will not initiate home dosing.

Table 1: Peanut Protein or Placebo (oat protein)
Dosage Escalation Schedule on the Initial Dose Escalation Day

Dose #	Peanut Dose	Cumulative Peanut Dose
1	0.5 mg	0.5 mg
2	0.8 mg	1.3 mg
3	1.5 mg	2.8 mg
4	3.0 mg	5.8 mg

5	6.0 mg	11.8 mg

Up-dosing phase (build-up phase) (Week 1-44): Subjects will receive subsequent doses (**Table 2**) at home for the next 14 days. Subjects who tolerate only 1.5 mg on the IDED will return in 7 days for updosing to 3 mg and then return 7 days later for updosing to 6 mg before proceeding to dose #6. Subjects who tolerate only 3 mg on the IDED will return in 7 days for updosing to 6 mg before proceeding to dose #6. Subjects will be instructed to continue dietary peanut avoidance throughout the entire study. They will also be instructed not to introduce any new foods to the diet and to continue avoidance of the subject's other known food allergens, if any. At 2-week intervals, the subjects will return for a possible increase in the daily oral dose until they reach 4,000 mg peanut protein build-up phase).

During dose escalation, there should be increased hydration (i.e. about 16 oz or more given orally) and restricted exercise for 2 hours after dosing.

Table 2*:* Daily Peanut Protein Dosing and Increase Schedule for Build-Up Phase

Dose #	Dose	Interval (Weeks)	% of Increase
5	6 mg	2	Initial Dose Escalation Day
6	12 mg	2	100%
7	25 mg	2	108%
8	50 mg	2	100%
9	75 mg	2	50%
10	100 mg	2	33%
11	125 mg	2	25%
12	156 mg	2	25%
13	195 mg	2	25%
14	245 mg	2	25%
15	306 mg	2	25%
16	383 mg	2	25%
17	479 mg	2	25%
18	599 mg	2	25%
19	749 mg	2	25%
20	936 mg	2	25%
21	1,170 mg	2	25%
22	1,463 mg	2	25%
23	1,829 mg	2	25%
24	2,286 mg	2	25%
25	2,858 mg	2	25%
26	3,573 mg	2	25%
27	4,000 mg	2	12%

Subjects will begin the CFRU dosing schedule as outlined above until 4,000 mg of peanut protein is reached. Any updosing attempts may be postponed for 1-2 extra visits based on clinical judgment. However, an updosing attempt must be made within a maximum of 3 consecutive scheduled clinic visits. Subjects should withhold their daily home dose and any prophylactic antihistamines on the in-CFRU updosing day but should take all other prescribed medications. Note that the daily home dose should be taken as part of a meal at a consistent time (within 24±2 hours of the previous day's dose), and it is critical to take the dose every day. Doses should be separated by at least 12 hours. Subjects who require dosing reduction during the 2-week period due to illness will undergo an attempted updosing only after resuming their full dose for a minimum 3 days.

As stated above, an updosing attempt must be made within 3 clinic visits on a given dose, unless updosing is delayed due to administration of epinephrine as defined in Section 7.4 or illness. If the subject fails to successfully increase updosing for three consecutive attempts, updosing will be halted at the last tolerated dose and the subject will continue on that dose as their maintenance dose for the remainder of the study. The subject will be followed for the remainder of the study for safety and immunologic monitoring.

Vigorous exercise is not permitted for at least 2 hours after the dose of oral allergen immunotherapy. Also, there must be at least 1 hour between vigorous exercise and taking a dose of oral allergen immunotherapy. Allergic reactions are still possible when exercise takes place more than 2 hours after the dose.

Should significant systemic symptoms, which may include mild symptoms based on physician discretion or moderate or greater symptoms, be reported during the daily home dosing, the symptom/dosing algorithm will be followed to determine the best course of action. The appropriate treatment will depend on the type and number of symptoms. Subjects will be allowed to take their other daily medications during the build-up and maintenance phases of the study (i.e., antihistamines, albuterol) except where prohibited in this protocol.

Every 13 weeks during the build-up phase, subjects will have blood drawn for mechanistic labs, including basophil activation studies and pregnancy testing, if applicable. Blood will be collected prior to attempted dose escalations, but the decision to updose will be made based on clinical parameters, not the results of the assays.

Weeks 52, 65, 78, and 91– Maintenance Phase

Subjects will undergo updosing until reaching a daily maintenance dose of 4,000 mg and they will remain at that dose and return for follow-up visits at Weeks 52, 65, 78, and 91. Each of these visits will include a physical assessment, spirometry, skin test, and blood draw for mechanistic studies. Based on our previous data using a similar dosing method (Table 2), we expect all subjects on active treatment to reach 4,000 mg between the Week 44 and Week 78 visits.

Week 104 – On Study DBPCFC (to 4,000 mg)

At Week 104 all subjects will have a DBPCFC to 4,000 mg (as per staged challenge above) to assess desensitization. The visit will also include a physical assessment, spirometry, skin prick test and blood draw for mechanistic studies.

The subject's sensitivity to peanut allergen is defined as the dose at which the subject experiences allergic reactions. All symptoms and signs will be evaluated and rated based on a standardized oral food challenge scoring system (**Appendix 4**).

During the oral food challenge, there should be increased hydration (i.e. about 16 oz or more orally).

Updosing during the DBPCFC will be stopped when the Principal Investigator (or designee) finds symptoms and/or signs that indicate a definite allergic reaction (Bock scoring system (objective, **Appendix 4**) has occurred based on clinically significant changes in reported symptoms, physical findings, or vital signs that the subject is experiencing to the challenge material. The challenge will consist of 7 doses (peanut or placebo), given about every 15-30 minutes for lower doses and about every 45 minutes or longer for higher doses (in bold): 5 mg, 50 mg, 220 mg, **625 mg, 1,000 mg, and 1,050 mg and 1,050 mg** (4,000 mg protein total). The doses for DBPCFCs conducted on or after Week 104 in this

protocol were selected with the rationale that some study subjects will be receiving placebo and would be expected to maintain the same level of sensitivity displayed at the screening DBPCFC to a cumulative dose of 500 mg of peanut protein. Both peanut and oat protein will be concealed in a food that masks the taste. After the last dose of the DBPCFC, the subject will be monitored for 2 hours and then discharged home. Subjects will be considered to have tolerated the OFC if they do not experience any objective reactions by Bock's Criteria (**Appendix 4**).

If the subject experiences reactions, they will be treated with the necessary rescue medications. They will be observed for a minimum two hours after the final administered dose and discharged home only when deemed clinically stable by a study physician.

After the Week 104 DBPCFC, subjects who meet the following criteria will reduce their daily maintenance dose to 300 mg peanut protein daily or to discontinue peanut protein daily dosing entirely (i.e., switch to 600mg oat flour):

- On OIT treatment for minimum 104 weeks,
- Taking daily maintenance dose of 4,000 mg protein for at least 3 months,
- No severe reactions (Bock's Criteria Grade 3, **APPENDIX 4**) to home dosing from Week 92-Week 104, and/or
- No objective reactions by Bock's Criteria, **Appendix 4** at the DBPCFC at Week 104

Subjects who do not meet these criteria at Week 104 will be considered desensitization failures and will be offered a follow-up protocol that is separate from this protocol once they reach the primary endpoint. They will be considered in statistical analyses of the intent-to-treat population.

After Week 104, double blinding will continue by using the same quantity of flour for all groups (600 mg total of oat flour daily for placebo group and 600 mg total of oat flour daily for avoidance group; approximately 600 mg total of peanut flour --to provide exactly 300 mg peanut protein—for the 300 mg peanut protein group).

Separate GI Sub Study.

Subjects will undergo the second endoscopy at week 52, and a third endoscopy at week 104 and a fourth endoscopy at week 117 (or equivalent). These will be performed by a board certified gastroenterologist at Stanford Endoscopy suite. This will be performed under mild anesthesia using fentanyl, versed and midazolam and subjects will be observed in the endoscopy recovery room per standard of care. Biopsies will be taken from the esophagus, stomach and duodenum.

Weeks 117 (or equivalent), 130, 143, and 156 – On Study DBPCFC (to 4,000 mg)

At Weeks 117 (or equivalent), 130, 143, and 156, subjects will have a DBPCFC to 4,000 mg (as per staged challenge above) to assess tolerance. Subjects who fail these challenges (i.e., who exhibit objective reactions by Bock's Criteria, **Appendix 4**) will be offered a follow-up protocol that is separate from this protocol.

Subjects who are randomized either to 300 mg peanut protein or peanut avoidance or the placebo subjects who pass the week 104 criteria will return to CFRU at Weeks 117 (or equivalent), 130, 143, and 156. Each of these visits will include a physical assessment, spirometry, skin test, blood draw for mechanistic studies, and a DBPCFC to 4,000 mg as outlined above to assess clinical reactivity.

During the oral food challenge, there should be increased hydration (i.e. about 16 oz or more given orally).

There are no data indicating that repeating food challenges every 3 months will or will not induce desensitization or otherwise affect the outcomes in this study. Our preliminary studies in which we have performed DBPCFCs every 3 months in a separate phase 1 study cohort (n=87 subjects) have demonstrated no increased risk of sensitization.

8.4.1. Unscheduled Visits

If disease activity increases or other concerns arise between regularly scheduled visits, participants should be instructed to contact study personnel and may be asked to return to the study site for an "unscheduled" visit.

Unscheduled visits may be performed for significant food allergy episodes which may be reported by the subject between regularly scheduled visits. Significant food allergy episodes are defined as those for which epinephrine is administered based on criteria in the subject's Food Allergy Action Plan. Unscheduled visits may include physical assessment, blood draw and/or skin prick test. Review of the circumstances around the episode and appropriate documentation of the adverse event will be recorded in the study chart.

Visit Windows

Table 3: Visit Windows

Visit Type	Target Date	Visit Window
Screening/Baseline/Randomization	Day -300 to 0	Day -300 to 0
Initial Dose Escalation Day	Day 0	Day 0 (by definition)
Dose Escalation Phase	Weeks 2, 4, 6, 8 until maintenance dose is reached]	±14 days
Maintenance Phase	Weeks 52, 65, 78, 91, and 104	
Tolerance Phase	Weeks 117 (or equivalent), 130, 143, and 156	

9. Mechanistic Assays

Comparisons for each of the parameters discussed below could occur between:

- Treatment vs. Placebo group, and
- On Treatment vs. Baseline for each subject, and
- Tolerant vs. Desensitized vs. Refractory (those that terminate early due to not being able to be desensitized) clinical outcomes

I) Serum Assays

Table 4: Serum Assays

Panel	Volume needed for each sample collection
Specific IgE, IgG4, IgA anti-peanut and the component-resolved (presume IgE and IgG4 anti-Ara h 1,2,3,6,8)	1 ml
Epitope Array Peanut	350 microliters

Table 5: Expected Results for Serum Parameters

Parameter	On Therapy	Tolerance	Desensitization	Refractory
Specific IgE And Specific IgG4	Progressive decrease in specific IgE to peanut and increase in specific IgG4	Low specific IgE and increased IgG4 which persists despite the 3 month period of abstinence	Low specific IgE and increased IgG4 which reverses in the 3 month period of abstinence	No change in specific IgG4 to peanut
Epitope Array for IgE for peanut	Progressive Inhibitory antibodies	Lowest epitope spreading at	Intermediate epitope spreading at	Highest epitope spreading at baseline predicts

peptides—predictive marker for outcome	present in epitope array	baseline predicts tolerance	baseline predicts tolerance	refractory outcome
Specific IgA	Progressive increases in specific IgA over time	Increased specific IgA which persists despite the 3 month period of abstinence	Intermediate levels of specific IgA which persists despite the 3 month period of abstinence	No change

Note: Compared to placebo, in which we assume no changes will occur.

II) Cell components for CyTOF Parameters

Table 6: Possible Cell Components for CyTOF Parameters

Panel A "T" Marker	**Rationale**	**Panel B "Non T" Marker**	**Rationale**
CD4	T cell panel for immunoprofiling	CD19	B cell panel for immunoprofiling
CD8	T cell panel for immunoprofiling	CD20	B cell panel for immunoprofiling
CD3	T cell panel for immunoprofiling	CD3	B cell panel for immunoprofiling
LAG3	Marker for Tr1	CD24	Mature B cell marker
CD45RA	Naïve phenotype	CD27	Memory B cell
Ki-67	Proliferation marker	CD38	B
CD40L	Activation marker	CD16	NK marker
CD69	Activation marker	CD56	NK marker
HLA-DR	MHC Class II	CD94	NK marker
PD-1	Programmed-death (Treg subset)	CD314	iNKT
Helios	Ikaros Family Transcription Factor, preferentially expressed on induced Treg	Lin	DC marker
Foxp3	Transcription Factor involved in Treg development and function	CD123	DC and basophil marker
CD127	Marker for native Treg	CD11c	DC marker
CD49b	Marker for Tr1	CD103	Pro-tolerance DC cell (GI tract?)
CCR4	Chemokine receptor for T cell trafficking into local tissues	CCR9	Pro-tolerance DC cell
CCR8	Chemokine receptor for T cell trafficking into local tissues	HLA DR	MHC Class II
CCR6	Chemokine receptor for T cell trafficking into local tissues	CD63	Basophil activation marker
IL-17	Th17 cell ICS	CD203c	Basophil activation marker
IL-5	Th2 cell ICS	Psyk	Basophil activation phosphoepitope
pSTAT1	Th1 ICS	mTOR	Basophil activation phosphoepitope

pSTAT3	Th17 ICS	pS6	Basophil activation phosphoepitope
pSTAT5	Treg ICS	TLR9	Innate immune pathway associated with allergy treatment
pSTAT6	Th2 ICS	CD8	T cell, NKT
GATA-3	Directs Th2 development	Ki67	proliferation
T-bet	Directs Th1 development	TSLP	Pro-allergy ICS
IL-10	Treg ICS	OX40L	Allergy modifier
TGF-b	Treg ICS	TSLP receptor	DC marker pro allergy
IFN-g	Th1 ICS		
IL-13	Th2 ICS		
IL-4	Th2 ICS	Live/Dead	
Tetramer Positive	Antigen-specific		
Live/Dead			

Subset Definitions:

- T cells: CD3, CD4, CD8, CD27, CD45RA, CD28, CCR4, CCR8
- Activated T cells: CD3, CD4, CD8, CD38, HLA-DR, PD-1
- NK/NKT cells: CD3, CD8, CD16, CD56, CD94, CD314 (NKG2D), HLA-DR
- B cells: CD3, CD19, CD20, CD24, CD27, CD38,
- Regulatory T cells: CD3, CD4, CD8, CD25, CD127, CD45RA, GITR, Helios, PD-1, Foxp3, CD49b/LAG3
- DC: Lin-, HLA DR+, CCR9, CD103
- Plasmacytoid DC: Lin-, HLA DR+, CD11c-, CD123+
- Myeloid DC: Lin-, HLA DR+, CD11c+, CD123-
- Basophils: HLADR-, CD123+, CD63, CD203c, psyk, mTOR, pS6
- Innate Immunity: TLR9
- Plus Tetramer Positive T cells to be gated

Typical Intracellular Staining:

- Ki-67
- IFNgamma
- IL-4
- IL-5
- IL-9
- IL-13
- IL-10
- TGF-beta
- IL-17
- pSTAT-1
- PSTAT-3
- pSTAT-5
- pSTAT-6
- Helios
- Foxp3
- GATA-3
- Tbet
- Psyk
- pS6
- mTOR

Table 7: Expected Results for Cell Parameters

Parameter	On Therapy	Tolerance	Desensitization	Refractory
Th2	Progressive decrease in Th2 absolute numbers and ICS transcription factors and Th2 cytokines	Low Th2 cell numbers and decreased ability to proliferate in response to peanut which persists despite the 3 month period of abstinence	Low Th2 cells and low ability to proliferate in response to peanut which does not persist within the 3 month period of abstinence	No change (compared to placebo or to baseline)
Th1	Progressive increase in Th1 absolute numbers and ICS transcription factors and Th1 cytokines	HighTh1 cell numbers and increased ability to proliferate in response to peanut which persists despite the 3 month period of abstinence	High Th1 cell numbers and ability to proliferate in response to peanut which does not persist within the 3 month period of abstinence	No change (ibid)
Th17	Do not expect change	Do not expect change	Do not expect change	Do not expect change (ibid)
Treg	Progressive increase in absolute counts of Treg but then decline by 12 mo.	High Treg cell numbers and decreased ability to proliferate in response to peanut which persists despite the 3 month period of abstinence	Intermediate Treg cell numbers and decreased ability to proliferate in response to peanut which does not persist within the 3 month period of abstinence	No change (ibid)
NKT	Progressive increase in absolute counts of NKT cells	High NKT cell numbers associated with tolerance	Intermediate NKT cell numbers associated with desensitization	No change (ibid)
DC	Progressive decrease of TSLP receptor in mDCs, progressive increase in CD103 and CCR9 in DCs	Low TSLP receptor expression in mDCs, High DC expression of CD103 and CCR9	Intermediate TSLP receptor expression in mDCs and intermediate DC expression of CD103 and CCR9	No change (ibid)
Cell death markers	Progressive increase in cell death of allergen-	Highest cell death of allergen-specific Th2 memory cells	Intermediate cell death of allergen-specific	No change (ibid)

	specific Th2 memory cells		Th2 memory cells	
Chemokine receptors	Progressive increase in CCR4 and CCR8 in Treg	Highest expression of CCR4 and CCR8 in Treg	Intermediate expression of CCR4 and CCR8 in Treg	No change (ibid)
Allergen specific cells	Switch from mostly Th2 to Th1 or Treg subset over course of therapy	Lack of Th2 cytokines and transc. factors in gated tetramer positive population (i.e. no pSTAT6, no IL-4, no IL-13, no IL-5, no GATA-3 expression upon peanut stimulation)	Intermediate decrease in Th2 cytokines and transc. factors in gated tetramer positive population	No change (ibid)

Note: Compared to placebo, in which we assume no changes will occur.

III) Sample Basophil Assay:

Table 8: Expected Results for Basophil Activation Parameters

Parameter	On Therapy	Tolerance	Desensitization	Refractory
CD203c/CD63	During course of therapy, will see decrease in basophil reactivity sooner than lowering of specific IgE	Lack of basophil reactivity to peanut stimulation persists after 3 mo abstinence	Basophil reactivity returns during the 3 mo abstinence.	No change in basophil reactivity (ibid)

Logistics: Blood samples will be collected every 12-13 weeks during the subject's participation in the study. Volumes collected will follow NIH guidelines (for children: 5 ml/kg at any single draw, no more than 9.5 ml/kg over an 8-week period; adults: the smaller of 10.5 ml/kg or 550 ml total at any single draw).

IV) GI biopsy assays:

We will perform three major procedures on the GI biopsies:

a. immunohistochemistry to identify cells-inflammatory and regulatory (mast cells, basophils, eosinophils, T cells, B cells, dendritic cells, and epithelial cells and associated markers –for example TSLP, IL-33, IL-18, IL-10, CD103, IL-4, IL-13, histamine, STAT6, GATA3, T-bet, IFN-g, TGF-b)
b. single cell sorting with RNA Seq
c. cryopreservation for future analysis outside the scope of the proposal

10. Biospecimen Storage

Biospecimen storage will occur in the Nadeau laboratory using a previously validated and published storage procedure for samples (available upon request).

11. Criteria for Participant and Study Completion and Premature Study Termination

11.1. Participant Completion

Completion of the study will be defined as reaching the Week 117 (or equivalent) visit and participating in at least 90% of CFRU visits.

11.2. Participant Stopping Rules and Withdrawal Criteria

Participants may be prematurely terminated from the study for the following reasons:

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
3. The participant dies.
4. The Investigator no longer believes participation is in the best interest of the participant.
5. Individual safety stopping rules
    a. Missing >7 consecutive days of OIT therapy (e.g., concurrent illness such as gastroenteritis)
    b. Missing >3 consecutive days of OIT therapy on 3 occasions without consulting with study staff
    c. Anaphylaxis resulting in hypotension, neurological compromise or mechanical ventilation secondary to OIT dosing or any peanut food challenge
    d. Any allergic reaction to study drug requiring more than 2 doses of epinephrine due to single event
    e. The subject develops biopsy-documented eosinophilic esophagitis (EoE) with symptoms or other eosinophilic gastrointestinal disease
    f. Any subject deemed to have severe allergic reactions and who receives aggressive therapy (e.g., IV fluid resuscitation, mechanical ventilation, repeated doses of epinephrine for a life threatening reaction) at any time should be discontinued from further therapy.
    g. Other circumstances including, but not limited to, the following:
        i. Poor control or persistent activation of secondary atopic disease (e.g., AD, asthma)
        ii. Started on beta-blockers, or other prohibited medications, with no alternative medications available per the prescribing physician
        iii. Pregnancy

11.3. Participant Replacement

Subjects who initiate therapy (i.e., who do not fail the Initial Dose Escalation Day AND also initiate home dosing) in this trial will not be replaced.

11.4. Follow-up after Early Study Withdrawal

Subjects who prematurely discontinue treatment with OIT may remain in the study until end of study visit at week 156. All willing subjects will be followed every 13 weeks for the duration of the study to monitor safety and efficacy parameters. These visits will include skin testing and a blood draw for mechanistic studies.

If the subject refuses this follow-up, or begins and then elects to discontinue the follow-up, they will be asked to come in for a final study visit consisting of a physical assessment, skin test, blood draw, review of their Food Allergy Action Plan, and instructions to discontinue any OIT dosing.

11.5. Study Stopping Rules

During the course of the study, if the investigator or the NIAID Medical Officer discovers conditions that indicate that the study should be discontinued, an appropriate procedure for stopping the study pending DSMB review will be instituted, including notification of the FDA and IRB.

If any of the stopping rules listed below are met, study enrollment will be suspended, the Initial Dose Escalation days will be suspended, dose escalation during Build-up will be stopped, and all enrolled participants will remain on their current dose pending expedited review of all pertinent data:

- Any death related to peanut OIT dosing
- One case of severe and prolonged anaphylaxis that does not respond to 3 doses of epinephrine, or that includes intubation and that is related to peanut dosing or to oral food challenge.
- More than 2 cases of hypotension related to peanut dosing or to oral food challenge.
- More than 3 participants require more than 2 injections of epinephrine for anaphylaxis during a single dosing event of the peanut product.
- More than 3 of either of the following events:
    - Severe adverse event, other than anaphylaxis, related to investigational product or
    - Eosinophilic esophagitis with clinical symptoms and confirmatory biopsy findings

12.Safety Monitoring and Reporting

12.1. Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data.

12.2. Definitions

12.2.1. Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2)

For this study, an adverse event will include any untoward or unfavorable medical occurrence associated with:

- **Study therapy regimen**:

  Home OIT Dosing
  - Food allergy episodes in response to home dosing that are objective Grade 1 or 2 by Modified Bock's Criteria (**APPENDIX 4**) will be recorded on the paper AE CRFs and graded by CTCAE v 4.03 criteria.
  - Food allergy episodes in response to home dosing that are Grade 3 by Modified Bock's Criteria (**APPENDIX 4**) or that are classified as SAEs defined in Section 12.2.3 below will be recorded on the AE/SAE CRF as appropriate and graded by CTCAE v 4.03 criteria.

- **Study mandated procedures**:

  For the procedures below, clinical situations are listed that are considered to be outside the normal range of outcomes and will be recorded as Adverse Events. These situations do not limit an investigator from recording and reporting any other events, associated or not with these procedures as AEs.

  Allergen Skin Testing
  - Prolonged (>24 hours) itching at test site
  - Swelling (> 10 cm) at site of test lasting more than 24 hours
  - Nasal allergic symptoms within 30 minutes from the procedure
  - Fainting /Vasovagal event within 30 minutes from the procedure

Phlebotomy

- Bruising at phlebotomy site >5 cm with onset within 24 hours of procedure
- Erythema at phlebotomy site >5 cm with onset within 24 hours of procedure
- Infection at phlebotomy site
- Fainting /Vasovagal event within 30 minutes from the procedure

Double-Blind Placebo Controlled Food Challenges

- During DBPCFCs, reactions will be recorded. DBPCFC material is not considered study drug, and as such, reactions will be recorded and reported separately. GI biopsies

- GI biopsies will be performed on a voluntary subset of participants via an endoscopy. Adverse events will be monitored and documented per the AE listings. Any adverse events related to the procedure or medications used and that meet the criteria for SAE will be reported per the SAE matrix to the FDA and the NIAID medical monitor.

12.2.1.1. Suspected Adverse Reaction (SAR)

Any adverse event for which there is a reasonable possibility that the investigational drug [or investigational study therapy regimen] caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

12.2.2. Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or package insert or is not listed at the specificity, severity or rate of occurrence that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the IND or protocol.

The Principal Investigator will review all adverse events related to skin prick testing, spirometry, DBPCFC, or other study procedures to determine if they are unexpected.

12.2.3. Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

12.3. Grading and Attribution of Adverse Events

12.3.1. Grading Criteria

The study physician will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v4.03. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the Principal Investigator and has been deemed appropriate for the subject population to be studied in this protocol.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.
Grade 2 = moderate adverse event.
Grade 3 = severe and undesirable adverse event.
Grade 4 = life-threatening or disabling adverse event.
Grade 5 = death.

Events Grade 1 or higher will be recorded on the appropriate paper AE case report form for this study.

Anaphylaxis will be defined when there is: 1) Symptomatic bronchospasm, with or without urticaria, with parenteral intervention indicated with edema and hypotension; or 2) Life-threatening consequences with urgent intervention indicated.

12.3.2. Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator/study physician and recorded on the appropriate AE/SAE paper case report form and according to SUSAR guidelines (http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf)Final determination of attribution of SAE for safety reporting will be determined by DAIT/NIAID.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: http://ctep.cancer.gov/reporting/ctc.html.

12.4. Collection and Recording of Adverse Events

12.4.1. Collection Period

Adverse events will be collected from the time of consent until a subject completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

12.4.2. Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the subject.
- Interviewing the subject [e.g., using a checklist, structured questioning, diary, etc.] .
- Receiving an unsolicited complaint from the subject.

12.4.3. Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 12.2, *Definitions)* on the appropriate AE/SAE paper CRF regardless of the relationship to study therapy regimen or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until 30 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

12.5. Reporting of Serious Adverse Events and Adverse Events

12.5.1. Reporting of Serious Adverse Events to Sponsor

This section describes the responsibilities of the site investigator to report serious adverse events to the sponsor. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

The site investigator will report to the NIAID Medical Monitor and the Independent Medical Monitor all serious adverse events within 24 hours of becoming aware of the event, regardless of relationship or expectedness.

CONTACT INFORMATION FOR NIAID MEDICAL MONITOR:

[redacted], **MD**
Division of Allergy, Immunology, and Transplantation – NIAID/NIH
[redacted]
Rockville, MD 20852[redacted], USA
Phone: [redacted]
Cell Phone: [redacted]
E-mail: [redacted]

For serious adverse events, all requested information on the AE/SAE paper CRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE paper CRF will be updated and submitted.

12.5.1.1. Reporting of Unexpected Non-Serious Adverse Events

An unexpected, non-serious adverse event that is of Grade 2 severity or higher **and** study related will be recorded and reported to the NIAID Medical Monitor and the Independent Medical Monitor.

12.5.2. Reporting to Health Authority

Dr. Nadeau will be the sponsor of the IND and has the responsibility of reporting all AEs and SAEs to the FDA within the reporting time limits set forth by the FDA. It is Dr. Nadeau's ultimate responsibility to report any serious adverse event to the Independent Medical Monitor at her site and to the NIAID Medical Monitor within 24 hours of becoming aware of the event. IND sponsor must report the event to the appropriate health authorities using one of these two options:

12.5.2.1. Standard Reporting (IND Annual Report)

This option applies if the AE is classified as one of the following:

- Serious, expected, suspected adverse reactions (see Section 12.2.1.1, *Suspected Adverse Reaction,* and Section 12.2.2, *Unexpected Adverse Event*).
- Serious and not a suspected adverse reaction (see Section 12.2.2, *Suspected Adverse Reaction*).
- Pregnancies

Note that all adverse events (not just those requiring 24-hour reporting) will be reported in the Annual IND Report.

12.5.2.2. Expedited Safety Reporting

- Expedited reporting is required.

This option applies if the AE is classified as one of the following:

Serious and unexpected suspected adverse reaction [**SUSAR]** (see Section 12.2.1.1, *Suspected Adverse Reaction* and Section 12.2, *Unexpected Adverse Event* and 21 CFR 312.32(c)(1)i

- The IND sponsor, Dr. Nadeau, must report any suspected adverse reaction that is both serious and unexpected. The IND sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure.
    - One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug
- Aggregate analysis of specific serious adverse events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.
- Any findings from clinical or epidemiological studies, analysis of data pooled across multiple studies, published or unpublished scientific papers, or from animal or in vitro testing that would result in a safety-related change in the protocol, informed consent, General Investigational Plan section of the IND or other aspects of the overall conduct of the trial.

SUSARs must be reported to the FDA within FDA calendar days; fatal or immediately and must be reported to the FDA within 7 calendar days. All of these must also be reported to the NIAID medical monitor within 24 hours so that s/he can report to the NIAID/DAIT DSMB within the same 15 or 7 day timeframe. The site principal investigator must report SAEs to their respective IRBs as mandated by them. The site principal investigator must report SAEs to their respective IRBs as mandated by them.

To report a SUSAR, a finalized, initial SAE case report form (**Appendix 2**) and a MedWatch 3500A form will be generated by the site Principal Investigator and must be approved by the NIAID Medical Monitor.

Any findings from studies that suggests a significant human risk

The IND sponsor, Dr. Nadeau, shall report any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or *in vitro* testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, investigator brochure or package insert or other aspects of the overall conduct of the study.

12.5.3. Reporting of Adverse Events to IRBs/IECs

The site investigator shall report adverse events, including expedited reports, in a timely fashion to their respective IRBs/IECs in accordance with applicable regulations and guidelines. All *Safety Reports to the FDA* shall be distributed by Dr. Nadeau.

12.6. Pregnancy Reporting

The investigator shall be informed immediately of any pregnancy in a study subject who has initiated study treatment. A pregnant subject shall be instructed to stop taking study medication. The investigator shall counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant subject shall continue until the conclusion of the pregnancy.

The investigator shall report to the DAIT/NIAID all pregnancies within 1 business day of becoming aware of the event using the Pregnancy paper CRF. All pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. The Pregnancy paper CRF shall be updated and submitted to the DAIT/NIAID when details about the outcome are available.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities.

Any complication to pregnancy such as a congenital abnormality or birth defect shall be submitted as an SAE to the DAIT/NIAID using the SAE reporting procedures described above and to the FDA.

12.7. Reporting of Other Safety Information

The site investigator shall promptly notify the site IRB as well as the DAIT/NIAID when an "unanticipated problem involving risks to subjects or others" is identified, which is not otherwise reportable as an adverse event.

12.8. Review of Safety Information

12.8.1. Medical Monitor Review

The DAIT/NIAID Medical Monitor shall receive annual reports from the protocol chair compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the study site(s) on appropriate paper CRFs.

In addition, the Medical Monitor shall review and make decisions on the disposition of the SAE and pregnancy reports received by the protocol investigator (See Sections 12.5.1, *Reporting of Serious Adverse Events to Sponsor*, and 12.6, *Pregnancy Reporting*).

12.8.2. DSMB Review

12.8.2.1. Planned DSMB Reviews

The NIAID Allergy and Asthma Data and Safety Monitoring Board (DSMB) shall review safety data at least yearly during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs.

The DSMB will be informed of an Expedited Safety Report submitted to the FDA.

12.8.2.2. *Ad hoc* DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for *ad hoc* reviews. The DSMB will review any event that potentially impacts safety at the request of the NIAID Medical Monitor. In addition, the following events will trigger an *ad hoc* comprehensive DSMB Safety Review:

- Any death that occurs in the study.
- The occurrence of the same unexpected SAE in 3 or more of the study participants who have received a study treatment.

After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

12.8.2.2.1. Temporary Suspension of Enrollment and/or Drug Dosing for *ad hoc* DSMB Safety Review

A temporary halt in enrollment and/or drug updosing will be implemented if an *ad hoc* DSMB safety review is required per the criteria outlined in section 12.8.2.2. above.

In the event of a study halt for DSMB review, subjects in the screening phase will continue to undergo screening procedures unless the review was triggered by events related to screening.

Subjects already receiving therapy will remain on study treatment at their current tolerated dose.

Based on the outcome of the DSMB review, the consent and/or assent forms may be revised. Upon approval of these revisions by the IRB, all subjects who have previously provided informed consent for the study and are affected by the new information will be re-consented.

13.Statistical Considerations and Analytical Plan

13.1 Overview

This double blind, randomized, placebo controlled study in peanut-allergic children and adults intends to identify basic immune mechanisms that explain the effects of OIT in individuals who do or do not become clinically tolerant and to determine whether immune monitoring can predict safety and outcomes in OIT protocols.

The 120 enrolled subjects will be randomized 2.4:1.4:1. Thus, there will be three arms: (1) Arm A (60 subjects) on peanut OIT until week 104 and once meeting criteria *[i.e. 1) assigned to OIT treatment for minimum 104 weeks, 2) reaching maintenance 13 weeks prior to DBPCFC at week 104 3) no severe reactions (Grade 3, APPENDIX 4) to home dosing from Week 92-Week 104, and/or 4) no objective reactions, (Appendix 4) at the Week 104 DBPCFC]* has been assigned to avoid peanut (i.e. 600 mg oat flour). (2) Arm B (35 subjects) on peanut OIT until week 104 and once meeting criteria, has been assigned to be maintained on 300 mg peanut protein (i.e. 600 mg peanut flour). (3) Arm C (25 subjects) that is maintained on placebo (oat flour) and once meeting criteria, will receive 600 mg oat flour beginning on week 104. This will be true even if a subject in the placebo group meets criteria at week 104. This way all participants will receive approximately the same volume of flour so that the subject blinding will be easier to maintain. The decision to maintain subjects on only 300 mg peanut protein after week 104 is for ease of eating peanut for so long. This upfront randomization is performed because our statistical analysis plan is focused on intent-to-treat principles.

The primary analysis is an intent-to-treat comparison of success rates between arms A and C, where success is defined by reaching and passing the DBPCFC at both 104 weeks and 117 (or equivalent) weeks.

13.2. Endpoints

Primary Endpoint

- Proportion of peanut allergic subjects who pass a DBPCFC after the 3 month avoidance period (Week 117 or equivalent) following the end of active treatment phase.

Measurement: A DBPCFC is considered a “pass” if the subject has no clinical reactivity during the challenge (from administration of first dose through observation period lasting 2 hours after administration of the final dose).

Secondary Endpoints:

- Proportion of PA subjects who pass a DBPCFC after a 6 month avoidance period.
- Proportion of PA subjects who pass a DBPCFC after a 9 month avoidance period.
- Proportion of PA subjects who pass a DBPCFC after a 12 month avoidance period.
- Proportion of PA subjects who can successfully complete the build-up phase of peanut OIT to the highest dose (4,000 mg of peanut protein) with only mild (Objective, **APPENDIX 4**) symptoms

- Proportion of PA subjects who can successfully undergo the build-up and maintenance phases of peanut OIT with only mild symptoms.
- Comparison of the proportion of subjects in placebo, avoidance, and 300 mg peanut protein groups who are able to undergo DBPCFCs with no clinical reactivity after initiating OIT.

Measurement of Secondary Endpoints: For measurement of Bullets 1-3 and Bullet 6, see Measurement of Primary Endpoint above. Data for measurement of Bullets 4 and 5 will be collected from subject diaries, reviewed at every updosing visit attempt and DBPCFC visit conducted after successful completion of the Initial Dose Escalation Day.

13.3. Measures to Minimize Bias

This study will employ a randomized, double-blind, placebo controlled design (peanut OIT vs. placebo OIT).

13.4. Analysis Plan

13.4.1 Analysis Populations

- Intent-to-treat (ITT) sample: All subjects who are randomized will comprise the ITT sample.

- Safety sample: All enrolled subjects who receive at least one dose of OIT or placebo. Participants in the safety sample will be analyzed according to the treatment they actually received, regardless of their randomized assignment.

13.4.2 Primary Analysis of Primary Endpoint(s)/Outcome(s)

The primary analysis is an ITT comparison of success rates between arms A and C (defined in Section 13.1), where success is defined by reaching and passing the DBPCFC at Week 117 (or equivalent). An unevaluable test will be considered a failure. The analysis will be performed using the binomial test of proportions. A two-sided alpha level of 0.05 will be used. The success rate in each of the three arms will also be estimated, with 95% exact binomial confidence interval.

13.4.3 Supportive Analyses of the Primary Endpoint(s)/Outcome(s)

If any relevant covariates are imbalanced between arms A and C, the primary comparison will also be performed using a multivariable logistic regression model controlling for those variables.

The primary comparison will be repeated between arms A and B, using the binomial test of proportions with two-sided alpha level of 0.05.

13.4.4 Analyses of Secondary and Other Endpoint(s)/Outcome(s)

The following proportions will be estimated, with 95% exact binomial confidence intervals:

- Proportion in arm A who pass the DBPCFC week 130, 143, and 156 of peanut avoidance,
- Proportion, in arms A and B combined, who can successfully complete the build-up phase of peanut OIT to the highest dose (4,000 mg of peanut protein) with only mild (Objective, APPENDIX 4) symptoms,
- Proportion, in arms A and B combined, who can successfully undergo the build-up and maintenance phases of peanut OIT with only mild symptoms,
- Proportion, in arms A and B combined, defined as treatment failures at initial dose escalation or at 1000 mg protein,
- Proportions, in arms A and B separately, who are defined as desensitization failures at week 117 (or equivalent), 130, 143, and 156, and

- Proportion, in arm A who are defined as tolerance failures at week 117 (or equivalent), 130, 143, and 156.

Adverse events will be tabulated, using the safety sample.

13.4.5 Analyses of Exploratory Endpoint(s)/Outcome(s)

We will use blood samples and clinical outcome measurements from this study to identify specific features of the immune response that are associated with "clinical tolerance" at week 104, 117 (or equivalent), 130, 143, and 156. We will also determine special immune features associated with subjects who are desensitized at week 104, 117 (or equivalent), 130, 143, and 156. It will be important to compare any of the immune features to those of the placebo arm, treatment failures, tolerance failures, and desensitization failures. This exploratory objective may be examined prior to study closeout. In such a case, only the statisticians will have access to identity of study arm. Study arm, however, will not be a variable in the analysis prior to study closeout. Instead the outcome of interest will be clinical tolerance/desensitization across study arms and the interest will lie in correlating molecular features to the outcome.
A number of post-hoc analyses for predicting clinical outcomes will be completed looking at clinical and mechanistic variables.

13.4.6 Descriptive Analyses

Descriptive statistics (proportions for categorical variables, means and standard deviations for continuous variables) will be reported for all key participant variables, including baseline and demographic characteristics, use of medications, compliance, and study completion status.

13.5.1 Interim Analyses

N/A – There will be no interim analyses in this protocol.

Although no formal interim analyses are specified, we will examine one set of exploratory objectives prior to study closeout that do not involve our primary efficacy endpoint, nor do they reveal data by study arm. Specifically, the outcome of interest will be clinical tolerance/desensitization aggregated across study arms and the interest will lie in correlating molecular features to the outcome.

13.6. Statistical Hypotheses

For the primary comparison, the following will be tested:

- Null hypothesis: The success rate (where success is passing the DBPCFC at both 104 and 117 (or equivalent) weeks) is equal in arms A (active treatment followed by 3 months of avoidance) and C (placebo).
- Alternative hypothesis: The success rate differs between arms A and C.

As a secondary comparison, the following will be tested:

- Null hypothesis: The success rate is equal in arms A and B (active treatment followed by 3 months of 300mg peanut protein treatment).
- Alternative hypothesis: The success rate differs between arms A and B.

13.7. Sample Size Considerations

In the previous trial by Burks et al, 2013 the rate of success among subjects treated as in arm A was 0.35. Literature (Sampson, et al. 2013) suggests that the rate of success among subjects on placebo (as in arm C) is

0.05 or less. Using a binomial test of proportions with two-sided alpha level 0.05, the sample size of 60 subjects on arm A and 25 subjects on arm C yields 90% power to detect that difference (between rates of 0.35 and 0.05). According to the definition of the endpoint – passing the DBPCFC at both 104 and 117 (or equivalent) weeks – subjects who drop out of the study are included in the analysis (counted as failures). Therefore, the analysis will include all subjects randomized to arm A or arm C, and the sample size is not decreased due to drop-outs.

The following table displays the power for other possible success rates in the two arms.

		Arm C Population Success Rate		
		0.025	0.05	0.075
Arm A Population Success Rate	0.25	76%	59%	44%
	0.30	89%	77%	64%
	0.35	96%	90%	80%
	0.40	99%	96%	91%
	0.45	100%	99%	97%

14. Identification and Access to Source Data

14.1. Source Data

Source documents and source data are considered to be the original documentation where subject information, visits consultations, assessments and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial.

In this protocol, source data will be recorded onto paper CRFs at the time of collection. Skin test results will be recorded via adhesive tape transfer of the outline of any wheal(s) and/or erythema. Spirometry results will be recorded as printouts from the software package used to perform the testing.

14.2. Access to Source Data

The site investigator and site staff will make all source data available to the PPD Monitor, DAIT/NIAID, as well as to the FDA. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identify individuals.

15. Protocol Deviations

15.1. Protocol Deviation Definitions

Protocol Deviation – The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site, approved by the NIAID and then implemented promptly.

Major Protocol Deviation - A major protocol deviation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, major protocol deviations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection

regulations, policies, or procedures. This also includes departures from GCPs and pharmacy handling of the investigational product and accountability.

Non-Major Protocol Deviation - A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

15.2. Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the NIAID (**Appendix 3**). However, protocol deviations may also be identified during site monitoring visits conducted by the PPD monitor, or during other forms of study conduct review.

Deviations from the protocol will be reviewed by the NIAID project manager, on a case-by-case basis, to determine if the deviation meets major or non-major criteria. All protocol deviations and the reasons for such deviations must be noted on the appropriate CRF.

Protocol Deviation reports will be submitted by study site personnel in accordance with requirements from the local IRB, the FDA, and the NIAID. Action plans to prevent deviations going forward will be reviewed and approved by the NIAID Project Manager and Medical Monitor.

16.Ethical Considerations and Compliance with Good clinical Practice

16.1. Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the IRB. Any amendments to the protocol or to the consent materials will also be approved by the IRB before they are implemented.

16.2. Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or study physician listed on the FDA 1572 will review the consent and answer questions with the potential participant and the study physician must sign the consent form with the participant and document the informed consent process. For minors participating in this study, informed consent will be obtained from their parent(s) or legal guardian(s). Minors participating in this study will provide assent if they are capable. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

16.3. Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

17.Publication Policy

Every possible effort will be made for the primary outcome of the trial to be published in a peer-reviewed journal within 12 months after the database is locked. The DAIT/NIAID will review and comment on any manuscript derived from this trial prior to submission and the NIH data sharing policy (http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm#goals). Data from this trial will be shared in accordance to the specific plan that was included in the grant application.]

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Appendix 1: Schedule of Events

Study Stage		**Screening**	**IDED***	**Build-up Phase**													
Time	***Week****	***Day -300 to Day 0***	***Day 0***	***2***	***4***	***6***	***8***	***10***	***12***	***14***	***16***	***18***	***20***	***22***	***24***	***26***	***28***
	Visit #	***X***	***0***	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***	***12***	***13***	***14***
Informed Consent**		X															
Medical History		X															
Physical Exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Peanut/Placebo Dosing			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total IgE		X															
Peanut Specific IgE and IgG4		X															
Peanut skin testing		X															
CBC with differential		X															
Mechanistic labs		X							X						X		
Serum or urine test*** pregnancy		X													X		
Spirometry		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Screening DBPCFC		X															
On-Study DBPCFC																	
Diaries			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EpiPen® Training		X															

*Initial Dose Escalation Day

**Informed consent obtained prior to completion of any study procedures ^Subjects return for up-dosing every 2 weeks. Blood to be obtained every 12 weeks

***Urine pregnancy test to be performed preferentially. Serum pregnancy test to be performed to confirm positive urine results, if any.

****Week number may be + or – 2 weeks.

Appendix 1 (cont'd)

Study Stage		**Build-up Phase (Week #)**								**Maintenance Phase**									**Early Completion**
Time	***Week*******	***30***	***32***	***34***	***36***	***38***	***40***	***42***	***44***	***52***	***65***	***78***	***91***	***104***	***117 ^***	***130***	***143***	***156***	***Withdrawal/ Early Termination***
	Visit #	***15***	***16***	***17***	***18***	***19***	***20***	***21***	***22***	***23***	***24***	***25***	***26***	***27***	***28***	***29***	***30***	***31***	
Informed Consent**																			
Medical History																			
Physical Exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Peanut/Placebo Dosing		X	X	X	X	X	X	X	X										
Total IgE										X	X	X	X	X	X	X	X	X	X
Peanut Specific IgE and IgG4										X	X	X	X	X	X	X	X	X	X
Peanut skin testing										X	X	X	X	X	X	X	X	X	X
CBC with differential										X	X	X	X	X	X	X	X	X	X
Mechanistic labs					X					X	X	X	X	X	X	X	X	X	X
Serum or urine pregnancy***										X		X		X		X		X	
Spirometry		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Screening DBPCFC																			
On-Study DBPCFC†														X	X	X	X	X	
Diaries		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EpiPen® Training																			

†First On-study DBPCFC to 4,000 mg performed at Week 104 in all subjects. Participants meeting criteria at week 104 (Part IV, Figure 1) may also have DBPCFCs at Weeks 117 (or equivalent), 130, 143, and 156.

^ Possible early completion visit for those participants who demonstrate objective allergic reactions (Appendix 4) at week 104 DBPCFC.

Appendix 2: Sample Serious Adverse Event Form

Serious Adverse Event Form

Date of Report: _____

MM/DD/YYYY

□ Initial Report

□ Follow-up Report *(if follow-up complete participant identification and then only enter new/revised information)*
Initial Report Date: _____

MM/DD/YYYY

Reason for SAE designation *(check all that apply)*:	
□ Death _____ MM/DD/YYYY	□ Congenital anomaly or birth defect
□ Hospitalization or prolonged hospitalization Date of admission/prolongation : _____	□ Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
□ Important medical event	□ Life Threatening event
	□ Form used for other than SAE _____ (e.g. unexpected, related ≥ Grade 2 AE or pregnancy

Event Description	
Date of SAE: _____ MM/DD/YYYY	Date site became aware of the SAE: _____ MM/DD/YYYY
SAE Event Term (Diagnosis) and/or Symptoms	
Describe clinical course of events (include subject's status in the study, how you became aware of the event, and relevant chronology):	

Other relevant information: including:
Pre-existing medical conditions (or attach Medical History CRF) (attach additional pages if necessary)
Concomitant medications: (or attach Concomitant Medication Log) attach additional pages if necessary)
Tests, and laboratory data relevant to the event: (attach additional pages sheet if necessary)

Relation to the Study:		
Study Medication:_____ □ Unrelated □ Possible □ Definite	Study Medication:_____ □ Unrelated □ Possible □ Definite □	If Unrelated to Study Medications Complete the following: <u>Possible Alternative Etiology</u>: □ Concomitant medication: _____ □ Concurrent illness: _____ □ Study Procedure/Rescue medication: _____ □ Other possible cause: _____
Date and time of last dose _____ _____ MM/DD/YYYY Time (or est)	**Date and time of last dose** _____ _____ MM/DD/YYYY Time (or est)	
Expectedness (*An adverse event is considered "unexpected" when its nature, severity or it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the IND (if applicable).*		
□ Yes □ No		
Please provide additional discussion:		

Action taken: Describe action taken in regard to Investigational Product (s) **and** the management of the event)
attach additional pages*, if needed)*

Outcome of Event
□ Resolved, no residual effects; date
□ Resolved with sequelae; date:
List Sequelae : _____
□ On-going
□ Death
Was a death certificate obtained? □ No □ Yes
Was autopsy obtained: □ No □ Yes, findings relevant to the relationship of the event_____

_____ _____

Name and Signature of Principal Investigator Date

Appendix 3: Sample Deviation Report Form

PROTOCOL DEVIATION REPORTING FORM

Instructions: Any noncompliance with the study protocol, Good Clinical Practice (GCP), or protocol specific Manual of Procedures (MOP) is considered a protocol deviation. Each protocol deviation of **any** nature or severity should be documented. Generally, one form should be used for each deviation. However, if one deviation impacted more than one subject and the effect was the same for each subject, then list all subjects on one form. Once completed and signed, the form is sent to the NIAID Project Manager

Subject ID:	**Report Date**
Deviation date:	**Date Site Staff became aware of Deviation**:
1.**Description of Deviation** *(attach continuation form, if needed)* :	
2. **Circumstances explaining /contributing to the deviation** *(attach continuation form, if needed)* :	
3. **Effect of Deviation on SAFETY or RISK from study participation**: ☐ No effect ☐ Safety concern or increased risk Explain why the deviation has (or has not) an effect on subject's safety or risk from study participation. In case that deviation has an effect please provide extent of potential safety impact. **Note:** if the deviation resulted in an AE/SAE; major deviation *(attach continuation form, if needed)* :	

4. **Effect of Deviation on the study endpoints or quality of study data**:

☐ No effect ☐ Potential effect on data quality

Explain why deviation has/has not had an effect on the quality of study data. In case that deviation has an effect please provide extent of potential effect on data quality major deviation *(attach continuation form, if needed* :

5. **Corrective action(s) to resolve this Deviation** *(attach continuation form, if needed)*:

6. **Corrective action(s) to prevent similar occurrences** *(attach continuation form, if needed)* :

7. **Participant(s) will continue as a study subject(s)**: *(attach continuation form, if needed)*

YES ☐ NO ☐ Justification:

8. **Notifications**

	Date Notified
NIAID Project Manager	
Independent Medical Monitor (if applicable)	
IRB (if applicable)	

9. **Was continuation form used?**

YES ☐ NO ☐

_____ _____ _____ _____

Principal Investigator Date Independent Medical Monitor Date *(if applicable)*

For NIAID Use

Major Deviation *(as determined by the NIAID Project Manager)* YES ☐ NO ☐_____

_____

Project Manager Date

Subject ID: Report Date

PROTOCOL DEVIATION REPORTING FORM CONTINUATION PAGE (do not submit if not used)

Appendix 4: Scoring of Clinical Food Allergic Reactions using objective criteria

Symptoms and/or Signs of an Objective (in bold) Allergic Reaction (Bock Scoring Challenge).

Category		Grade and Symptom(s)
Skin		
Rash	Grade 0:	Sign or symptom not observed
	Grade 1:	**Few areas of faint erythema**
	Grade 2:	**Areas of erythema, macular and raised rash**
	Grade 3:	**Generalized marked erythema (>50%); extensive raised lesion (>25%); vesiculation and/or piloerections**
Pruritus	Grade 0:	Sign or symptom not observed
	Grade 1:	**Occasional scratching**
	Grade 2:	**Scratching continuously for >2 minutes at a time**
	Grade 3:	**Hard continuous scratching leading to excoriations**
Urticaria	Grade 0:	Sign or symptom not observed
	Grade 1:	**<3 Hives**
	Grade 2:	**3 to <10 Hives**
	Grade 3:	**Generalized involvement**
Angioedema	Grade 0:	Sign or symptom not observed
	Grade 1:	**One site of angioedema**
	Grade 2:	**Two or more sites of angioedema**
	Grade 3:	**Generalized involvement, including airway** involvement

Nasal		
Sneezing	Grade 0:	Sign or symptom not observed
	Grade 1:	**Rare bursts of sneezing**
	Grade 2:	**<10 bursts of sneezing**
	Grade 3:	**Continuous rubbing of nose and/or eyes; periocular swelling &/or long bursts of sneezing**

Grade 1-mild, Grade 2-moderate, Grade 3-severe

Appendix 4 (cont'd)

Symptoms and/or Signs of an Allergic Reaction (Bock Scoring Challenge)

Category		Grade and Symptom(s)
Nasal itching	Grade 0:	Sign or symptom not observed
	Grade 1:	**Mild itching**
	Grade 2:	**Intermittent rubbing of nose or eyes**
	Grade 3:	**Continuous rubbing of nose and/or eyes; periocular swelling and/or long bursts of sneezing**
Nasal congestion	Grade 0:	Sign or symptom not observed
	Grade 1:	**Some hindrance to breathing**
	Grade 2:	**Nostrils feel blocked, breathes through mouth most of the time**
	Grade 3:	**Nostrils occluded**
Rhinorrhea	Grade 0:	Sign or symptom not observed
	Grade 1:	**Occasional sniffing**
	Grade 2:	**Frequent sniffing, requires tissues**
	Grade 3:	**Nose runs freely despite sniffing and tissues**
Airway obstruction	Grade 0:	Sign or symptom not observed
	Grade 1:	**Voice change mild**
	Grade 2:	**Voice change moderate**
	Grade 3:	**Voice change severe**
Chest		
Wheezing	Grade 0:	Sign or symptom not observed
	Grade 1:	**Expiratory wheezing to auscultation or 15% decrease from highest FEV1 value observed on study or FEV1 ≤65%**
	Grade 2:	**Dyspnea, inspiratory, and expiratory wheezing**
	Grade 3:	**Dyspnea, use of accessory muscles, audible wheezing**

Appendix 4 (cont'd)

Symptoms and/or Signs of an Allergic Reaction (Bock Scoring Challenge)

Category		Grade and Symptom(s)
Abdomen		
Nausea	Grade 0:	Sign or symptom not observed
	Grade 1:	Mild complaint of nausea
	Grade 2:	**Frequent complaint of nausea**
	Grade 3:	**Nausea causing notable distress**
Abdominal pain	Grade 0:	Sign or symptom not observed
	Grade 1:	*Complaint of abdominal pain*
	Grade 2:	**Frequent complaints of abdominal pain, decreased activity**
	Grade 3:	**In bed, crying, or notably distressed**
Emesis	Grade 0:	Sign or symptom not observed
	Grade 1:	**1 Episode of emesis**
	Grade 2:	**2–3 Episodes of emesis or 1 of emesis and 1 of diarrhea**
	Grade 3:	**>3 Episodes of emesis or ‡2 of emesis and ‡2 of diarrhea**
Diarrhea	Grade 0:	Sign or symptom not observed
	Grade 1:	**1 Episode of diarrhea**
	Grade 2:	**2–3 Episodes of diarrhea or 1 of emesis and 1 of diarrhea**
	Grade 3:	**>3 Episodes of diarrhea or ≥2 of emesis and ≥2 of diarrhea**

Bock SA, Sampson HA, Atkins FM, Zieger RS, Lehrer S, Sachs M, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. J Allergy Clin Immunol 1988;82:986–97.

Appendix 5: EpiPen Training Form

EpiPen Training Form

By signing the EpiPen training form, I acknowledge being appropriately trained and demonstrate understanding in the use and proper storage of EpiPens and have read the accompanying directions for use (instructions).

_____ _____
Signature of Adult Participant Date

_____ _____
Signature of LAR (Parent, Guardian or Conservator) Date

_____
Authority to act for participant

_____ _____
Signature of Trainer Date

_____
Printed Name of Trainer

Current Wt: _____kg q **EpiPen** q **EpiPen Junior**

ANAPHYLAXIS INFORMATION (All boxes must be checked)

- ❑ Reviewed epinephrine pictogram with subject and/or family
- ❑ Subject and/or family given an Food Allergy Action Plan with a verbal review to ensure understanding
- ❑ Subject and/or family given information on how to purchase medical identification jewelry tag (e.g. MedicAlert bracelet)

Appendix 6: Evaluation of Asthma

The evaluation of asthma severity will be assessed using the NHLBI classification published August 18, 2007 as described in the table below.

Classification	Symptoms	Nighttime awakenings	Lung Function	Interference with normal activity	Short acting beta-agonist use
Intermittent (Step 1)	≤ 2 days per week	≤ 2x /month	Normal FEV_1 between exacerbations FEV_1>80% predicted FEV_1/FVC normal*	None	≤2 days /week
Mild Persistent (Step 2)	> 2 days per week but not daily	3-4x /month	FEV_1 ≥ 80% predicted FEV_1/FVC normal*	Minor limitation	>2 days /week but not >1x/day
Moderate Persistent (Step 3 or 4)	Daily	> 1x /week but not nightly	FEV_1 ≥60% but <80% predicted FEV_1/FVC reduced 5%*	Some limitation	Daily
Severe Persistent (Step 5 or 6)	Throughout the day	Often 7x /week	FEV_1<60% predicted FEV_1/FVC reduced >5%*	Extremely limited	Several times per day

*Normal FEV1/FVC: 8-19 yr = 85%; 20-39 yrs = 80

Appendix 7: Sample Certificate of Analysis for Peanut Flour

GOLDEN PEANUT SPECIALTY PRODUCTS DIVISION
3886 Martin Luther King Jr Blvd. Blakely, GA 39823
Tel. (770)-752-8190 * Fax (770)-752-8209
EMAIL – bruce.kotz@goldenpeanut.com
WEB PAGE – www.goldenpeanut.com

Certificate of Analysis

Customer:	**Byrd Mill**
PO	Shannon-9/6/12
Lot Number:	112FA22711
Product:	Partially Defatted Peanut Flour - 12% Fat - Light Roast
Product Code:	521271
Date Processed:	8/14/2012

Physico-Chemical			**Method**
Aflatoxin:	Total 1.9	ppb	HPLC
Aflatoxin:	B1 1.6	ppb	HPLC
Aflatoxin:	B2 0.3	ppb	HPLC
Aflatoxin:	G1 None Detected	ppb	HPLC
Aflatoxin:	G2 None Detected	ppb	HPLC
Color:	70.83	Hunter "L" Value	Hunter Colorimeter
Protein:	(N x 6.25) 58	%	AOCS Current Ed.
Protein:	(N x 5.46) 51	%	AOCS Current Ed.
Fat:	12.78	%	AOCS Current Ed.
Moisture:	1.51	%	AOCS Current Ed.
Ash:	3.80	%	AOCS Current Ed.
Peroxide:	0.57	meq/Kg	AOCS Current Ed.
Sensory:	Acceptable		

Microbiological -tested at Deibel Laboratories, Madison, WI			**Method**
APC:	<10	cfu/g	AOAC 966.23
Coliforms:	<0.3	MPN/g	AOAC 966.24
E. coli:	<0.3	MPN/g	AOAC 966.24
E. coli:	<0.3	MPN/g	AOAC 966.24
E. coli:	<0.3	MPN/g	AOAC 966.24
E. coli:	<0.3	MPN/g	AOAC 966.24
E. coli:	<0.3	MPN/g	AOAC 966.24
E. coli (O157:H7):	Negative	25 g	MLG Ch5 5A.4.N
Salmonella:	Negative	4 x 375 g	AOAC 996.08/2004.003
L. monocytogenes:	Negative	25 g	AOAC 999.06
S. aureus (Coagulase +):	<10	cfu/g	FDA BAM
Yeast and Mold:	<10		

Dr. Lori Bunch
Quality Assurance Manager

OU
THIS PRODUCT IS KOSHER

This product contains peanuts that were sourced only from the USA.

Appendix 8: Open Label Follow-Up

An open label protocol will be offered to placebo subjects, desensitization failures, and treatment failures. This separate study will mainly focus on collecting safety data and will be conducted as per IND 14830.

List of Tables

List of Figures

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