DAIT/Rho STATISTICAL ANALYSIS PLAN ACKNOWLEDGMENT AND SIGNATURE SHEET

Oral Immunotherapy for Induction of Tolerance and Desensitization in Peanut-Allergic Children

Approved: _____ Date: _____
Wesley Burks, MD
Protocol Chair

Approved: _____ Date: 4/19/19
Stacie M. Jones, MD
Protocol Co-chair

Approved: Lisa M. Wheatley -S Digitally signed by Lisa M. Wheatley -S Date: 2019.04.19 07:29:36 -04'00' Date: _____
Lisa Wheatley, MD
NIAID Medical Monitor

Approved: _____ Date: _____
Srinath Sanda, MD
ITN Clinical Trial Physician

Approved: _____ Date: _____
Michelle Sever, PhD
Rho Scientist

Approved: _____ Date: _____
Jacqueline Johnson, DrPH
Rho Statistician

DAIT/Rho STATISTICAL ANALYSIS PLAN ACKNOWLEDGMENT AND SIGNATURE SHEET

Oral Immunotherapy for Induction of Tolerance and Desensitization in Peanut-Allergic Children

Approved: _____ Date: _____
Wesley Burks, MD
Protocol Chair

Approved: _____ Date: _____
Stacie M. Jones, MD
Protocol Co-chair

Approved: _____ Date: _____
Lisa Wheatley, MD
NIAID Medical Monitor

Approved:  Date: 4/18/19
Srinath Sanda, MD
ITN Clinical Trial Physician

Approved: _____ Date: _____
Michelle Sever, PhD
Rho Scientist

Approved: _____ Date: _____
Jacqueline Johnson, DrPH
Rho Statistician

DAIT/Rho STATISTICAL ANALYSIS PLAN ACKNOWLEDGMENT AND SIGNATURE SHEET

Oral Immunotherapy for Induction of Tolerance and Desensitization in Peanut-Allergic Children

Approved: _____ Date: _____
Wesley Burks, MD
Protocol Chair

Approved: _____ Date: _____
Stacie M. Jones, MD
Protocol Co-chair

Approved: _____ Date: _____
Lisa Wheatley, MD
NIAID Medical Monitor

Approved: _____ Date: _____
Srinath Sanda, MD
ITN Clinical Trial Physician

Approved: Michelle Sever Digitally signed by Michelle Sever DN: dc=com, dc=rhoworld, dc=ms, ou=Departments, ou=_Users, ou=Red, cn=Michelle Sever, email=Michelle_Sever@rhoworld.com Date: 2019.04.18 15:27:13 -04'00' Date: _____
Michelle Sever, PhD
Rho Scientist

Approved: _____ Date: _____
Jacqueline Johnson, DrPH
Rho Statistician

DAIT/Rho STATISTICAL ANALYSIS PLAN ACKNOWLEDGMENT AND SIGNATURE SHEET

Oral Immunotherapy for Induction of Tolerance and Desensitization in Peanut-Allergic Children

Approved: _____ Date: _____
Wesley Burks, MD
Protocol Chair

Approved: _____ Date: _____
Stacie M. Jones, MD
Protocol Co-chair

Approved: _____ Date: _____
Lisa Wheatley, MD
NIAID Medical Monitor

Approved: _____ Date: _____
Srinath Sanda, MD
ITN Clinical Trial Physician

Approved: _____ Date: _____
Michelle Sever, PhD
Rho Scientist

Approved: Jacqueline Johnson _____ Date: _____
Digitally signed by Jacqueline Johnson
DN: dc=com, dc=rhoworld, dc=ms, ou=Departments, ou=_Users, ou=Red, cn=Jacqueline Johnson, email=Jacqueline_Johnson@rhoworld.com
Date: 2019.04.18 13:55:05 -04'00'
Jacqueline Johnson, DrPH
Rho Statistician

DAIT/Rho STATISTICAL ANALYSIS PLAN
18 April 2019

Oral Immunotherapy for Induction of Tolerance and Desensitization in Peanut-Allergic Children

VERSION: **1.1**

DATE: **April 18, 2019**

SPONSOR: Division of Allergy, Immunology, and Transplantation
National Institute of Allergy and Infectious Diseases – NIH
5601 Fishers Lane
Rockville, MD 20852
Telephone: (301) 496-5717
Fax: (301) 402-3573

PREPARED BY: Rho, Inc
2635 East NC Highway 55
Durham, NC 27713
Telephone: (919) 408-8000
Fax: (919) 408-0999

DAIT/Rho STATISTICAL ANALYSIS PLAN ACKNOWLEDGMENT AND SIGNATURE SHEET

Oral Immunotherapy for Induction of Tolerance and Desensitization in Peanut-Allergic Children

Approved: _____ Date: _____
Wesley Burks, MD
Protocol Chair

Approved: _____ Date: _____
Stacie M. Jones, MD
Protocol Co-chair

Approved: _____ Date: _____
Lisa Wheatley, MD
NIAID Medical Monitor

Approved: _____ Date: _____
Srinath Sanda, MD
ITN Clinical Trial Physician

Approved: _____ Date: _____
Michelle Sever, PhD
Rho Scientist

Approved: _____ Date: _____
Jacqueline Johnson, DrPH
Rho Statistician

Document History

Version	Date	Change(s)	Author
0.1	01-18-2018	Initial Draft	Jacqueline Johnson, Yunjung Kim
0.2	12-03-2018	Implemented changes discussed by the SMT in Spring, 2018	Jacqueline Johnson
0.3	01-10-2019	Implement changes from Lisa Wheatley who replaced previous medical monitor Marshall Plaut	Jacqueline Johnson
0.4	02-05-2019	Implemented changes from SMT discussion on 1/10/2019	Jacqueline Johnson
0.5	02-14-2019	Implemented changes to PP population definition from email	Jacqueline Johnson
1.0	02-18-2019	Versioned to final 1.0 version	Jacqueline Johnson
1.1	04-09-2019	Edited PP population definition. Edited handling of indeterminate placebo challenges. Added survival analysis as a sensitivity analysis.	Jacqueline Johnson

Table of Contents

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
CBC	complete blood count
CFR	US Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
DBPCFC	Double Blind Placebo Controlled Food Challenge
DSMB	Data and Safety Monitoring Board
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HEENT	Head, Eyes, Ears, Nose, Throat
ICH	International Conference on Harmonisation
IDE	Initial Dose Escalation
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITN	Immune Tolerance Network
MedDRA	Medical Dictionary for Regulatory Activities v 16.0
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events v 4.03
OFC	Oral Food Challenge
OIT	Oral Immunotherapy
OpFC	Open Food Challenge
SAP	Statistical Analysis Plan
SOC	System Organ Class
SPT	Skin Prick Test
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reactions
WHO	World Health Organization

1. PROTOCOL SYNOPSIS

Title	Oral Immunotherapy for Induction of Tolerance and Desensitization in Peanut-Allergic Children
Short Title	Peanut OIT in Children
Sponsored by	National Institute of Allergy and Infectious Diseases
Conducted by	Immune Tolerance Network
Protocol Chair	Protocol Chair: Wesley Burks, MD Protocol Co-chair: Stacie M. Jones, MD
Accrual Objective	144 participants
Study Design	This is a randomized, double-blind, placebo-controlled, multi-center study comparing peanut oral immunotherapy to placebo. Eligible participants with peanut allergy will be randomly assigned to receive either peanut OIT or placebo for 134 weeks followed by peanut avoidance for 26 weeks. An initial blinded oral food challenge (OFC) to 1 g of peanut flour (500 mg peanut protein) will be conducted. Participants must have a clinical reaction during this blinded OFC to initiate study dosing. After the initial blinded OFC, the study design includes the following: **Initial Dose Escalation:** This will occur on a single day in which multiple doses are given. Peanut or placebo dosing will be given incrementally and increase every 15-30 minutes until a dose of 12 mg peanut flour (6 mg peanut protein) or placebo flour is given. The first four doses will be administered as a peanut flour extract of 0.1 to 0.8 mg peanut protein, which is 10 to 80 microliters peanut flour extract, or placebo flour extract and the last three doses will be given as peanut flour of 3 to 12 mg peanut flour 1.5 to 6 mg peanut protein or placebo flour. Participants must tolerate a dose of at least 3 mg peanut flour (1.5 mg peanut protein) or placebo flour to remain in the study. **Build-up:** After the initial dose escalation day, the participant will return to the research unit the next morning for an observed dose administration of the highest tolerated dose from the initial escalation day. The participant will then continue on the daily OIT dosing at home and return to the research unit every 2 weeks for a dose escalation. The dosing escalations will be consistent with previous similar OIT studies. Participants who do not reach the 4000 mg peanut flour (2000 mg peanut

protein) or placebo flour dose during the build-up phase may enter maintenance phase at their highest tolerated dose, which must be at least 500 mg peanut flour (250 mg peanut protein) or placebo flour.

The build-up phase will comprise 30 weeks.

Maintenance: The participant will continue on daily OIT with return visits every 13 weeks. At the end of this phase the participant will undergo a blinded OFC to 10 g peanut flour (5 g peanut protein).

This phase will comprise 104 weeks.

Avoidance: In this final phase participants stop OIT and will avoid peanut consumption They will be seen 2 weeks and 26 weeks after initiating this phase**.** At the completion of this phase participants will have a final blinded OFC to 10 g peanut flour (5 g peanut protein). Participants who do not have a clinical reaction to the challenge will receive an Open Food Challenge (OpFC).

Avoidance will comprise 26 weeks.

Post-challenge: If participants do not have a clinical reaction during the OpFC at the end of avoidance, they will be allowed to consume peanut and will have one visit which will include peripheral blood sampling for mechanistic assays assessments.

Post-challenge will comprise 2 weeks.

Study Duration

Total study duration will be up to 238 weeks (slightly more than 4 and one-half years).

- Enrollment will be up to 78 weeks.
- Study participation will be 162 weeks, which includes the initial dose escalation, build-up, and maintenance, avoidance, and post-challenge.

Primary Endpoint

The primary endpoint is the proportion of participants desensitized to peanut after 134 weeks OIT.

Participants who pass a blinded OFC to 10 g of peanut flour (5 g of peanut protein) at this time without significant symptoms as described in Section 6.4.4 will be considered desensitized to peanut. Failure will be defined as either unable to undergo the final food challenge or inability to tolerate the maximum dose because of significant symptoms such as hives, wheezing, vomiting, or laryngeal edema.

Secondary Endpoints

Efficacy

- Tolerance Endpoint

  The proportion of participants who pass both the blinded OFC to

10 g peanut flour (5 g peanut protein) and the Open OFC to 8 g peanut protein in natural food form at week 160.
Passing a blinded OFC is defined in Section 3.3.1.
Passing an Open OFC is defined in Section 6.4.3.

- Transient Desensitization Endpoint

  This is the change in proportion of participants who pass the blinded OFC to 10 g peanut flour (5 g peanut protein) at week 134 and week 160.
  Passing a blinded OFC is defined in Section 3.3.1.
- Highest Tolerated Cumulative Dose Endpoint

  The highest tolerated cumulative dose of peanut protein during the blinded OFCs will also be collected and analyzed.

Safety:

- The incidence of all adverse events.
- Rates of withdrawal from OIT or placebo.

Mechanistic:

Changes in the following markers of immune mediation:

- Secreted cytokines
- Anti-peanut IgE, IgG, IgG4 and secretory IgA
- Epitope arrays
- IgE-facilitated, CD23-dependent allergen binding to B cells
- Serum, stools, and saliva assays
- PBMC expression of transcription factors and cytokines relevant to food allergy
- CD4+ CD25+ FoxP3+ Tregs
- DNA-HLA genotyping
- Peanut-specific T cells
- Ara h 1 and Ara h 2 reactive T cells
- Th2A Subset Analysis
- Basophil activation
- B cells

Inclusion Criteria

1. Age 12 months to less than 48 months, either gender.
2. Clinical history of peanut allergy or avoidance of peanut without ever having eaten peanut.
3. Serum IgE to peanut of $\geq$ 5 kUA/L determined by UniCAP^{TM}
4. Wheal ≥ 3mm on skin prick test to peanut extract compared to a negative control.
5. A clinical reaction as defined in Section 6.4.4 at or below ingestion of 1 g peanut flour (500 mg peanut protein) during screening blinded OFC.

6. Written informed consent from parent/guardian.

Exclusion Criteria

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

2. INTRODUCTION

This statistical analysis plan (SAP) only includes analyses related to the clinical endpoints outlined in the protocol. Mechanistic analyses will be performed at the Immune Tolerance Network (ITN), and a separate analysis plan will be created to detail the planned analyses. Relevant clinical data from the study will be submitted to the ITN Biomarker and Discovery Research (BDR) and ITN Bioinformatics Groups (BiG) to augment the mechanistic analyses.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following analyses and reporting conventions will be used:

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form "n (%)." Percentages will be rounded to one decimal place.

- Numeric variables will be summarized using n, mean, standard deviation (SD), median, minimum (min), maximum (max). The min/max will be reported at the same level of significance as original data. The mean and median will be reported at one more significant digit than the precision of the data, and SD will be reported at two more significant digits than the precision of the data.

- The median will be reported as the average of the two middle numbers if the dataset contains an even number of observations.

- Test statistics including *t* and *z* test statistics will be reported to two decimal places.

- *P*-values will be reported to three decimal places if greater than or equal to 0.001. If less than 0.001, the value will be reported as "<0.001." A *p*-value can be reported as "1.000" only if it is exactly 1.000 without rounding. A *p*-value can be reported as "0.000" only if it is exactly 0.000 without rounding.

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

4. ANALYSIS SAMPLES

- Intent-to-treat (ITT) sample: All subjects who are randomly assigned to treatment or placebo will comprise the ITT sample.
- Per-protocol maintenance phase (PP-M) sample: All ITT subjects who are also study-compliant through the maintenance phase and have an evaluable blinded peanut flour OFC at the end of the maintenance phase. Compliance is defined as completion of the maintenance phase as described in the protocol Section 6.7.4; fewer than 3 occasions on which more than 3 consecutive home doses of study medication were missed with reason for missed doses given as non-compliance; and fewer than 3 visits at which non-protocol specified ingestions of peanut-containing food was reported within a year.
- Per-protocol avoidance phase (PP-A) sample: All participants included in the PPM sample who are compliant with peanut avoidance during the avoidance phase and have an evaluable blinded peanut flour OFC at the end of the avoidance phase. Compliance is defined as completion of the avoidance phase as described in the protocol Section 6.7.5 and fewer than 3 visits at which non-protocol specified ingestions of peanut-containing food was reported within a year.
- As-treated sample: All evaluable subjects, analyzed according to the amount of peanut therapy received, regardless of their randomized assignment.
- 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.

5. STUDY SUBJECTS

5.1. Disposition of Subjects

The disposition of all enrolled subjects will be summarized in tables and listed.

The numbers and percentages of subjects randomized, in each analysis sample, and completing build-up (weeks 0-30), maintenance (weeks 31-134), avoidance (weeks 135-160), and post-challenge (weeks 161-162) phases, as well as reasons for early termination from the study will be presented. For subjects discontinuing study treatment early, the reasons for discontinuing study treatment early will also be presented.

Randomization will be stratified by site and will be accomplished through a password-protected, web-based, randomization system (RhoRAND™) maintained by the SDCC.

5.2. Demographic and Other Baseline Characteristics

Summary descriptive statistics for baseline and demographic characteristics will be reported for all analysis samples. Demographics data include age, ethnicity, and sex. Baseline characteristics consist of medical history including asthma and atopic dermatitis history, peanut allergy history, diet and allergy assessment including egg allergy, IgE to food allergens, IgE to inhalant allergens, skin prick test results, gastrointestinal assessment, and modified Aceves questionnaire scores. Continuous variables will be summarized using mean, standard deviation, median, IQR, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages. To see if the distributions of demographic and baselines characteristics are comparable across different sites, the summary statistics for the ITT population will be reported for each site separately and for all sites combined.

6. STUDY OPERATIONS

6.1. Protocol Deviations

Protocol deviations will be listed by site with information such as type of deviation, severity of the deviation (major or non-major), date of occurrence, and the reason for the deviation. Protocol deviations will be summarized in tabular format by type of deviation.

6.2. Treatment Adherence

During the maintenance period, participants will maintain diary logs to document daily dosing of the study product. Additionally, subjects will be instructed to return all empty packages as well as all unused study product at each visit, which will be recorded by the site. Participant compliance with administration of study product will be performed regularly. Treatment adherence will be summarized by treatment arm (i.e. peanut OIT and placebo) for the maintenance period of the study. Treatment adherence will be assessed based on the number of occasions on which more than 3 consecutive home doses of study medication were missed and the number of occasions when non-protocol specified ingestions of peanut-containing food occurred. The reason for missed doses (e.g. concurrent illness) will also be assessed. The number of consecutive missed doses, percent of missed doses over all expected doses, and reason for missed doses will be summarized in the ITT, PP-M, and PP-A populations by treatment group.

7. ENDPOINT EVALUATION

7.1. Overview of Efficacy Analysis Methods

7.1.1. Multicenter Studies

Study subjects will be recruited from 5 study sites. Site will be included as a covariate in analyses as specified.

7.1.2. Assessment Time Windows

Allowable visit windows for all scheduled visits are provided in the Appendix 1 and Appendix 2. All other visits that must occur within the time limits are specified in the protocol Section 6.1. Visits that occur outside specified visit windows will be tabulated as protocol deviations. All data will be included in analyses, regardless of time of assessment.

7.2. Primary Endpoint

The primary endpoint is the proportion of participants desensitized to peanut after 134 weeks OIT.

Participants who pass a blinded OFC to 10 g of peanut flour (5 g of peanut protein) at this time without significant symptoms as described in protocol Section 6.4.3 will be considered desensitized to peanut. Failure will be defined as being either unable to undergo the final peanut flour food challenge or inability to tolerate the maximum dose because of significant symptoms such as hives, wheezing, vomiting, or laryngeal edema.

If a placebo flour challenge is a failure, and the associated peanut challenge is failed at a dose at or above the dose of placebo challenge failure, the peanut flour challenge will be considered a failure at the observed dose of failure. If a placebo flour challenge is stopped early without reaction due to participant refusal to continue, the associated peanut flour challenge will be considered a passed challenge.

Any randomized subject without an evaluable blinded peanut flour OFC will be imputed as not desensitized.

7.2.1. Primary Analysis of the Primary Endpoint

We will model the probability of being desensitized using a multivariate logistic regression model in which treatment as a primary variable of interest and site, peanut-specific IgE level, and age as covariates for adjustment are used.

In addition to the main effects model, we will investigate the interaction effects between each covariate and the treatment. If no interaction is present, only the main effects and adjusted proportions and confidence intervals will be reported. Unadjusted proportions and odds ratios will also be presented with confidence intervals. The primary analysis of the primary endpoint will be performed on the ITT sample.

7.2.2. Sensitivity Analyses of the Primary Endpoint

The analysis of the primary endpoint will be repeated using the PP-M sample. Sensitivity analyses for the primary analysis of the primary endpoint will additionally be performed to

investigate impact of imputation on analysis results. The primary analysis of the primary endpoint will be repeated:

- In the ITT sample with imputation as follows:
    - Missing peanut flour OFC outcomes = failure
    - Peanut flour challenge with a placebo flour challenge that stopped early without reaction due to participant refusal to continue = failure
- In the ITT sample without imputation of missing peanut flour OFC outcomes; and
- In the ITT sample with imputation of missing peanut flour OFC outcomes performed using multiple imputation via regression methods.

A discrete time survival analysis on cumulative tolerated dose will additionally be performed in the ITT and PP-M samples as a further sensitivity analysis to compare treatments with respect to desensitization. In this analysis, participants with a missing peanut flour OFC outcome will be censored at the first dose.

7.3. Secondary Endpoints

We will conduct the following efficacy analyses for secondary endpoints. All analyses will be performed in the ITT, PP-M, and PP-A samples, as appropriate. Sensitivity analyses as described in the primary analysis of the primary endpoint will be performed to investigate the impact of imputation on analysis results.

1. Tolerance Endpoint

This is the proportion of participants who pass the blinded OFC to 10 g peanut flour (5 g peanut protein) and the Open OFC to 8g peanut protein in natural food form at week 160. We will model the probability of being tolerant using a multivariate logistic regression model in which treatment will be used as a primary variable of interest and site, peanut-specific IgE level, and age will be used as covariates for adjustment. Unadjusted proportions and odds ratios will also be presented with confidence intervals. Any randomized subject without an evaluable blinded OFC will be imputed as not tolerant.

2. Transient Desensitization Endpoint

This is the change in proportion of participants who pass the blinded OFC to 10 g peanut flour (5 gram peanut protein) at week 134 and 160. The proportions of participants in each treatment group who pass the blinded OFC at the week 134 desensitization endpoint and week 160 tolerance endpoint are calculated as primary and secondary endpoints. Transient desensitization within each treatment group will be calculated within each treatment as the difference in these two proportions for that treatment. Transient desensitization will be compared between the treatment groups using a McNemar's test at a 0.05 level of significance. As a sensitivity analysis, the proportion of participants who pass the week 160 OFC at the tolerance endpoint will be compared between the treatment groups in the sample of only those participants who achieved desensitization at week 134. As in the analyses of the primary and secondary desensitization and tolerance endpoints, any randomized subject without an evaluable blinded OFC will be imputed as not desensitized or not tolerant, respectively.

.

3. Highest Tolerated Cumulative Dose Endpoint

The highest tolerated cumulative dose of peanut protein during each blinded OFC will be analyzed within and between both placebo and peanut OIT groups. This will allow the investigation of desensitization at 134 weeks, tolerance at 160 weeks, and possible changes between week 134 and week 160. Each of these analyses will be performed in a similar manner as all other endpoint analyses. However, instead of a binary (pass or fail) blinded OFC outcome, the highest cumulative dose of peanut protein tolerated for each subject will be analyzed as a continuous outcome. Depending on the distribution of the data, parametric or non-parametric statistical methods may be performed. Sensitivity analyses will additionally be performed on a change from baseline outcome adjusting for baseline highest tolerated cumulative dose. As in the analyses of the primary and secondary desensitization and tolerance endpoints, any randomized subject without an evaluable blinded OFC will be imputed as not desensitized or not tolerant, respectively. For the continuous highest cumulative dose endpoint, this will be defined as having a highest cumulative dose imputed as zero. As a sensitivity analysis, cumulative tolerated dose will be imputed as zero for any failed peanut flour challenge with a failed associated placebo flour challenge.

7.4. Examination of Subgroups

An earlier version of the protocol allowed participants to miss 7 or fewer consecutive home doses before study discontinuation. This was later amended to allow up to 14 consecutive doses.

Primary and secondary endpoint analyses will be repeated for the subgroup of participants who meet the original criteria of missing 7 or fewer consecutive home doses. Data for participants who at any time missed more than 7 doses will be included in this subgroup analysis only up until the time of the first missed 8th dose.

Primary and secondary endpoint analyses will additionally be repeated in the subgroup of participants who missed at least one period of 7 or more days of oral immunotherapy.

8. SAFETY EVALUATION

8.1. Overview of Safety Analysis Methods

All safety analyses will be carried out using the safety sample unless otherwise noted. Missing safety information will not be imputed. These analyses will not be stratified by site.

8.2. Adverse Events

Safety will be analyzed through the reporting of AEs. All AEs will be classified by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0. The severity of AEs will be classified using the specific grading scale for allergic reactions associated with study procedures related to administration of peanut flour or placebo which was adapted from the CoFAR3 protocol (DAIT/NIAID IND # 13239). The National Cancer Institute's Common Toxicity Criteria for Adverse Events, Version 4.03 (NCI-CTCAE) toxicity scale will be used for all other AEs. The total number of events and the number of participants experiencing AEs will be summarized by body system and preferred term for each treatment group and overall. Separate summaries will be provided for serious AEs, treatment-related AEs, and AEs leading to study discontinuation. Abnormal vital signs, physical examination results, and laboratory values that the investigator deems clinically significant will be graded according to the NCI-CTCAE toxicity scale and reported as AEs. Rates of withdrawal from therapy will be compared in the ITT, per protocol and safety samples.

Each AE is entered on the electronic case report form once at the highest severity. As such, no additional data manipulation is needed to identify events.

An overall summary table will be developed to report the number of events and the number and percentage of subjects having at least one event in the following categories:

- AEs
- AEs indicated as serious
- AEs that lead to study drug discontinuation
- AEs with an outcome of death
- AEs that were reported as being related to a study drug
- AEs reported by maximum severity

In addition, AEs classified by MedDRA SOC and preferred term will be summarized for each treatment group and overall for each of the following:

- All AEs
- Participants who missed at least one period of 7 or more days of oral immunotherapy
- Participants who did not miss more than 3 consecutive days or oral immunotherapy.

Summary tables will present the total number of events as well as the number and percentage of subjects experiencing the events. If a subject experiences the same AE on multiple occasions, the event will be counted once for each occurrence when reporting the number of AEs. When reporting the number of subjects experiencing the events, a subject will only be

counted once if they experience an event within the particular SOC or preferred term. Percentages will be based on the number of subjects in the safety population.

8.3. Deaths and Serious Adverse Events

Serious adverse events (SAEs) defined in the protocol section 8.2.4 will be listed and summarized in the same manner described in Section 8.2. Separate displays listing and summarizing death, including time to death and cause of death, will also be created.

8.4. Clinical Laboratory Evaluation

Clinical laboratory measurements include hematology performed at screening and during build-up, maintenance, avoidance, and post-challenge visits. They will be converted to standardized units where possible. For numeric data, descriptive statistics of laboratory values and the change from baseline of laboratory values will be presented for each treatment group and overall. For categorical data, the number and percentage of subjects reporting each result will be presented for each treatment group and overall. Laboratory normal ranges will be included and out-of-range flags (H or L) will be used to denote abnormal values.

8.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

8.5.1. Vital Signs

Vital signs measurements include systolic blood pressure, diastolic blood pressure, temperature, pulse, respiratory rate, weight, height, and height that are collected at screening and all subsequent visits. Descriptive statistics tables will summarize vital signs values at each visit and change from baseline for each treatment arm and overall. Data listings sorted by treatment group, subject, vital sign parameter, and time of assessment will be provided for vital signs measurements. Figures will present participant line graphs for participants in both treatment arms presented in separate figure panels.

8.5.2. Physical Examinations

Physical examination results of normal, abnormal, not done, and not worsening since previous visit will be summarized as frequencies and percentages by body system and visit. Data listings will be provided for physical examination results and sorted by treatment group, subject, body system, and time of assessment.

9. OTHER ANALYSES

9.1. Use of Medications

Medications will be coded according to the World Health Organization (WHO) Drug Dictionary (version 2012.03). Medications reported on the CRF will be categorized for analysis as prior, concomitant, or after study treatment by comparing the medication start and stop dates with the first and last dose of study medication dates. Prior medications will have both the medication start and stop dates prior to the first dose of study medication date. After medications will have both the medication start and stop dates after the last dose of study medication date. All other medications will be classified as concomitant, indicating that use of the medication overlapped with use of the study medication by at least one day.

The number and percentage of subjects receiving prior, concomitant, and after medications will be presented overall and by medication class. When reporting the number of subjects receiving the medication, a subject will only be counted once if they ever received the medication within the medication class. Percentages will be based on the number of subjects in the analysis population.

10. INTERIM ANALYSES AND DATA MONITORING

The progress of the study will be monitored by the Data and Safety Monitoring Board (DSMB). The DSMB will be chartered to review safety data and to make recommendations regarding continuation, termination, or modification of the study. The DSMB will formally review the safety data at least yearly. The discontinuation of study treatment will also be periodically reported to the DSMB.

In addition, safety data will be reviewed by the DSMB when an event occurs that is of sufficient concern to the National Institute of Allergy and Infectious Diseases (NIAID) medical monitor or protocol chair to warrant review, or when an event occurs that could contribute to a predefined stopping rule specified in the protocol.

Findings will be reported to Institutional Review Boards (IRBs) and health authorities.

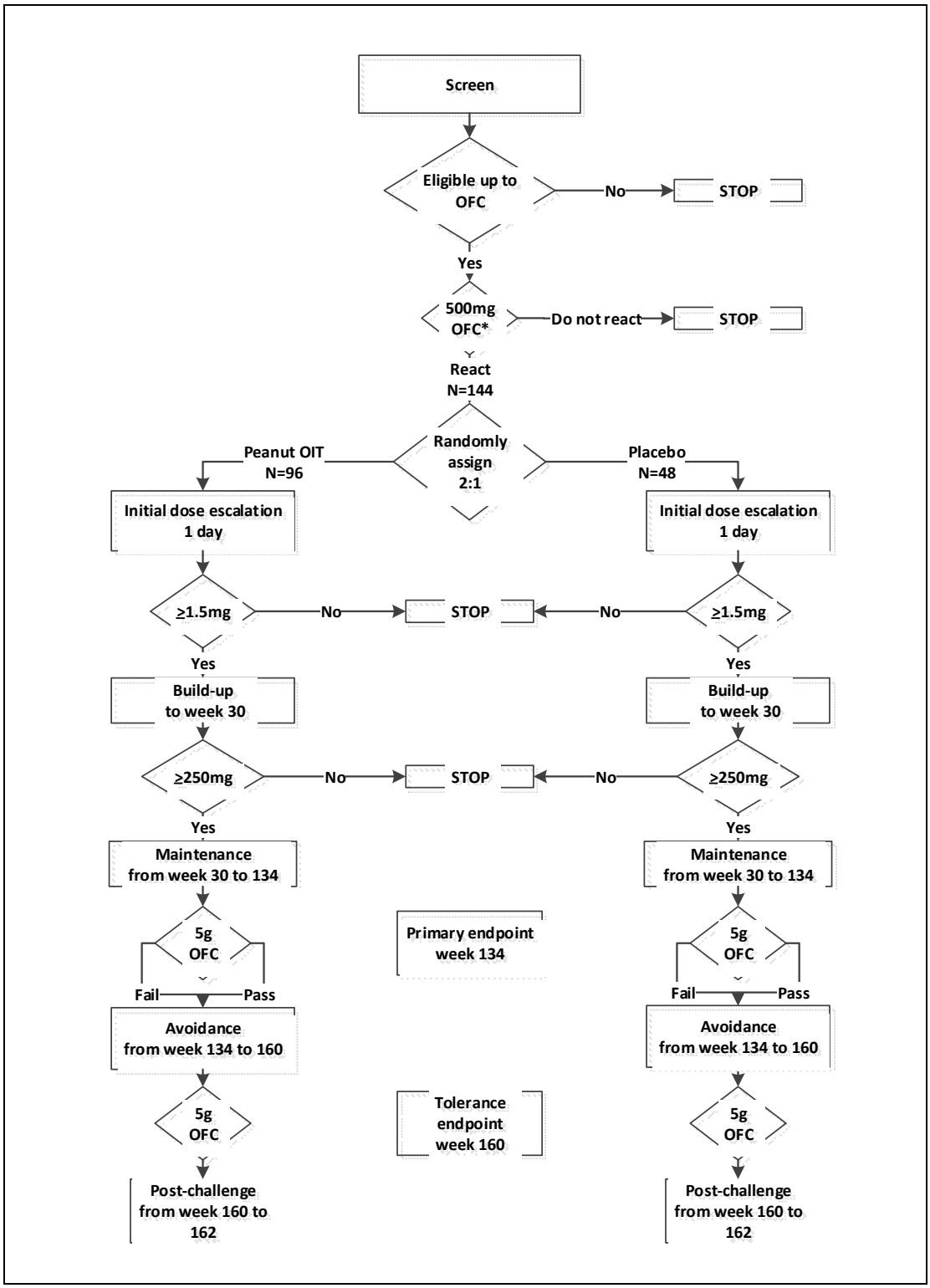
11. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

The compliance definition in the per-protocol population for the maintenance sample was changed. The original text was: "Compliance is defined as fewer than 3 occasions on which more than 3 consecutive home doses of study medication were missed". The current text is: "Compliance is defined as fewer than 3 occasions on which more than 3 consecutive home doses of study medication were missed with reason for missed doses given as non-compliance".

Additional language was added to define handling of indeterminate placebo challenges with respect to primary and secondary oral food challenge outcome endpoints:
"If a placebo flour challenge is a failure, and the associated peanut challenge is failed at a dose at or above the dose of placebo challenge failure, the peanut flour challenge will be considered a failure at the observed dose of failure. If a placebo flour challenge is stopped early without reaction due to participant refusal to continue, the associated peanut flour challenge will be considered a passed challenge."

12. APPENDICES

12.1. Study Flow Chart



Screening, Initial Dose Escalation, Build-up, Maintenance, Avoidance and Post-Challenge

*Amounts expressed in mg of peanut protein

12.2. Schedule of Events

Schedule of Events: Screening, Initial Dose Escalation and Build-up

Phase of trial			IDE[3]	**Build-up**														
Week	**-2 to -1**		**0**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**
Day	**-30 to -1**		**0**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**182**	**196**
Visit	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
GENERAL ASSESSMENTS																		
Informed Consent	x																	
Demographics	x																	
Medical History	x																	
Peanut Allergy History	x																	
Prior Baseline GI Symptoms	x																	
Ongoing GI Symptoms			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Comprehensive Physical Exam	x																	
Brief Physical Exam			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs	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
ADMINISTRATION OF STUDY MEDICATION																		
Randomization			x															
Initial Dose Escalation			x															
OIT or Placebo			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
DISEASE-SPECIFIC ASSESSMENTS																		
Diet and Allergy Assessment	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Skin Prick Test[1 5]	x																	
0.5 g Oral Food Challenge[4]		x																
5 g Oral Food Challenge[4]																		
LOCAL LAB ASSESSMENTS																		
CBC with differential	x					x				x					x			
MECHANISTIC ASSESSMENTS																		
IgE to food allergens[15]	x																	
IgE to inhalant allergens[15]	x																	
Basophil Activation Assay[2]	x					x				x					x			
Cellular Assays	x					x				x					x			
Plasma Assays	x					x				x					x			
Stool & Saliva Assays	x																	
HLA																		

[1] Please refer to visit windows in Section 6.1.
[2] Venous blood samples drawn at Stanford University will be assayed for basophil activation one day after the blood draw for comparison with samples from other sites that are shipped overnight to Stanford University.
[3] IDE: Initial Dose Escalation (refer to Section 3).
[4] Amounts expressed in peanut protein.
[5] Please see complete list of allergens in Section 6.4.2

Schedule of Events: Maintenance, Avoidance and Post-Challenge (PC)

Phase of trial	**Maintenance**								**Avoidance**			**PC**		
Week	**30**[1]	**43**	**56**	**69**	**82**	**95**	**108**	**121**	**134**	**136**	**160**	**162**[17]		
Day	**210**	**301**	**392**	**483**	**574**	**665**	**756**	**847**	**938**	**952**	**1120**	**1134**		**Discontinuation**
Visit	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**Un-scheduled**	
GENERAL ASSESSMENTS														
Informed Consent														
Demographics														
Medical History														
Peanut Allergy History														
Prior Baseline GI Symptoms														
Ongoing GI Symptoms	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Comprehensive Physical Exam							x		x		x			
Brief Physical Exam	x	x	x	x	x	x		x		x			x	x
Vital Signs	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
Adverse Events	x	x	x	x	x	x	x	x	x	x	x		x	x
ADMINISTRATION OF STUDY MEDICATION														
Randomization														
Initial Dose Escalation														
OIT or Placebo	x	x	x	x	x	x	x	x						
DISEASE-SPECIFIC ASSESSMENTS														
Diet and Allergy Assessment	x	x	x	x	x	x	x	x	x	x	x		x	x
Skin Prick Test[5]	x				x				x		x			
0.5 g Oral Food Challenge[3]														
5 g Oral Food Challenge[3]									x		x			
Open Food Challenge											x			
LOCAL LABORATORY ASSESSMENTS														
II: CBC with differential	x		x			x			x	x	x	x	x	x
MECHANISTIC ASSESSMENTS														
IgE to food allergens[4]	x				x				x		x		x	x
IgE to inhalant allergens[4]					x				x				x	x
Basophil Activation Assay[2]	x		x			x			x	x	x	x		
Cellular Assays	x		x			x			x	x	x	x	x	x
Plasma Assays	x		x			x			x	x	x	x	x	x
Saliva & Stool Assays	x				x				x		x		x[5]	x[5]
HLA[6]						x							x	

[1] Please refer to visit windows in Section 6.1.
[2] Venous blood samples drawn at Stanford University will be assayed for basophil activation one day after the blood draw for comparison with samples from other sites that are shipped overnight to Stanford University.
[3] Amounts expressed in peanut protein.
[4] Please see complete list of allergens in Section 6.4.2.
[5] Stool collection only, no saliva on Unscheduled visits or Discontiuation visits.
[6] Buccal swabs
[7] Only participants who tolerate peanut during the OpFC at the end of avoidance will return for Visit 27