PROTOCOL CoFAR-11

Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Children and Adults

OUtMATCH

IND # 140847

National Clinical Trial (NCT) # NCT03881696

Version 6.0 / 13Jun2022

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SITE INVESTIGATOR SIGNATURE PAGE	
Protocol Number: CoFAR-11	Version/Date: 6.0/13Jun2022
Title: **Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Children and Adults**	
IND Sponsor: The Division of Allergy, Immunology, and Transplantation (DAIT), The National Institute of Allergy and Infectious Diseases (NIAID)	
Return Signed Form to: *Retain the original signed signature page for your records. Return an electronic PDF copy of the signed signature page (*as described below) to the DAIT Regulatory Management Center (DRMC) via the applicable DAIT RMC email address for the protocol/network. During the site registration process, return to: DAITRegulatory_SiteRegistration (SM) DAITReg@ppd.com.* Once your site completes registration at the DRMC, return to DAITRegulatory_CoFA@ppd.com	
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 Harmonisation (ICH) document entitled *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)*. 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**	

Protocol Synopsis

Title	Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Children and Adults
Short Title	OUtMATCH
Clinical Phase	Phase III
Number of Sites	10 Clinical Research Units (CRUs) in the United States
IND Sponsor/Number	IND Sponsor: DAIT/NIAID IND#: 140847
Study Objectives	The primary objective is to compare the ability to consume foods without dose-limiting symptoms during a double-blind placebo-controlled food challenge (DBPCFC) after treatment with either omalizumab or placebo for omalizumab. Secondary objectives are: Stage 1 1. To evaluate safety during treatment with either omalizumab or placebo for omalizumab. Stage 2 2. To compare the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab-facilitated Oral Immunotherapy (OIT) or omalizumab + placebo OIT. This is the primary objective for Stage 2. 3. To evaluate safety during treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT. Stage 3 4. To compare dietary consumption of foods after the conclusion of treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods. 5. To evaluate safety after the conclusion of treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.

	Exploratory objectives are: Stage 1 1. To compare quality of life after treatment with either omalizumab or placebo for omalizumab. Stage 1 Open Label Extension (OLE) 2. To assess the safety and efficacy of either 24 or 40 weeks of treatment with omalizumab. 3. To assess quality of life at the end of either 24 or 40 weeks of treatment with omalizumab. Stage 2 4. Among participants who do not respond to treatment with omalizumab alone, compare the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with omalizumab-facilitated OIT or omalizumab + placebo OIT. 5. Among participants who respond to treatment with omalizumab alone, compare the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with omalizumab-facilitated OIT or omalizumab + placebo OIT. 6. To compare the change in the dose of each food that is consumed without dose-limiting symptoms during a DBPCFC at the end of Stage 1 and during a DBPCFC at the end of Stage 2 between treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT. 7. To compare quality of life after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT. Stage 3 8. To compare quality of life after the conclusion of treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT during a follow-up period in which participants either receive guided dietary instructions and/or rescue OIT for up to three foods. 9. To describe dietary consumption of foods after the conclusion of either 24 or 40 weeks of treatment with omalizumab during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods. 10. To assess safety after the conclusion of either 24 or 40 weeks of treatment with omalizumab during a follow-up period in which

	participants either received guided dietary instructions and/or rescue OIT for up to three foods. 11. To measure quality of life after the conclusion of either 24 or 40 weeks of treatment with omalizumab during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods. Pharmacokinetic (PK) objectives are: Stage 1 12. To evaluate serum omalizumab concentrations during treatment with omalizumab. Stage 1 OLE 13. To assess serum omalizumab concentrations at the end of either 24 or 40 weeks of treatment with omalizumab. Stage 2 14. To evaluate serum omalizumab concentrations during treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT. Biomarker objectives are: Stage 1 15. To compare immunological responses after treatment with either omalizumab or placebo for omalizumab. 16. To determine whether immunological responses can be used to predict the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab or placebo for omalizumab. Stage 1 OLE 17. To assess immunological responses at the end of either 24 or 40 weeks of treatment with omalizumab. Stage 2 18. To compare immunological responses during and after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT. 19. To determine whether immunological responses can be used to predict the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.

	Stage 3 20. To compare immunological responses after the conclusion of treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods. 21. To assess immunological responses after the conclusion of either 24 or 40 weeks of treatment with omalizumab during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.
Study Design	This study is a multi-center, randomized, double-blind, placebo-controlled study in participants 1 year to less than 56 years of age who are allergic to peanut and at least two other foods (including milk, egg, wheat, cashew, hazelnut, or walnut). While each participant may be allergic to more than two other foods, the primary endpoint in this study will only be assessed in peanut and two other foods for each participant. There are three stages: Stage 1, Stage 2, and Stage 3. Stage 1 includes Stage 1 OLE. **Stage 1:** Participants who experience dose-limiting symptoms to a single dose of ≤100 mg of peanut protein, ≤300 mg protein for each of the other two foods, and no dose-limiting symptoms to placebo at any single dose up to 300 mg protein during the Screening DBPCFC will be randomized 2:1 to 16-20 weeks of treatment with omalizumab or placebo for omalizumab per a standard omalizumab dosing table. After 16 weeks of treatment, each participant will complete a DBPCFC consisting of placebo and each of their three specific foods to a cumulative dose of 6044 mg protein of each food. The first 60 participants who complete Stage 1 will participate in the Stage 1 OLE. All other participants who complete Stage 1 will move to Stage 2 of the study. **Stage 1 OLE:** Each participant will receive 24-28 weeks of open label omalizumab. After 24 weeks of treatment, each participant will complete a DBPCFC consisting of placebo and each of their three specific foods to a cumulative dose of 8044 mg protein of each food. Each participant who completes Stage 1 OLE will move on to Stage 3 of the study. **Stage 2:** Each participant will receive eight weeks of treatment with open label omalizumab. One week after beginning Stage 2, participants will be randomized 1:1 to:

- Omalizumab-facilitated OIT: Open label omalizumab + Multi-allergen OIT for eight weeks, followed by placebo for omalizumab + Multi-allergen OIT for 44 weeks.
- Omalizumab + placebo OIT: Open label omalizumab + placebo for Multi-allergen OIT for eight weeks, followed by omalizumab + placebo for Multi-allergen OIT for 44 weeks.

After completion of eight weeks of treatment with open label omalizumab, each participant will receive an additional eight weeks of open label omalizumab followed by either 44 weeks of omalizumab or placebo for omalizumab (depending on the arm). While receiving omalizumab or placebo for omalizumab injections, each participant will complete 52 weeks of Multi-allergen OIT or placebo for Multi-allergen OIT. Each participant who tolerates at least 9 mg protein of Multi-allergen OIT or placebo for Multi-allergen OIT during an Initial Dose Escalation (IDE) Visit will enter a Build-Up Phase for up to 24 weeks to reach a maximum maintenance dose of 1000 mg protein of each of their three specific foods (i.e., a total maximum dose of 3000 mg protein or 3000 mg placebo for Multi-allergen OIT, depending on arm). Each participant who reaches a minimum total maintenance dose of 750 mg protein (equivalent to 250 mg protein of each of their three specific foods or 750 mg of placebo) within 24 weeks of completing the IDE will remain on this dose during the Maintenance Phase until 52 weeks after the IDE is completed, at which time each participant will complete a DBPCFC consisting of placebo and each of their three specific foods to a cumulative dose of 8044 mg protein of each food. Each participant who completes Stage 2 will move to Stage 3 of the study.

Stage 3: Upon completion of Stage 1 OLE or Stage 2, each participant will receive a separate treatment plan for peanut and each of the two other participant-specific foods based on the results of the DBPCFC. A treatment plan will include instructions for one of the following:

- **Long-term follow-up with dietary consumption of a food;**
- **Long-term follow-up with avoidance of a food; or**
- **Rescue OIT for a food**.

The treatment plan for each food may change throughout Stage 3 depending on a participant's response to treatment. Once a participant enters Stage 3, the participant will have a minimum of 12 months of follow-up in Stage 3 and will remain in Stage 3 until at least December 2022.

Long-term follow-up with dietary consumption of a food: For each food the participant receives long-term follow-up with dietary consumption of a food, there will be an initial open feeding of the food in the CRU. Following completion of each open feeding, the participant will be

	provided individualized guided dietary food instructions that will include a minimum and maximum quantity deemed to be safe for the participant. After the last open feeding, the participant will receive a follow-up call or email weekly for the first four weeks, every other week between six and sixteen weeks, and every two months thereafter during follow-up. During long-term follow-up, each participant will also complete a CRU visit every six months. A participant who does not tolerate ≥300 mg protein of the food during the first six months of long-term follow-up will either receive rescue OIT for the food or long-term follow-up with avoidance of that food, as appropriate. **Long-term follow-up with avoidance of a food:** For each food the participant receives long-term follow-up with avoidance of a food, the participant will avoid eating the food and will return to the CRU every six months for follow-up. **Rescue OIT for a food:** If the participant receives rescue OIT for the food immediately after completing Stage 1 OLE or Stage 2, the participant may skip the IDE Visit and enter the Build-Up Phase (depending on the results of the DBPCFC). Otherwise, the participant will attend an IDE Visit. The participant must tolerate at least 3 mg protein of the food during the IDE Visit to enter the Build-Up Phase. Participants will remain in the Build-Up Phase for up to 24 weeks to reach a maximum maintenance dose of 1000 mg protein of the food. Each participant who reaches a maintenance dose of 560 mg, 800 mg, or 1000 mg protein of the food within 24 weeks of entering rescue OIT and tolerates this dose for eight weeks after starting the Maintenance Phase will complete an open feeding in CRU to determine if they will transition to Long-Term Follow-Up with Dietary consumption of the food. Each participant who reaches maintenance dose of <560 protein of the food within 24 weeks of entering rescue OIT will remain on this dose during the Maintenance Phase until 52 weeks after rescue OIT begins. Fifty-two weeks after the start of rescue OIT, the participant will complete an open oral food challenge (OFC) consisting of their specific rescue food to a cumulative dose of 8044 mg protein of the food. Depending on the results of the open OFC, the participant will either receive long-term follow-up with avoidance of the food or long-term follow-up with dietary consumption of the food.
Primary Endpoint	The primary endpoint is consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1. Dose-limiting symptoms are defined in Appendix 1. A participant who meets this endpoint will be considered a ‘success’ while a participant who does not meet this endpoint will be considered a ‘failure’.

Secondary Endpoints	Key secondary endpoints: Stage 1 1. Consumption of a single dose of ≥1000 mg of cashew protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1. 2. Consumption of a single dose of ≥1000 mg of milk protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1. 3. Consumption of a single dose of ≥1000 mg of egg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1. Stage 2 4. Consumption of ≥1 dose of 2000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2. This is the primary endpoint for Stage 2. Other secondary endpoints: 5. Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 (except those endpoints already defined by the primary and key secondary endpoints in Stage 1). 6. Number of foods consumed at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 1. 7. Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2 (except the endpoint already defined by the primary endpoint for Stage 2). 8. Number of foods consumed at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 2. 9. Number of weeks in each eight-week period during Stage 3 where ≥300 mg protein of each food is consumed at least twice per week. 10. Number of weeks in each eight-week period during Stage 3 where each food protein is not consumed. Safety endpoints include: 11. An AE related to study therapy regimen received during Stage 1.

	12. An AE related to study therapy regimen received during Stage 1 OLE. 13. An AE related to study therapy regimen received during Stage 2. 14. An AE related to oral food intake received during Stage 3.
Exploratory Endpoints	Exploratory endpoints: 1. Percent change in the maximum dose of food protein consumed without dose-limiting symptoms during the DBPCFC at the end of Stage 1 and during the DBPCFC at the end of Stage 2. 2. Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE. 3. Number of foods consumed at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE. 4. Change in quality of life between Week 0 in Stage 1 and the following times: • First DBPCFC Visit at the end of Stage 1; • For those participants who move to Stage 1 OLE: o First omalizumab injection visit in Stage 1 OLE; o First DBPCFC Visit at the end of Stage 1 OLE; o Last DBPCFC Visit at the end of Stage 1 OLE. • For those participants who move to Stage 2: o First omalizumab injection visit in Stage 2; o First DBPCFC Visit at the end of Stage 2; o Last DBPCFC Visit at the end of Stage 2. • Six months after beginning Stage 3. Quality of life is measured by the Food Allergy Quality of Life Questionnaire – Parent Form (FAQLQ-PF) for participants aged 0-12 years, Food Allergy Quality of Life Questionnaire – Child Form (FAQLQ-CF) for children/adolescents aged 8-12 years, Food Allergy Quality of Life Questionnaire – Teenager Form (FAQLQ-TF) for participants aged 13-17 years, and Food Allergy Quality of Life Questionnaire – Adult Form (FAQLQ-AF) for participants aged 18 years and older. PK endpoints: 5. Omalizumab trough concentration, measured at the following times: • First Screening DBPCFC Visit; • First DBPCFC Visit at the end of Stage 1;

	• First DBPCFC Visit at the end of Stage 1 OLE (for those participants who move to Stage 1 OLE); • IDE Visit during Stage 2 (for those participants who move to Stage 2); and • First DBPCFC Visit at the end of Stage 2 (for those participants who move to Stage 2). Biomarkers include the following: 6. Total immunoglobulin E (IgE) 7. Total free IgE 8. Allergen-specific IgE 9. Allergen-specific immunoglobulin G4 (IgG4) 10. Allergen-specific immunoglobulin A (IgA) 11. IgG4/IgE ratio 12. Basophil activation 13. Skin prick tests (SPTs) Allergen-specific immune biomarkers (allergen-specific IgE, allergen-specific IgG4, allergen-specific IgA, basophil activation, and SPTs) will be evaluated using peanut and the two other participant-specific foods. Immune biomarkers will be measured at the following times: • First Screening DBPCFC Visit; • First DBPCFC Visit at the end of Stage 1; • First DBPCFC Visit at the end of Stage 1 OLE (for those participants who move to Stage 1 OLE); • IDE Visit during Stage 2, except the SPTs, total IgE, and allergen-specific IgE (for those participants who move to Stage 2); • Initial Maintenance Dose Visit during Stage 2, except the SPTs, total IgE, and allergen-specific IgE (for those participants who move to Stage 2); • First DBPCFC Visit at the end of Stage 2 (for those participants who move to Stage 2); and • Six months after beginning Stage 3. Mechanistic endpoints will be measured at the following times: • First Screening DBPCFC Visit; • First DBPCFC Visit at the end of Stage 1; • IDE Visit during Stage 2 (for those participants who move to Stage 2); • Initial Maintenance Dose Visit during Stage 2 (for those participants who move to Stage 2); and • First DBPCFC Visit at the end of Stage 2 (for those participants who move to Stage 2).

<table>
<tr><td>Accrual Objective</td><td>225 participants (≥50 participants aged 1 year to less than 6 years, approximately 160 participants aged 6 years to less than 18 years, and approximately 15 participants aged 18 years to less than 56 years)</td></tr>
<tr><td>Study Duration</td><td>Individual study participation will consist of a maximum of 84 weeks for treatment and a minimum of 12 months of follow-up. All participants will be followed up until at least December 2022.</td></tr>
<tr><td>Treatment Description</td><td>Multi-allergen OIT: peanut, milk, egg, wheat, cashew, hazelnut, walnut flour or powder.

Placebo for Multi-allergen OIT: oat flour.

Multi-allergen OIT and placebo for Multi-allergen OIT will be manufactured by the Sean N. Parker Center for Allergy & Asthma Research with Stanford University (Mountain View, CA).

The dosing schedule for IDE for Multi-allergen OIT or placebo for Multi-allergen OIT in Stage 2 is as follows:

<table>
<tr><th>Dose #</th><th>Food Allergen Dose (mg protein of each allergen)</th><th>Total Food Allergen Dose (mg protein)</th></tr>
<tr><td>1</td><td>3</td><td>9</td></tr>
<tr><td>2</td><td>30</td><td>90</td></tr>
<tr><td>3</td><td>60</td><td>180</td></tr>
<tr><td>4</td><td>125</td><td>375</td></tr>
<tr><td>5</td><td>250</td><td>750</td></tr>
<tr><td>6</td><td>375</td><td>1125</td></tr>
</table>

The dosing schedule for Stage 3 IDE per allergen for rescue OIT in Stage 3 is as follows:

<table>
<tr><th>Dose #</th><th>Food Allergen Dose (mg protein of each allergen)</th></tr>
<tr><td>1</td><td>3</td></tr>
<tr><td>2</td><td>10</td></tr>
<tr><td>3</td><td>30</td></tr>
<tr><td>4</td><td>60</td></tr>
<tr><td>5</td><td>125</td></tr>
<tr><td>6</td><td>250</td></tr>
<tr><td>7</td><td>375</td></tr>
</table>
</td></tr>
</table>

All Multi-allergen OIT or placebo for Multi-allergen OIT dose build-ups for Stage 2 will occur under observation in the CRU per the dosing schedule below:

Dose #[1]	Food Allergen Dose (mg protein of each allergen)	Total Food Allergen Dose (mg protein)	Interval (weeks)
1	3	9	2
2	30	90	2
3	60	180	2
4	125	375	2
5	250	750	2
6	375	1125	2
7	560	1680	2
8	800	2400	2
9	1000	3000	2

1. Dose build-up will begin at the last dose the participant was able to tolerate on the IDE Visit.

All rescue OIT dose build-ups per allergen for Stage 3 will occur under observation in the CRU per the dosing schedule below:

Dose #[1]	Food Allergen Dose (mg protein of each allergen)	Interval (weeks)
1	3	2
2	10	2
3	30	2
4	60	2
5	125	2
6	250	2
7	375	2
8	560	2
9	800	2
10	1000	2

1. Dose build-up will begin at the last dose the participant was able to tolerate on the IDE Visit.

Omalizumab: Omalizumab is a recombinant humanized immunoglobulin G1 monoclonal antibody that binds to the FcεR1 binding epitope of human IgE, preventing human IgE from binding to its specific high-affinity receptors on mast cells and basophils. Omalizumab is approved by the European Commission and US FDA for patients with moderate-severe asthma ≥6 years of age and for patients with chronic idiopathic urticaria ≥12 years of age. Omalizumab is not approved for treating food allergy.

Placebo for omalizumab: The composition of the placebo for omalizumab is the same as the active study drug without the omalizumab.

	Omalizumab and placebo for omalizumab will be administered as a subcutaneous injection and will be dosed according to the omalizumab dosing table given in Appendix 2. Omalizumab and placebo for omalizumab will be provided by Genentech Inc. Throughout Stage 1, Stage 1 OLE, and Stage 2, each participant will be instructed to strictly avoid all foods to which they are allergic. Each participant will also be instructed to strictly avoid a food if they receive rescue OIT for the food during Stage 3.
Inclusion Criteria	Individuals who meet all of the following criteria are eligible for enrollment as study participants: 1. Participant and/or parent/legal guardian must be able to understand and provide informed consent and/or assent, as applicable 2. Male or female, 1 year to less than 56 years of age at Screening 3. Peanut allergic; participant must meet all of the following criteria to minimize the chance that the participant will develop natural tolerance to peanut over the course of the study: a. Positive SPT (≥4 mm wheal greater than saline control) to peanut b. Positive peanut IgE (≥6 kUA/L) at Screening or within three months of Screening, determined by ImmunoCap c. Positive blinded OFC to peanut during the Screening DBPCFC, defined as experiencing dose-limiting symptoms at a single dose of ≤100 mg of peanut protein 4. Allergic to at least two of the six other foods (milk, egg, wheat, cashew, hazelnut, walnut); allergy to milk and egg is defined as unable to tolerate both cooked and uncooked forms; each participant must meet all of the following criteria for at least two of the six other foods to minimize the chance that the participant will develop natural tolerance to at least two of the six other foods over the course of the study: a. Milk, egg, or wheat: i. Positive SPT (≥4 mm wheal greater than saline control) to food ii. Positive food specific IgE (≥6 kUA/L) at Screening or within three months of Screening, determined by ImmunoCap iii. Positive blinded OFC to food during the Screening DBPCFC, defined as experiencing dose-limiting symptoms at a single dose of ≤300 mg of food protein b. Cashew, hazelnut, or walnut:

	i. Positive SPT (≥4 mm wheal greater than saline control) to food or positive food specific IgE (≥6 kUA/L) at Screening or within three months of Screening, determined by ImmunoCap ii. Positive blinded OFC to food during the Screening DBPCFC, defined as experiencing dose-limiting symptoms at a single dose of ≤300 mg of food protein 5. With body weight (as measured at Screening) and total serum IgE level (as measured within three months of Screening) suitable for omalizumab dosing 6. If female of child-bearing potential, must have a negative urine or serum pregnancy test 7. For women of childbearing potential, must agree to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods (barrier methods or oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy) during the treatment period and for 60 days after the last dose of study drug. 8. Plan to remain in the study area of an OUtMATCH CRU during the trial 9. Be willing to be trained on the proper use of an epinephrine autoinjector and be willing to provide an epinephrine autoinjector for the duration of the study
Exclusion Criteria	Individuals who meet any of the following criteria are not eligible for enrollment as study participants: 1. Inability or unwillingness of a participant and/or parent/legal guardian to give written informed consent and/or assent or comply with the study protocol 2. Clinically significant laboratory abnormalities at Screening 3. Dose-limiting symptoms to the blinded OFC to placebo during the Screening DBPCFC 4. Sensitivity or suspected/known allergy to any ingredients (including excipients) of the active or placebo OFC material, Multi-allergen OIT, or drugs related to omalizumab (e.g., monoclonal antibodies, polyclonal gamma globulin). Guidance for determination of sensitivity to excipients will be detailed in the Manual of Procedures (MOP). 5. Poorly controlled atopic dermatitis (AD) at Screening, per the PI's discretion 6. Poorly controlled or severe asthma/wheezing at Screening, defined by at least one of the following criteria: a. Global Initiative for Asthma (GINA) criteria regarding asthma control latest guidelines; see Appendix 3);

	b. History of two or more systemic corticosteroid courses within six months of Screening or one course of systemic corticosteroids within three months of Screening to treat asthma/wheezing; c. Prior intubation/mechanical ventilation for asthma/wheezing; d. One hospitalization or ED visit for asthma/wheezing within six months of Screening; e. Forced expiratory volume in one second (FEV_1) <80% of predicted or FEV_1/forced vital capacity (FVC) <75%, with or without controller medications (only for participants who are aged seven years or older and are able to perform spirometry); f. Inhaled corticosteroid (ICS) dosing of >500 mcg daily fluticasone (or equivalent ICS based on the CoFAR Inhaled Corticosteroid Equivalency Tables MOP). 7. History of severe anaphylaxis to participant-specific foods that will be used in this study, defined as neurological compromise or requiring intubation 8. Treatment with a burst of oral, intramuscular (IM), or intravenous (IV) steroids of more than two days for an indication other than asthma/wheezing within 30 days of Screening 9. Currently receiving oral, IM, or IV corticosteroids, tricyclic antidepressants, or β-blockers (oral or topical) 10. Past or current history of eosinophilic gastrointestinal (GI) disease within three years of Screening 11. Past or current history of cancer, or currently being investigated for possible cancer 12. Previous adverse reaction to omalizumab 13. Past or current history of any immunotherapy to any of the foods being treated in this study (e.g., OIT, sublingual immunotherapy [SLIT], epicutaneous immunotherapy [EPIT]) within 6 months of Screening 14. Treatment with monoclonal antibody therapy, such as omalizumab (Xolair®), dupilumab (Dupixent®), benralizumab (Fasenra™), mepolizumab (Nucala®), reslizumab (Cinqair®), or other immunomodulatory therapy within six months of Screening 15. Currently on “build-up phase” of inhalant allergen immunotherapy (i.e., has not reached maintenance dosing). Individuals tolerating maintenance allergen immunotherapy can be enrolled 16. Inability to discontinue antihistamines for the minimum wash-out periods required for SPTs or OFCs 17. Current participation in another therapeutic or interventional clinical trial or participation within 90 days of Screening

	18. Use of investigational drugs within 24 weeks of Screening 19. Pregnant or breastfeeding, or intending to become pregnant during the study or within 60 days after the last dose of omalizumab or placebo for omalizumab 20. Has a first-degree relative already enrolled in the study 21. Past or current medical problems (e.g., severe latex allergy), history of other chronic diseases (other than asthma/wheezing, AD, or rhinitis) requiring therapy (e.g., heart disease, diabetes), findings from physical assessment, or abnormalities in clinical laboratory testing that are not listed above, which, in the opinion of the PI, 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	If any of the stopping rules listed below are met, study enrollment will be suspended, IDE Visits will be suspended, and dose escalation of OIT during Stage 2 and 3 will be stopped pending expedited review of all pertinent data by the NIAID Allergy and Asthma Data and Safety Monitoring Board (DSMB). Depending on the stopping rule, additional study procedures (as outlined below) will also be suspended pending expedited review of all pertinent data. • Any death related to OIT dosing, an OFC, omalizumab, or placebo for omalizumab: If this stopping rule is met, all OIT maintenance visits, all OFCs, all open feedings, and all omalizumab or placebo for omalizumab injections will be suspended. • More than three participants requiring more than two injections of epinephrine during a single OIT dosing: If this stopping rule is met, no additional study procedures aside from those outlined above will be suspended and all omalizumab or placebo for omalizumab injections will continue to be received. • More than one participant requiring more than two injections of epinephrine during a single omalizumab/placebo for omalizumab injection: If this stopping rule is met, all omalizumab or placebo for omalizumab injections will be suspended. • More than one participant with more than one CoFAR Grade 4 AE related to OIT dosing (see Table 12.4.1.2): If this stopping rule is met, all OFCs and all open feedings will be suspended but all OIT maintenance visits and all omalizumab or placebo for omalizumab injections will continue to be received. • More than three CoFAR Grade 4 AEs related to an OFC (see Table 12.4.1.2): If this stopping rule is met, all OFCs and all open feedings

	will be suspended but all OIT maintenance visits and all omalizumab or placebo for omalizumab injections will continue to be received. • 5% or more of the randomized participants have been diagnosed with biopsy-proven eosinophilic esophagitis (EoE), as assessed on a rolling basis during regular AE reviews, and the total number of cases of EoE is at least five: If this stopping rule is met, no additional study procedures aside from those outlined above will be suspended and all omalizumab or placebo for omalizumab injections will continue to be received.

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Glossary of Abbreviations

Abs	antibodies
AD	atopic dermatitis
ADAs	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATEs	arterial thrombotic events
BAT	basophil activation test
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CIU	chronic idiopathic urticaria
CMP	comprehensive metabolic panel
CoFAR	Consortium for Food Allergy Research
CRU	clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
CyTOF	cytometry by time of flight
DAIT	Division of Allergy, Immunology, and Transplantation
DBPCFC	double-blind placebo-controlled food challenge
DC	dendritic cell
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
EDC	electronic data capture
EGPA	Eosinophilic Granulomatosis with Polyangiitis
EoE	eosinophilic esophagitis
EPIT	epicutaneous immunotherapy
FA-S1	pediatric full analysis set-Stage 1
FA-S1OLE	pediatric full analysis set-Stage 1 OLE
FA-S2	pediatric full analysis set-Stage 2
FA-S3	pediatric full analysis set-Stage 3
FAQLQ	Food Allergy Quality of Life Questionnaire
FAQLQ-PF	Food Allergy Quality of Life Questionnaire – Parent Form

FAQLQ-CF	Food Allergy Quality of Life Questionnaire – Child Form
FAQLQ-TF	Food Allergy Quality of Life Questionnaire – Teenager Form
FAQLQ-AF	Food Allergy Quality of Life Questionnaire – Adult Form
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GCP	Good Clinical Practice
GI	gastrointestinal
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
HEENT	head, eyes, ears, nose, and throat
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
IDE	initial dose escalation
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG1	immunoglobulin G1
IgG4	immunoglobulin G4
IM	intramuscular
IND	Investigational New Drug
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
NCI	National Cancer Institute
NIH	National Institutes of Health
OFC	oral food challenge
OLE	open label extension
OIT	oral immunotherapy
PEF	peak expiratory flow
PBMCs	peripheral blood mononuclear cells
PFS	pre-filled syringes
PK	pharmacokinetic

PI	(CRU) Principal Investigator
PP-S1	pediatric per-protocol set-Stage 1
PP-S2	pediatric per-protocol set-Stage 2
PP-S3	pediatric per-protocol set-Stage 3
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SCORAD	SCORing Atopic Dermatitis
SLIT	sublingual immunotherapy
SPT	skin prick test
SS1-S1	pediatric pre-randomization safety set-Stage 1
SS1-S2	pediatric pre-randomization safety set-Stage 2
SS2-S1	pediatric safety set-Stage 1
SS2-S2	pediatric safety set-Stage 2
SS-S1OLE	pediatric safety set-Stage 1 OLE
SS-S3	pediatric safety set-Stage 3
SUSAR	Serious and Unexpected Suspected Adverse Reaction
ULN	upper limit of normal
UNC-CH	University of North Carolina at Chapel Hill

1 Background and Rationale

1.1 Background and Scientific Rationale

Food allergy affects approximately 15 million patients in the US, including six million children. It causes substantial morbidity and mortality, and is the most common cause of anaphylaxis in pediatric patients seen in emergency departments across the US. Importantly, because accidental exposures to offending foods can be extremely difficult to avoid, particularly for multiple-foods (herein "multi-foods"), food allergy has a major negative impact on a patient's quality of life and is a significant burden on our health care system, estimated to cost approximately $25 billion annually.[1] The burden of food allergy in adults is less often recognized, but in reality most peanut and tree nut allergies persist into adulthood, as do a substantial subset of milk, egg, and wheat allergies.[2]

Since its initiation in 2005, the Consortium for Food Allergy Research (CoFAR) has worked to develop potential treatments for food allergy, with studies focused on both peanut and egg. While substantial progress has been made in the development of treatment of peanut allergy, even with the potential of US Food and Drug Administration (FDA) approved treatments in the next few years, substantial gaps remain in many areas. Most important among these include treatment for foods other than peanut, treatment of patients who are allergic to multi-foods, and maximizing safety. The overarching goal of this study is to address each of these substantial gaps, especially in patients who are highly allergic to multi-foods. This is clearly an unmet need, and a perfect opportunity for CoFAR to take the lead, as 30% to 70% of children and adults with peanut allergy are indeed allergic to other foods.[3,4]

As described in detail below, this study is designed to study three major questions for the patient with multi-food allergies. First, Stage 1 will study the potential value of omalizumab for the treatment of patients who are allergic to peanut as well as at least two other common food allergens. If successful, this could lead to a major advance in the treatment of those patients with multi-food allergies, with the potential to provide effective treatment without the need for a food specific treatment such as oral immunotherapy (OIT). Second, Stage 2 will directly compare the treatment of patients with multi-food allergies using omalizumab as monotherapy versus treatment with Multi-allergen OIT using omalizumab as an adjunctive treatment that may improve the safety and/or efficacy of the OIT. Third, Stage 3 will address the potential longer-term outcomes of these treatment approaches, including the introduction of dietary forms of these allergenic foods into the diets of these multi-allergic patients.

Substantial preliminary data exist to support these study objectives. With regard to omalizumab as potential monotherapy for the treatment of food allergy, multiple studies have shown that omalizumab may increase the threshold dose for inducing allergic symptoms following food exposure, reduces allergic symptoms that occur during an OFC, and facilitates food OIT, resulting in faster yet safe dose escalation (see Table 1.4). Most importantly, the effects of omalizumab do not appear limited to any particular food; omalizumab is unique in being potentially effective for multi-food allergies in patients with single or multi-food allergies.

There are also numerous studies demonstrating the likely benefit of omalizumab in conjunction with OIT to peanut and other foods. A pilot study was the first of its kind to show that milk desensitization can occur relatively rapidly when combined with omalizumab treatment in patients with severe milk allergy.[5] In other food allergy studies, omalizumab has been shown to be efficacious and safe even in patients with severe food allergy: patients with a history of anaphylaxis, those who have failed prior OIT, and patients with multi-food allergies. These studies demonstrate that the majority of omalizumab-treated patients tolerated acute exposures of at least 400-2000 mg of the offending foods with minimal or no symptoms within 8-12 weeks of starting treatment.[5-11] Several pilot studies have also addressed the possibility that omalizumab may also be useful as an adjunctive treatment with Multi-allergen OIT.[7,12]

1.2 Rationale for Selection of Investigational Product or Intervention

The rationale for the proposed study interventions in this protocol is based on substantial preliminary data regarding both approaches, omalizumab as monotherapy and as an adjunct to Multi-allergen OIT (see Table 1.4). In Stage 1, monotherapy with omalizumab will be compared to placebo for omalizumab to study the hypothesis that omalizumab can increase oral food challenge (OFC) thresholds in a clinically significant manner. In Stage 2, longer term treatment with omalizumab, now combined with placebo for Multi-allergen OIT, will be compared to active Multi-allergen OIT initiated under the protection of open label omalizumab. Study participants will then proceed into Stage 3, where the possibility that these treatments will allow for the introduction of the allergenic foods into the diet will be studied. Whatever the outcomes, the study will provide groundbreaking data that will impact the future of treatment for both peanut allergy and multi-food allergy. Further, as described below, the safety and efficacy of these treatments down to the age of one year will be studied, another groundbreaking advance in the study of potential treatments for food allergy.

1.2.1 Omalizumab

Omalizumab is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to the FcεR1 binding epitope of human immunoglobulin E (IgE), preventing human IgE from binding to its specific high-affinity receptors on mast cells and basophils. Omalizumab is produced by a mammalian cell (Chinese hamster ovary cell) suspension culture under Good Manufacturing Practice conditions using standard processes.

Omalizumab is approved by the European Commission and US FDA for patients six years of age or older with allergic asthma and for patients 12 years of age or older with chronic idiopathic urticaria (CIU). Although the drug carries warnings about a risk of anaphylaxis as well as other potential adverse effects, its overall safety profile has been well established (see current Investigator Brochure for Omalizumab (Xolair®)). Further, use in children two years of age and older is being evaluated in other protocols, including, for food allergy, in a protocol conducted under IND #14831 (PI and IND Sponsor, K. Nadeau, MD, PhD, Stanford University) and for possible effects on the natural course of asthma in children down to two years of age in a study (Protocol # U01-BCH-03, PARK) conducted under NIAID-sponsored IND#134003 (Protocol Chair: W. Phipatanakul, MD, Children's Hospital, Boston, MA). While this will be the first study to expand down to one year of age, this is an important population to study given the prevalence of food allergy in young children, as well as data suggesting that treatment of food allergy may be most effective if initiated early in childhood.[13]

The approach for the use of omalizumab proposed in this study is based on the rationale that this medication may be effective as monotherapy and/or as an adjunct to Multi-allergen OIT. As monotherapy, data from the clinical studies described below suggest the effects on OFCs are seen early in the course of treatment, leading to the proposal for a 16-week course of treatment in Stage 1. Fewer data are available regarding the effects of longer treatment with omalizumab for food allergy, and this question will be addressed by including an open label extension (OLE) for a subset of participants in Stage 1. This extension will be used to assess if the effects of omalizumab on OFC outcomes persist, or even increase, with a longer duration of treatment. For Stage 2, data suggest that pretreatment with omalizumab, prior to the initiation of OIT, significantly augments safety, and that ongoing treatment through the OIT build-up provides additional benefit, leading to the proposal to use open label omalizumab for eight weeks prior to the initiation of OIT, and then continued for the first eight weeks of OIT.[5,7,8,11,12,14] Most importantly, however, Stage 2 will provide the unique opportunity to directly compare these two potential treatment approaches, with one treatment arm receiving omalizumab with placebo OIT and the other receiving omalizumab-facilitated OIT.

1.2.2 Oral Immunotherapy

Substantial data exist to support the efficacy of OIT for peanut, milk, egg, and other foods for the treatment of food allergy.[15,16] While the safety profile of OIT is generally acceptable[17], adverse reactions are common, especially during the build-up phase of gradual increased OIT dosing toward the eventual maintenance dose. Data suggest that the use of omalizumab may substantially reduce these adverse reactions, leading to more rapid dose build-up with fewer adverse reactions.[5,7,8,11,12,14]

For this study, commercially available food flours for peanut and the six other common food allergens (milk, egg, wheat, cashew, walnut, and hazelnut) will be purchased and manufactured into Multi-allergen OIT drug products by the Manufacturing Facility for the Sean N. Parker Center for Allergy & Asthma Research with Stanford University (Mountain View, CA). The Multi-allergen OIT dosing will be based on a 1:1:1 allocation ratio of the three food proteins. OIT dosing schedules will be built on those previously reported and used in other active Multi-allergen OIT clinical trials.

1.3 Preclinical Experience

Not applicable.

1.4 Clinical Studies

Studies of omalizumab with or without OIT are summarized in Table 1.4, including the study of another anti-IgE molecule referred to as TNX-901. The data from these studies provide a consistent theme demonstrating the effects of anti-IgE treatment in patients with allergy to peanut and other foods. A recent study highlights the potential benefit of omalizumab with Multi-allergen OIT. In this study, Andorf and colleagues[6] studied 48 children between 4 and 15 years of age treated with two to five foods along with omalizumab or placebo for omalizumab. Participants were randomized 3:1 (omalizumab versus placebo for omalizumab) followed by eight weeks of treatment before starting Multi-allergen OIT. On the first day of Multi-allergen OIT, participants received six doses of mixed food up to a maximum cumulative dose of 2380 mg protein (each participant had a custom mix of the foods to which they were allergic combined in equal amounts by protein). Nineteen of 36 (53%) omalizumab treated participants tolerated the highest dose of their mixed food (2380 mg protein) on the first day. The median cumulative tolerated total food dose was 2380 mg protein in the omalizumab arm, while the median cumulative threshold dose in the placebo for omalizumab arm was 55 mg protein ($p < 0.0001$). The median cumulative threshold dose for each individual food in the omalizumab arm on the first day was 476 mg compared with 21 mg protein per food in the placebo arm ($p < 0.0001$). After completing the full updosing phase of OIT, a double-blind placebo-controlled food challenge (DBPCFC) at 36 weeks after randomization showed that a significantly greater proportion of the omalizumab-treated participants (30 of 36 [83%]) versus placebo for omalizumab participants (4 of 12 [33%]) tolerated 2 g of protein of two or more of their offending foods (odds ratio 10.0 [95% CI: 1.8 - 58.3, $p < 0.004$]).[6]

Table 1.4 Studies Using Omalizumab in Food Allergy

Reference	Study Design	Food	Study Population (actual)	Relevant Objectives	Results
Studies with Omalizumab or Other anti-IgE Monotherapy in Food Allergy					
Sampson et al. 2011 (TOPS)[9]	**Omalizumab monotherapy** RCT, multi-center DBPCFC	Peanut	14 patients (median age 19 years) with peanut allergy: 9 patients received omalizumab 5 patients received placebo	Tolerability of peanut flour at baseline and after 24 weeks of treatment	Omalizumab increased the mean cumulative threshold dose from 63 mg peanut flour at baseline to 2881 mg flour at Week 24, cumulative dose. Placebo increased the mean tolerated threshold dose from 57 mg

Reference	Study Design	Food	Study Population (actual)	Relevant Objectives	Results
					at baseline to 440 mg peanut flour at Week 24, cumulative dose.
Savage et al. 2012[10]	**Omalizumab monotherapy** Open label single arm drug, DBPCFC	Peanut	14 patients (median age 23 years) with peanut allergy failing DBPCFC at baseline	Tolerability of peanut protein at baseline and after 4-8 weeks of treatment.	The median cumulative threshold dose of peanut protein increased from 80 mg (range: 30-380 mg) at baseline to 6,500 mg (range: 1830-10000 mg) at Weeks 4-8 (p=0.002).
Leung et al. 2003[18]	**TNX-901** monotherapy RCT, multi-center DBPCFC	Peanut	84 patients (13-59 years) with peanut allergy: 59 patients received TNX-901 (150 mg [19 patients], 300 mg [19 patients] or 450 mg [21 patients]) 23 patients received placebo	Tolerability of peanut flour at baseline and after 24 weeks of treatment with various doses of TNX-901.	A 450 mg dose of TNX-901 significantly increased threshold dose of peanut from 178 mg to 2805 mg peanut flour.
Studies of Omalizumab with OIT in Food Allergy					
Nadeau et al. 2011[5]	**Omalizumab + OIT** Open label drug, DBPCFC	Milk	11 patients (median age 8 years) with high-risk for developing severe reactions to milk.	To examine the ability of omalizumab to facilitate milk OIT after 9 weeks of treatment.	After 9 weeks of omalizumab monotherapy, 82% of patients were able to tolerate at least a cumulative challenge dose of 1990 mg of milk powder.
Schneider et al. 2013[11]	**Omalizumab + OIT** Open label drug, DBPCFC	Peanut	13 patients (median age 10 years) with high risk for developing severe reactions to peanut demonstrated in DBPCFC at baseline.	Tolerability of peanut protein after first dose. To examine the ability of omalizumab to facilitate peanut OIT (8-12 weeks).	After 12 weeks of omalizumab monotherapy, 100% of patients tolerated the maximum first day OIT dose of 490 mg with minimal or no symptoms. After completing subsequent peanut OIT (median time 8 weeks) to a maintenance dose of 2000 mg of peanut protein, and discontinuing omalizumab treatment, 92% of the patients tolerated a challenge with 4000 mg of peanut protein.
Begin et al. 2014[7]	**Omalizumab + OIT** Open label drug, DBPCFC	Multiple foods	25 patients (median age 7 years) with allergy to 2-5 foods (mean 3.6 foods)	Tolerability of mixed food after OIT with omalizumab.	After 8 weeks of omalizumab monotherapy, 76% of patients reached the maximum first day OIT dose with minimal or no symptoms. After completing OIT, all patients reached a dose of 1000 mg/food by 3 months of OIT; 88% reached the maximum dose of 4000 mg/food by 9 months.
Wood et al. 2016[14]	**OIT + omalizumab or placebo**	Milk	57 patients 7-32 years of age	Desensitization, sustained unresponsiveness, and safety	Significant improvements in measurements of safety but not in outcomes of efficacy (desensitization and SU).
MacGinnitie et al. 2017[8]	**Omalizumab + OIT** RCT, DBPCFC, multi-center	Peanut	37 patients (median age 10 years) with high-risk peanut allergy: 29 patients received omalizumab 8 patients received placebo	To evaluate whether omalizumab facilitated rapid peanut desensitization in highly allergic patients.	<u>First Day of OIT</u> Omalizumab: 85% of patients reached the maximum 490 mg dose of peanut protein Placebo: 13% of patients reached the maximum 490 mg dose of peanut protein <u>After 8-12 Weeks Additional OIT</u> Omalizumab: 81% of patients reached the maximum 4000 mg dose of peanut protein

Reference	Study Design	Food	Study Population (actual)	Relevant Objectives	Results
					Placebo: 13% of patients reached the maximum 4000 mg dose of peanut protein
Andorf et al. 2017[12]	**Omalizumab + OIT** RCT, DBPCFC	Multiple foods	48 patients (median age 8 years) with allergy to 2-5 foods (mean 3.3 foods): 36 patients received omalizumab 12 patients received placebo	To evaluate whether omalizumab facilitated desensitization in patients with multi-food allergies.	After completing 8 weeks of omalizumab monotherapy, treated patients tolerated a median dose of mixed food of 2380 mg (max dose 2380 mg) compared to 55 mg in the placebo group.

2 Study Hypotheses/Objectives

2.1 Hypotheses

The primary null hypothesis for this study is that in children and adults aged 1 year to less than 56 years who are allergic to peanut and at least two other foods (milk, egg, wheat, cashew, hazelnut, or walnut), the dose of oral food protein that is consumed without dose-limiting symptoms (defined in Appendix 1) during a DBPCFC after treatment with either omalizumab or placebo for omalizumab is the same.

Secondary null hypotheses related to the use of omalizumab as monotherapy as well as adjunct therapy to Multi-allergen OIT for the treatment of food allergy include:

1. The effects of omalizumab will be maintained with 24 weeks of additional treatment.
2. The dose of oral food protein that is consumed without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT is the same.
3. Dietary consumption of food after the conclusion of treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT is the same.
4. Treatment of food allergy with either omalizumab as monotherapy or as adjunct therapy to Multi-allergen OIT is safe.

2.2 Primary Objective

To compare the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab or placebo for omalizumab.

2.3 Secondary Objectives

Stage 1

1. To evaluate safety during treatment with either omalizumab or placebo for omalizumab.

Stage 2

2. To compare the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT. This is the primary objective for Stage 2.
3. To evaluate safety during treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.

Stage 3

4. To compare dietary consumption of foods after the conclusion of treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.
5. To evaluate safety after the conclusion of treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.

2.4. Exploratory Objectives Exploratory objectives are:

Stage 1

1. To compare quality of life after treatment with either omalizumab or placebo for omalizumab.

Stage 1 OLE

2. To assess the safety and efficacy of either 24 or 40 weeks of treatment with omalizumab.
3. To assess quality of life at the end of either 24 or 40 weeks of treatment with omalizumab.

Stage 2

4. Among participants who do not respond to treatment with omalizumab alone, compare the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.
5. Among participants who respond to treatment with omalizumab alone, compare the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.
6. To compare the change in the dose of each food that is consumed without dose-limiting symptoms during a DBPCFC at the end of Stage 1 and during a DBPCFC at the end of Stage 2 between treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.
7. To compare quality of life after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.

Stage 3

8. To compare quality of life after the conclusion of treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT during a follow-up period in which participants either receive guided dietary instructions and/or rescue OIT for up to three foods.
9. To describe dietary consumption of foods after the conclusion of either 24 or 40 weeks of treatment with omalizumab during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.
10. To assess safety after the conclusion of either 24 or 40 weeks of treatment with omalizumab during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.
11. To measure quality of life after the conclusion of either 24 or 40 weeks of treatment with omalizumab during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.

Pharmacokinetic (PK) objectives are:

Stage 1

12. To evaluate serum omalizumab concentrations during treatment with omalizumab.

Stage 1 OLE

13. To assess serum omalizumab concentrations at the end of either 24 or 40 weeks of treatment with omalizumab.

Stage 2

14. To evaluate serum omalizumab concentrations during treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.

Biomarker objectives are:

Stage 1

15. To compare immunological responses after treatment with either omalizumab or placebo for omalizumab.
16. To determine whether immunological responses can be used to predict the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab or placebo for omalizumab.

Stage 1 OLE

17. To assess immunological responses at the end of either 24 or 40 weeks of treatment with omalizumab.

Stage 2

18. To compare immunological responses during and after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.
19. To determine whether immunological responses can be used to predict the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.

Stage 3

20. To compare immunological responses after the conclusion of treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.
21. To assess immunological responses after the conclusion of either 24 or 40 weeks of treatment with omalizumab during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.

3 Study Design

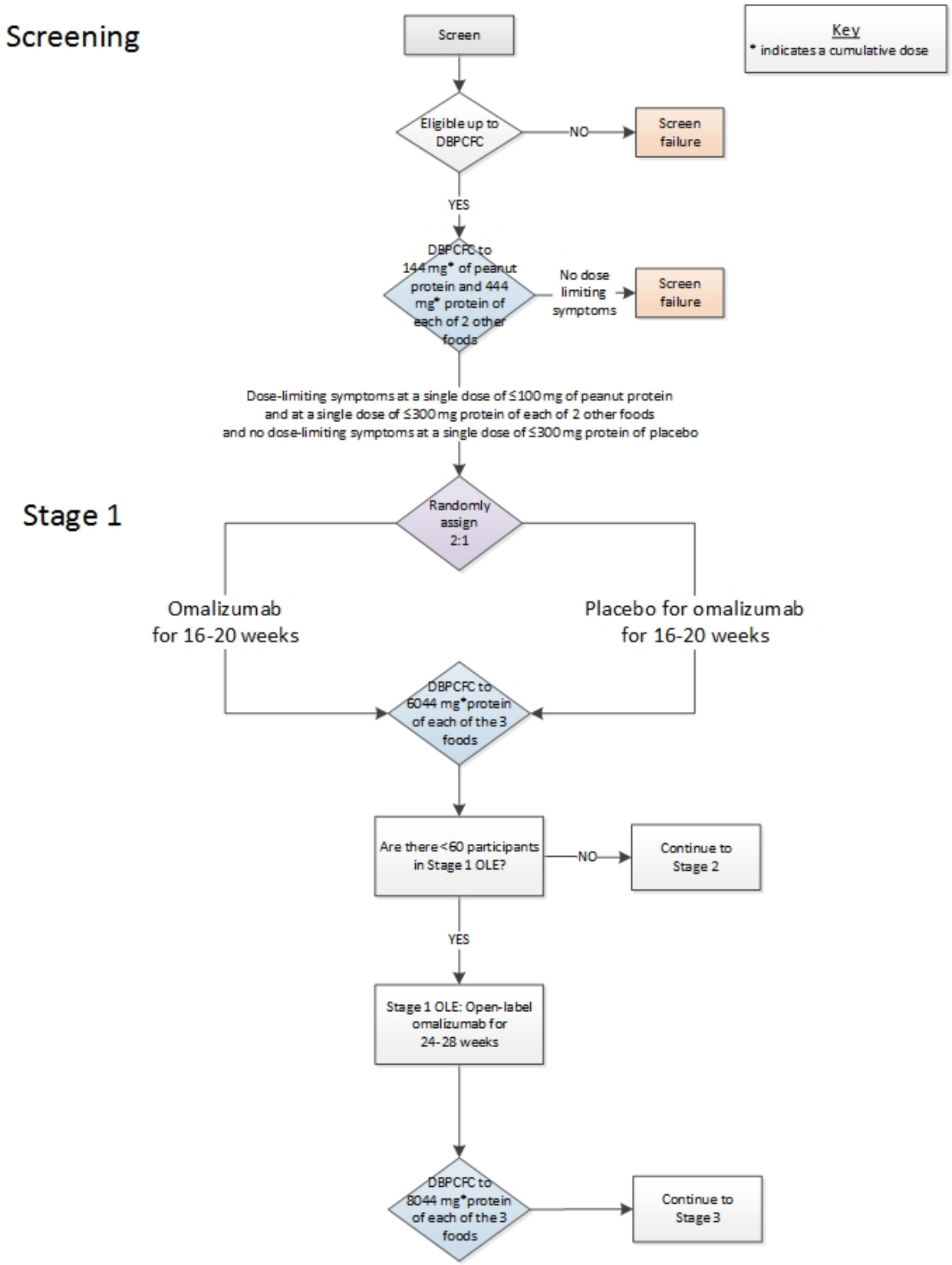
3.1 Description of Study Design

This study is a multi-center, randomized, double-blind, placebo-controlled study in participants 1 year to less than 56 years of age at the Screening Visit who are allergic to peanut and at least two other foods (including milk [i.e., cow's milk], egg [i.e., egg white], wheat, cashew, hazelnut, or walnut [i.e., English walnut]). While each participant may be

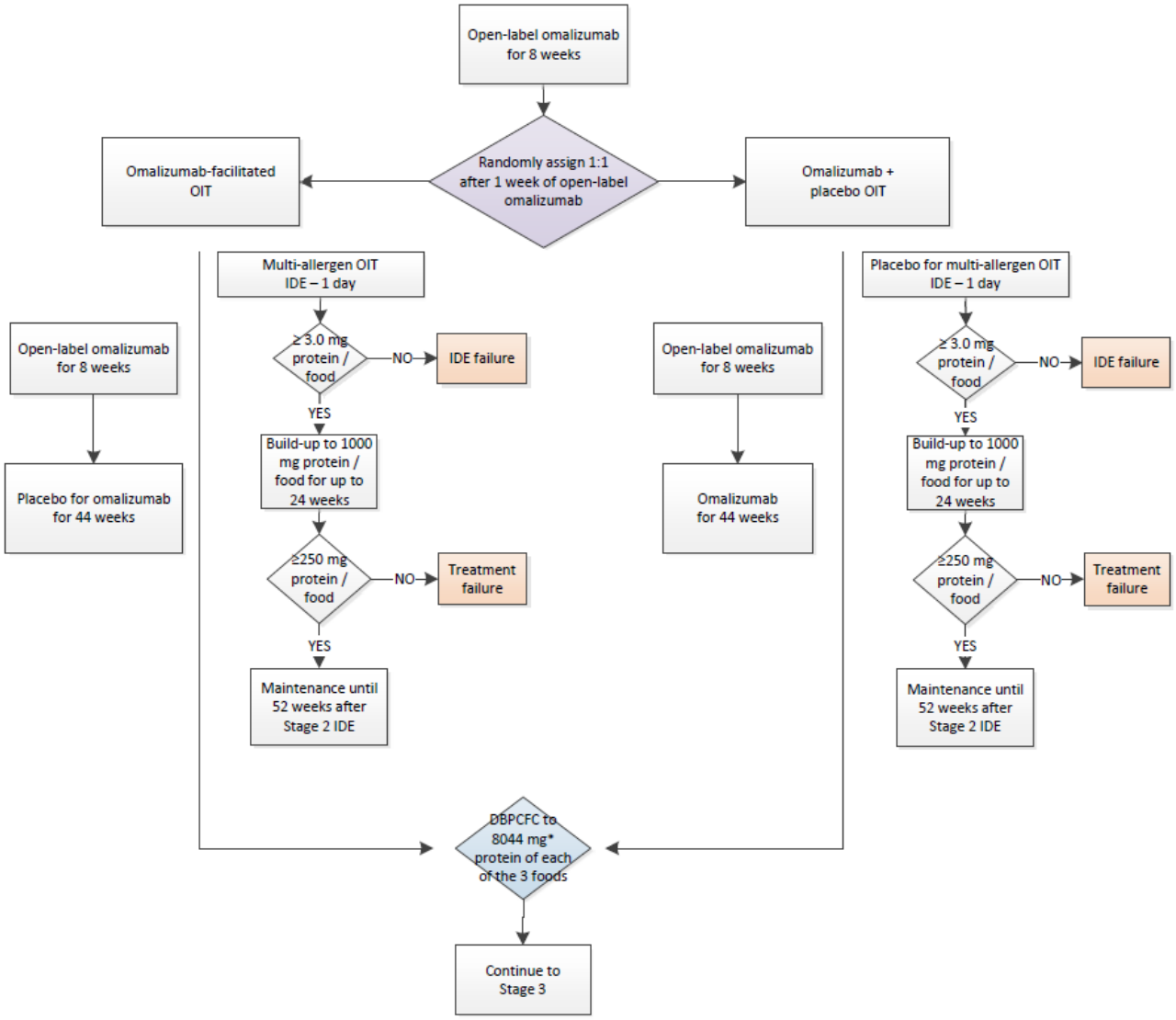
allergic to more than two other foods, the primary endpoint in this study will only be assessed in peanut and two other foods for each participant. The choice of which foods are treated is described in Section 3.1.1.

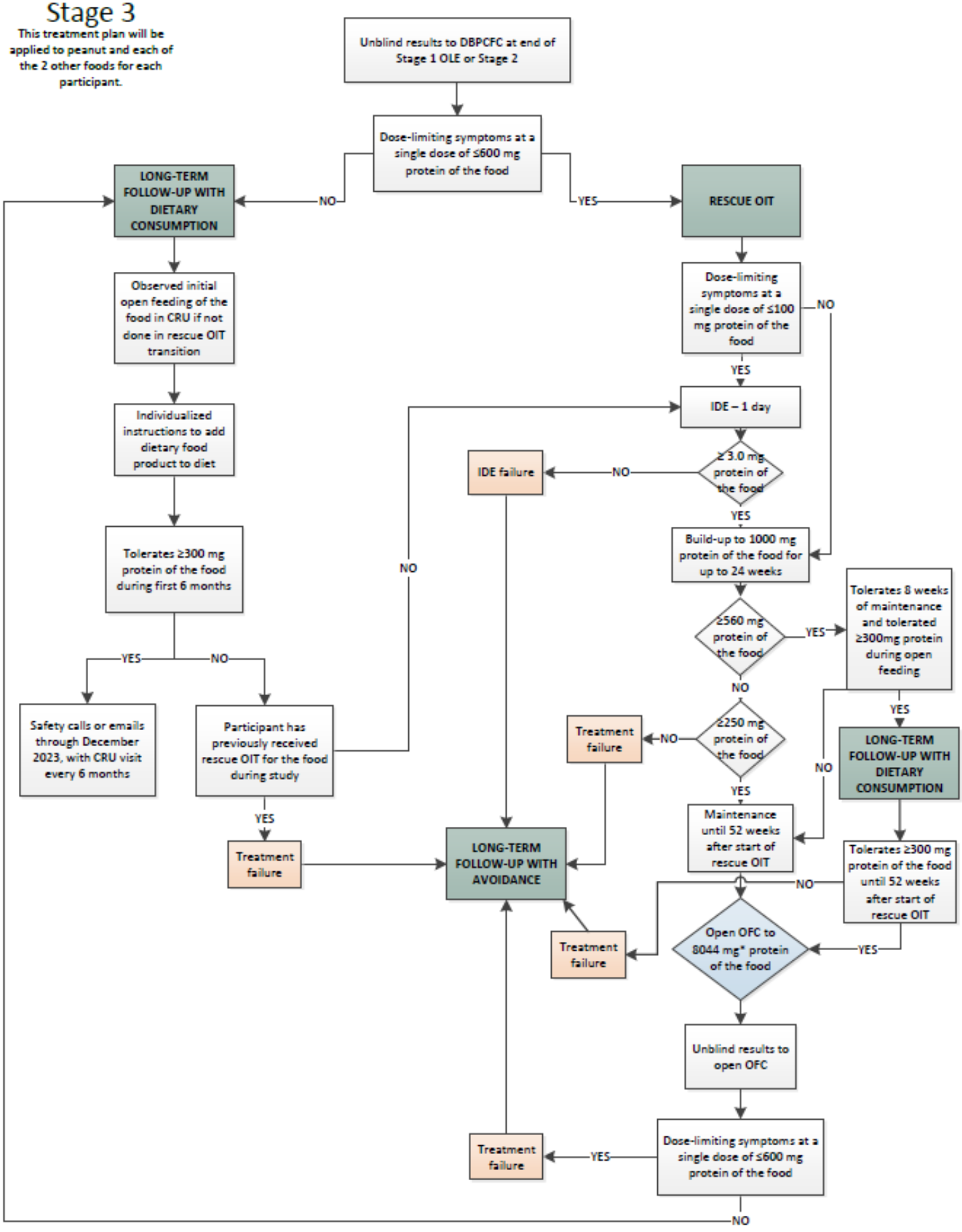
There are three stages (see Figure 3.1). The study will randomize 225 participants at the beginning of Stage 1 (≥50 participants aged 1 year to less than 6 years, approximately 160 participants aged 6 to less than 18 years, and approximately 15 participants aged 18 to less than 56 years). Individual study participation will consist of a maximum of 84 weeks for treatment and a minimum of 12 months of follow-up. All participants will be followed up until at least December 2022. Throughout Stage 1, Stage 1 OLE, and Stage 2, each participant will be instructed to strictly avoid all foods to which they are allergic. Each participant will also be instructed to strictly avoid a food if they receive rescue OIT for the food during Stage 3.

Figure 3.1 Study Design



Stage 2


Open-label omalizumab for 8 weeks
Randomly assign 1:1 after 1 week of open-label omalizumab
Omalizumab-facilitated OIT
Omalizumab + placebo OIT
Multi-allergen OIT IDE – 1 day
≥ 3.0 mg protein / food
NO
IDE failure
YES
Build-up to 1000 mg protein / food for up to 24 weeks
≥250 mg protein / food
NO
Treatment failure
YES
Maintenance until 52 weeks after Stage 2 IDE
Placebo for multi-allergen OIT IDE – 1 day
≥ 3.0 mg protein / food
NO
IDE failure
YES
Build-up to 1000 mg protein / food for up to 24 weeks
≥250 mg protein / food
NO
Treatment failure
YES
Maintenance until 52 weeks after Stage 2 IDE
Open-label omalizumab for 8 weeks
Placebo for omalizumab for 44 weeks
Open-label omalizumab for 8 weeks
Omalizumab for 44 weeks
DBPCFC to 8044 mg* protein of each of the 3 foods
Continue to Stage 3


Stage 3
This treatment plan will be applied to peanut and each of the 2 other foods for each participant.
Unblind results to DBPCFC at end of Stage 1 OLE or Stage 2
Dose-limiting symptoms at a single dose of ≤600 mg protein of the food
NO
YES
LONG-TERM FOLLOW-UP WITH DIETARY CONSUMPTION
RESCUE OIT
Observed initial open feeding of the food in CRU if not done in rescue OIT transition
Dose-limiting symptoms at a single dose of ≤100 mg protein of the food
NO
YES
Individualized instructions to add dietary food product to diet
IDE – 1 day
IDE failure
NO
≥ 3.0 mg protein of the food
YES
Tolerates ≥300 mg protein of the food during first 6 months
Build-up to 1000 mg protein of the food for up to 24 weeks
NO
≥560 mg protein of the food
YES
Tolerates 8 weeks of maintenance and tolerated ≥300mg protein during open feeding
YES
NO
Safety calls or emails through December 2023, with CRU visit every 6 months
Participant has previously received rescue OIT for the food during study
Treatment failure
NO
≥250 mg protein of the food
YES
LONG-TERM FOLLOW-UP WITH DIETARY CONSUMPTION
NO
YES
Treatment failure
Maintenance until 52 weeks after start of rescue OIT
LONG-TERM FOLLOW-UP WITH AVOIDANCE
Tolerates ≥300 mg protein of the food until 52 weeks after start of rescue OIT
NO
Treatment failure
Open OFC to 8044 mg* protein of the food
YES
Unblind results to open OFC
Treatment failure
YES
Dose-limiting symptoms at a single dose of ≤600 mg protein of the food
NO

3.1.1 Screening

During an initial Screening Visit, a participant and/or parent/legal guardian will provide informed consent and/or assent for study participation. A consented participant will then be assessed for study eligibility through the collection of medical, diet and allergy histories; a physical exam, including an assessment of atopic dermatitis (AD) severity; skin prick tests (SPTs); and blood sample collection to measure complete blood count (CBC), comprehensive metabolic panel (CMP), and IgE (total IgE and allergen-specific IgE).

A participant who is eligible up to this point will complete a DBPCFC (see Table 3.1.1). The DBPCFC will consist of four blinded OFCs: three active OFCs (peanut and two additional foods) and one placebo OFC (oat). The DBPCFC may be conducted over four separate visits. The PI and the participant and/or parent/legal guardian will make an individualized decision regarding the selection of the two additional foods, as defined in the OUtMATCH OFC MOP. Completion of a blinded OFC is defined as ingesting any amount of protein/placebo during that blinded OFC. Participants who begin a blinded OFC at Screening but refuse to continue OFC dosing to the end of the OFC despite not experiencing dose-limiting symptoms will be allowed to repeat the blinded OFC one time on a different day. Participants who do not experience dose-limiting symptoms to two non-peanut foods but who may be allergic to additional foods will receive an additional DBPCFC consisting of up to two active OFCs for other non-peanut foods and one placebo OFC.

The maximum cumulative dose for each blinded OFC during the Screening DBPCFC is 444 mg of protein. For the blinded OFC to peanut during the Screening DBPCFC, the maximum single dose given will be 100 mg of peanut protein with the final single 300 mg dose consisting of placebo. For the additional blinded OFCs to two foods and the blinded OFC to placebo during the Screening DBPCFC, the maximum single dose given will be 300 mg of the respective food protein/placebo.

After the participant completes each blinded OFC during the Screening DBPCFC, the CRU dietitian/pharmacist (as applicable) will review the results of the blinded OFC to confirm that the participant still meets those inclusion criteria and does not meet those exclusion criteria that are based on the blinded OFCs. If the participant is no longer eligible for the trial, the participant will not undergo any further blinded OFCs as part of the Screening DBPCFC, will be considered a screen failure, and will be referred to an allergist for further evaluation.

After completing the Screening DBPCFC, participants who experience dose-limiting symptoms to a single dose of ≤100 mg of peanut protein, ≤300 mg protein for each of the other two foods, and no dose-limiting symptoms during the blinded OFC to placebo will move to Stage 1. A participant who does not experience dose-limiting symptoms to peanut and two other foods, or reacts to the blinded OFC to placebo during the Screening DBPCFC will be considered a screen failure and will be referred to an allergist for further evaluation.

Table 3.1.1 Dosing Schedule for the Screening DBPCFC

Dose #	Food Protein/Placebo (mg protein)	Cumulative Dose (mg protein)
1	1	1
2	3	4
3	10	14
4	30	44
5	100	144
6[1]	300	444

1. During the blinded OFC to peanut, the 300 mg dose will be placebo so as not to surpass a maximum dose of 100 mg of peanut protein during the Screening DBPCFC and to preserve blinding.

3.1.2 Stage 1 – Omalizumab as Monotherapy

Stage 1 of the study will test whether 16-20 weeks of treatment with omalizumab versus placebo for omalizumab increases the proportion of participants who consume each of the foods under study without dose-limiting symptoms, as assessed by a DBPCFC.

Participants who meet eligibility criteria will be randomized 2:1 to 16-20 weeks of treatment with omalizumab or placebo for omalizumab per a standard omalizumab dosing table (see Appendix 2). During Stage 1, all participants, PIs, and clinical research unit (CRU) staff will be blinded to treatment assignments, except for an unblinded CRU pharmacist/pharmacy staff and a CRU staff member who will administer omalizumab or placebo for omalizumab injections. The CRU staff member administering injections will not be involved in any other aspect of the study that would threaten blinding and/or that could be influenced by an unblinded CRU staff member performing the procedure.

During Stage 1, each randomized participant will be instructed to strictly avoid all foods to which they are allergic. Each randomized participant will visit the CRU every two or four weeks (depending on omalizumab dosing frequency) for an injection of omalizumab or placebo for omalizumab. Each participant must be observed for at least two hours after the first three injections and at least 30 minutes after all subsequent injections to assess adverse events (AEs).

After 16 weeks of treatment, each participant will complete a DBPCFC (see Table 3.1.2) consisting of placebo and each of their three specific foods to a cumulative dose of 6044 mg protein of each food. The DBPCFC may occur over four separate visits to accommodate blinded OFCs for three foods and placebo. Each participant will continue to receive omalizumab or placebo for omalizumab injections while these blinded OFCs are completed. All blinded OFCs comprising the DBPCFC must occur within a maximum period of 28 days; therefore, Stage 1 may last between 16 and 20 weeks.

Table 3.1.2 Dosing Schedule for a DBPCFC at the End of Stage 1, Stage 1 OLE, and Stage 2

Dose #	Food Protein/Placebo (mg protein)	Cumulative Dose (mg protein)
1	1	1
2	3	4
3	10	14
4	30	44
5	100	144
6	300	444
7	600	1044
8	1000	2044
9	2000	4044
10	2000	6044
11[1]	2000	8044

1. Dose #11 will only be performed for the DBPCFC at the end of Stage 1 OLE and Stage 2.

Each participant who does not complete Stage 1 (i.e., does not complete all four blinded OFCs comprising the DBPCFC at the end of Stage 1) will be withdrawn from the study and will attend an Early Discontinuation Visit (see Section 8.9). Each participant who completes Stage 1 will move on to either Stage 1 OLE or Stage 2 of the study. The first 60 participants will participate in the Stage 1 OLE.

Once all participants complete Stage 1 and Stage 1 OLE (as appropriate) and the database is frozen, analyses of endpoints measured during Stage 1 and Stage 1 OLE will be conducted (see Section 13.5.2).

3.1.3 Stage 1 Open Label Extension – Long-Term Treatment with Omalizumab

During the OLE, each participant will receive 24-28 weeks of treatment with open label omalizumab followed by a DBPCFC to test the durability of long-term treatment with omalizumab. A blinded CRU staff member can administer injections during this stage of the study.

During the OLE, each participant will be instructed to strictly avoid all foods to which they are allergic. Each participant will visit the CRU every two or four weeks (depending on omalizumab dosing frequency) for an injection of omalizumab. To maintain blinding to Stage 1 treatment arm, each participant must be observed for at least two hours after the first three injections and at least 30 minutes after all subsequent injections given in the OLE to assess AEs.

After 24 weeks of treatment, each participant will complete a DBPCFC (see Table 3.1.2) consisting of placebo and each of their three specific foods to a cumulative dose of 8044 mg protein of each food. The DBPCFC may occur over four separate visits to accommodate blinded OFCs to the three foods and placebo. Each participant will continue to receive omalizumab injections while these blinded OFCs are completed. All blinded OFCs comprising the DBPCFC must occur within a maximum period of 28 days; therefore, the OLE may last between 24 and 28 weeks.

Each participant who does not complete Stage 1 OLE (i.e., does not complete all four blinded OFCs comprising the DBPCFC at the end of the OLE) will be withdrawn from the study and will attend an Early Discontinuation Visit (see Section 8.9). Each participant who completes Stage 1 OLE will move on to Stage 3 of the study.

3.1.4 Stage 2 – Omalizumab as Adjunct Therapy to Multi-Allergen Oral Immunotherapy Compared to Omalizumab Monotherapy

Stage 2 of the study will test if eight weeks of treatment with open label omalizumab followed by 52-56 weeks of treatment with omalizumab-facilitated OIT or omalizumab + placebo OIT increases the proportion of participants who consume each of the foods under study without dose-limiting symptoms, as assessed by a DBPCFC.

During Stage 2, each participant will be instructed to strictly avoid all foods to which they are allergic. Each participant will receive eight weeks of treatment with open label omalizumab. To maintain blinding to Stage 1 treatment arm, each participant must be observed for at least two hours after the first three injections and at least 30 minutes after all subsequent injections given in Stage 2 to assess AEs.

One week after beginning Stage 2, participants will be randomized 1:1 to:

- Omalizumab-facilitated OIT: Open label omalizumab + Multi-allergen OIT for eight weeks, followed by placebo for omalizumab + Multi-allergen OIT for 44 weeks.
- Omalizumab + placebo OIT: Open label omalizumab + placebo for Multi-allergen OIT for eight weeks, followed by omalizumab + placebo for Multi-allergen OIT for 44 weeks.

During Stage 2, all participants, PIs, and CRU staff will be blinded to randomized treatment assignments, except for an unblinded CRU pharmacist/pharmacy staff and a CRU staff member who will administer omalizumab or placebo for omalizumab injections only. The CRU staff member administering injections during the blinded portion of Stage 2 will not be involved in any other aspect of the study that would threaten blinding and/or that could be influenced by an unblinded CRU staff member performing the procedure. However, a blinded CRU staff member can administer injections during the open label portion of Stage 2.

After completion of eight weeks of open label omalizumab, each participant will receive an additional eight weeks of open label omalizumab followed by either 44 weeks of omalizumab or placebo for omalizumab (depending on the arm). While receiving omalizumab or placebo for omalizumab injections, each participant will also complete 52 weeks of Multi-allergen OIT or placebo for Multi-allergen OIT as follows:

Initial Dose Escalation (IDE): IDE will occur on a single day in which multiple doses of Multi-allergen OIT or placebo for Multi-allergen OIT will be given to the participant.

If the participant chooses to receive their injection of open label omalizumab during the IDE Visit, the injection will be performed prior to the initiation of IDE to ensure that sufficient time (at least two hours or at least 30 minutes, depending on participant's omalizumab dosing frequency) is given to assess AEs related to the injection. Otherwise, the participant will receive their injection of open label omalizumab either the day after the IDE Visit (i.e., Initial Dose Build-Up Visit) or at a separately scheduled visit.

Multi-allergen OIT or placebo for Multi-allergen OIT IDE doses will be administered incrementally and increased every 15 minutes up to a total dose of 1125 mg protein of Multi-allergen OIT or equivalent placebo for Multi-allergen OIT (see Table 3.1.4a). The participant must tolerate a dose of at least 9 mg protein of Multi-allergen OIT or equivalent placebo for Multi-allergen OIT. A participant who does not tolerate at least 9 mg protein of Multi-allergen OIT or equivalent placebo for Multi-allergen OIT will be considered an IDE failure and be referred to an allergist for standard clinical care. Each participant defined as an IDE failure will not complete any additional study visits and/or sample collections.

Table 3.1.4a Dosing Schedule for Initial Dose Escalation in Stage 2

Dose #	Multi-Allergen OIT/Placebo for Multi-Allergen OIT Food Allergen Dose (mg protein of each allergen)	Multi-Allergen OIT/Placebo for Multi-Allergen OIT Total Food Allergen Dose (mg protein)
1	3	9
2	30	90
3	60	180
4	125	375
5	250	750
6	375	1125

Build-Up Phase: The day after the IDE Visit, the participant will return to the CRU for an observed administration of the last tolerated dose of Multi-allergen OIT or placebo for Multi-allergen OIT. The participant will then continue Multi-allergen OIT or placebo for Multi-allergen OIT daily at home, as prescribed. The participant will return to the CRU every two weeks for a dose build-up (see Table 3.1.4b) to reach a maximum maintenance dose of 1000 mg protein of each of their three specific foods (i.e., a total maximum dose of 3000 mg food protein or 3000 mg placebo for Multi-allergen OIT, depending on the arm). A participant who does not tolerate OIT dosing during a Dose Build-Up Visit will remain at the previously tolerated dose until the next Dose Build-Up Visit. Each participant must reach a dose of at least 750 mg food protein (equivalent to 250 mg protein of each of their three specific foods or 750 mg of placebo) within 24 weeks of IDE to enter the Maintenance Phase; otherwise, the participant will be considered a

treatment failure and referred to an allergist for standard clinical care. A participant who has met this definition of a treatment failure will attend an Early Discontinuation Visit (see Section 8.9).

Table 3.1.4b Dosing Schedule for Multi-allergen OIT/Placebo for Multi-allergen OIT Dose Build-Up in Stage 2

Dose #[1]	Multi-allergen OIT/Placebo for Multi-allergen OIT Food Allergen Dose (mg protein of each allergen)	Multi-allergen OIT/Placebo for Multi-allergen OIT Total Food Allergen Dose (mg protein)	Interval (weeks)
1	3	9	2
2	30	90	2
3	60	180	2
4	125	375	2
5	250	750	2
6	375	1125	2
7	560	1680	2
8	800	2400	2
9	1000	3000	2

1. Dose build-up will begin at the last tolerated dose from the IDE Visit.

Omalizumab or placebo for omalizumab injections during the Build-Up Phase may be performed on the same day as a Dose Build-Up Visit, with the injection occurring at least 30 minutes prior to the build-up dose to assess AEs.

Maintenance Phase: Once each participant reaches the maintenance dose, the participant will continue daily home OIT dosing until 52 weeks after the IDE is completed. Each participant will return to the CRU two weeks after the end of the Build-Up Phase for their Initial Maintenance Dose Visit and every eight weeks thereafter for Follow-Up Maintenance Dose Visits. Each participant will also return to the CRU for injections of omalizumab or placebo for omalizumab according to their omalizumab dosing frequency; these visits may also occur on the Initial or Follow-Up Maintenance Dose Visits, with an observation period of at least 30 minutes prior to the maintenance dose to assess AEs. Depending on when a participant reaches the maintenance dose during the Build-Up Phase, the number and timing of Follow-Up Maintenance Dose Visits may vary among participants.

If a participant does not tolerate a dose during the Maintenance Phase, the dose may be adjusted (see Section 6.4.2). In the event a participant, undergoing dose adjustments, does not tolerate at least 750 mg of Multi-allergen OIT or equivalent placebo for Multi-allergen OIT by two weeks before the first DBPCFC Visit at the end of Stage 2, the participant will be considered a treatment failure and will be referred to an allergist for standard clinical care. A participant defined as a treatment failure will attend an Early Discontinuation Visit (see Section 8.9).

At the end of the Maintenance Phase, each participant will complete a DBPCFC (see Table 3.1.2) consisting of placebo and each of their three specific foods to a cumulative dose of 8044 mg protein of each food. The DBPCFC may occur over four separate visits to accommodate blinded OFCs to the three foods and placebo. Each participant will continue on OIT while all these blinded OFCs are completed. All blinded OFCs comprising the DBPCFC must occur within a maximum period of 28 days; therefore, Stage 2 may last between 60 and 64 weeks.

Each participant who does not complete Stage 2 (i.e., does not complete all four blinded OFCs comprising the DBPCFC at the end of Stage 2) will be withdrawn from the study and will attend an Early Discontinuation Visit (see Section 8.9). Each participant who completes Stage 2 will move on to Stage 3 of the study.

3.1.5 Stage 3 – Long-Term Follow-Up and Rescue Oral Immunotherapy

During Stage 3, a participant will be offered a separate treatment plan for peanut and each of the two other participant-specific foods. A treatment plan will include instructions for one of the following:

- Long-term follow-up with dietary consumption of a food; or
- Long-term follow-up with avoidance of a food; or
- Rescue OIT for a food.

The treatment plan for each food may change throughout Stage 3 depending on a participant's response to treatment. Because the visit schedule for each treatment plan differs, a participant's visits during Stage 3 will be combined accordingly to minimize the number of visits a participant attends.

Once a participant enters Stage 3, the participant will have a minimum of 12 months of follow-up in Stage 3 and will remain in Stage 3 until at least December 2022. A participant who enters rescue OIT from dietary consumption for a food will have a minimum of 12 months of follow-up from the start of the rescue OIT.

3.1.5.1 Long-Term Follow-Up with Dietary Consumption of a Food

A participant will undergo long-term follow-up with dietary consumption of a specified food(s) if the participant meets the following requirements:

- Completed Stage 1 OLE or Stage 2 within the last seven days and consumed a single dose of ≥600 mg protein of the food without dose-limiting symptoms.
- Completed the open OFC at the end of 52 weeks of rescue OIT for the food within the last seven days and consumed a single dose of ≥600 mg protein of the food without dose-limiting symptoms.

Long-term follow-up with dietary consumption of a food will begin with the participant being given an observed initial open feeding of the dietary food during a CRU visit. Open feedings to more than one dietary food may occur on the same day with a two-hour waiting period between each food. An open feeding may occur on the day of the last blinded OFC at the end of Stage 1 OLE or Stage 2 if the blinded OFC to placebo is performed on that day. The amount of dietary food eaten at the open feeding will be based on the maximum quantity deemed to be safe, as determined by the participant's most recent OFC (see Table 3.1.5.1).

Participants who undergo long-term follow-up with dietary consumption of a food immediately after completing Stage 1 OLE or Stage 2 will remain on the treatment they were receiving until all open feedings are completed.

Following completion of the open feeding(s), the participant will be provided with individualized instructions for inclusion of the food into their diet. For participants undergoing long-term follow-up with dietary consumption of a food immediately after completing Stage 2, all open feedings must be completed prior the participant's receipt of the individualized instructions for the inclusion of the food into the diet.

After the open feeding(s), the participant will be called or emailed weekly for the first four weeks, every other week between six and sixteen weeks, and then every two months for safety follow-up. In addition, the participant will be required to return to the CRU for a long-term follow-up visit every six months. Starting at seven months of follow-up, the participant will be called or emailed every month to complete

monthly long-term follow-up phone calls/emails. These phone calls/emails may be combined with other study visits in Stage 3.

Table 3.1.5.1 Minimum and Maximum Amounts of Protein Contained in a Single Food That Should Be Consumed by Participants at Open Feeding

Minimum Amount (mg protein of food)	Cumulative Dose Consumed Without Dose-Limiting Symptoms During Most Recent OFC (mg protein)	Dose Consumed Without Dose-Limiting Symptoms During Most Recent OFC (mg protein)	Maximum Amount (mg protein of food)
300	1044	600	600
300	2044	1000	1000
300	4044	1st dose of 2000	2000
300	6044	2nd dose of 2000	4000
300	8044	3rd dose of 2000	6000

If the participant does not tolerate ≥300 mg protein of the food during the first six months of long-term follow-up with dietary consumption, the participant will either:

- Receive rescue OIT for the food, if this option previously has not been provided for that food; or
- Receive long-term follow-up with avoidance of that food, if the participant chooses to not undergo rescue OIT or if rescue OIT was provided for the food previously. In this case, the participant would be considered a treatment failure for that food.

If the participant tolerates ≥300 mg protein of the food for the first six months but does not tolerate ≥300 mg protein of the food after the first six months of long-term follow-up with dietary consumption, the participant will be considered a treatment failure for that food and will receive long-term follow-up with avoidance of that food.

3.1.5.2 Long-Term Follow-Up with Avoidance of a Food

A participant will undergo long-term follow-up with avoidance of a food if the participant:

- Does not tolerate ≥300 mg protein of the food during the first six months of long-term follow-up with dietary consumption of the food and rescue OIT was provided for the food previously; or
- Does not tolerate ≥300 mg protein of the food after the first six months of long-term follow-up with dietary consumption.
- Was an IDE failure or treatment failure during rescue OIT for the food; or
- The participant chooses to avoid that food.

During long-term follow-up with avoidance of a food, the participant will avoid eating the food. The participant will return to the CRU for a long-term follow-up visit every six months for follow-up. Starting at seven months of follow-up, the participant will be called or emailed every month to complete monthly long-term follow-up phone calls/emails. These phone calls/emails may be combined with other study visits in Stage 3.

3.1.5.3 Rescue Oral Immunotherapy for a Food

A participant will be offered rescue OIT for a food if the participant:

- Completed Stage 1 OLE or Stage 2 within the last 14 days and had dose-limiting symptoms at a single dose of ≤600 mg protein of the food; or
- Completed the DBPCFC at the end of Stage 1 OLE or Stage 2 within the last 14 days but refused to continue the blinded OFC to a single dose of 600 mg protein of the food, despite not experiencing dose-limiting symptoms at a single dose less than 600 mg protein of the food; or
- Does not tolerate ≥300 mg protein of the food during the first six months of long-term follow-up with dietary consumption of the food and rescue OIT has not been provided for the food at any time during the study.

Participants who enter rescue OIT for a food will have a minimum of 12 months of follow-up from the start of the rescue OIT for that food.

IDE Visit during Rescue OIT: A participant will have an IDE Visit during rescue OIT if the participant:

- Has dose-limiting symptoms at a single dose of ≤100 mg protein of the food during the DBPCFC at the end of Stage 1 OLE or Stage 2; or
- Completed the DBPCFC at the end of Stage 1 OLE or Stage 2 but refused to continue the blinded OFC to a single dose of 100 mg protein of the food, despite not experiencing dose-limiting symptoms at a single dose less than 100 mg protein of the food; or
- Does not tolerate ≥300 mg protein of the food during the first six months of long-term follow-up with dietary consumption of the food.

A participant who attends an IDE Visit immediately after completing Stage 1 OLE or Stage 2 will remain on the treatment they received in the previous stage until the IDE Visit and any needed Open Feedings (if needed immediately after completing Stage 1 OLE, Stage 2) are completed.

Rescue OIT IDE doses for a food will be administered incrementally and increased every 15 minutes up to a dose of 375 mg protein of rescue OIT (see Table 3.1.5.3a). The participant must tolerate a dose of at least 3 mg protein of rescue OIT for the food. A participant who does not tolerate 3 mg protein of the food during the IDE Visit will be considered an IDE failure, will be removed from rescue OIT for that food, and will receive long-term follow-up with avoidance of that food.

Alternatively, a participant will skip the IDE Visit during rescue OIT if the participant consumed a dose of ≥100 mg protein of the food without dose-limiting symptoms during the participant's DBPCFC at the end of Stage 1 OLE or Stage 2.

Table 3.1.5.3a Dosing Schedule for Initial Dose Escalation in Stage 3

Dose #	Food Allergen Dose (mg protein of each allergen)
1	3
2	10
3	30
4	60
5	125
6	250
7	375

Dose Build-Up during Rescue OIT: A participant who attended an IDE Visit during rescue OIT will return to the CRU the next day for an observed administration of the last tolerated dose of OIT and continue with build-up based on doses given in Table 3.1.5.3b.

Table 3.1.5.3b Dosing Schedule for rescue OIT dose build-up in Stage 3

Dose #[1]	Food Allergen Dose (mg protein of each allergen)	Interval (weeks)
1	3	2
2	10	2
3	30	2
4	60	2
5	125	2
6	250	2
7	375	2
8	560	2
9	800	2
10	1000	2

1. Dose build-up will begin at the last dose the participant was able to tolerate on the IDE Visit.

A participant who skipped the IDE Visit will return to the CRU for an observed administration of OIT based on the starting dose given in Table 3.1.5.3c.

Table 3.1.5.3c Starting dose of OIT

Cumulative Dose Consumed Without Dose-Limiting Symptoms During Most Recent DBPCFC (mg protein)	Dose Consumed Without Dose-Limiting Symptoms During Most Recent DBPCFC (mg protein)	Starting Dose of OIT During Build-Up Phase (mg protein)
144	100	60
444	300	250

The participant will return to the CRU every two weeks for a dose build-up to reach a maintenance dose for each food. The target maintenance dose for each individual participant may be any dose ≥560 mg protein for each food, as determined by the investigator and participant, the maximum being 1000 mg protein of the food. A participant who does not tolerate OIT dosing during a Dose Build-Up Visit will remain at the previously tolerated dose until the next Dose Build-Up Visit. Each participant must reach a dose of at least 250 mg of protein of the food within 24 weeks after beginning rescue OIT to enter the Maintenance Phase; otherwise, the participant will be considered a treatment failure, will be removed from rescue OIT for that food, and will receive long-term follow-up with avoidance of that food.

Maintenance Phase during Rescue OIT: The design of the Maintenance Phase for participants depends on the maintenance dose reached within 24 weeks after beginning rescue OIT.

- Maintenance Dose reached within 24 weeks after beginning rescue OIT: <560 mg protein of the food

  A participant who reaches a maintenance dose of <560 mg protein of the food (250 mg or 375 mg) will continue daily home OIT dosing until 52 weeks after beginning rescue OIT. The participant will return to the CRU two weeks after the end of the Build-Up Phase for their Initial Maintenance Dose Visit and every eight weeks thereafter for Follow-Up Maintenance Dose Visits. Depending on when a participant reaches the maintenance dose during the Build-Up Phase, the number and timing of Follow-Up Maintenance Dose Visits may vary among participants.

  If a participant does not tolerate a dose during the Maintenance Phase, the dose may be adjusted (see Section 6.4.2). In the event a participant, undergoing dose adjustments, does not tolerate at least 250 mg of protein of the food by two weeks before the first Open OFC Visit at the end of rescue OIT, the participant will be considered a treatment failure, will be removed from rescue OIT for that food, and will receive long-term follow-up with avoidance of that food.

  After 52 weeks of rescue OIT, the participant will complete an open OFC (see Table 3.1.5.3d) consisting of their specific rescue food to a cumulative dose of 8044 mg protein of the food. If a participant has dose-limiting symptoms at a single dose of ≤600 mg protein of the food or refuses to continue the open OFC to a single dose of 600 mg protein of the food despite not experiencing dose-limiting symptoms at a single dose less than 600 mg protein of the food, the participant will be considered a treatment failure and will receive long-term follow-up with avoidance of the food. Otherwise, the participant will receive long-term follow-up with dietary consumption of the food.

Table 3.1.5.3d Dosing Schedule for Open OFC

Dose #	Food Protein (mg protein)	Cumulative Dose (mg protein)
1	1	1
2	3	4
3	10	14
4	30	44
5	100	144
6	300	444
7	600	1044
8	1000	2044
9	2000	4044
10	2000	6044
11	2000	8044

- Maintenance Dose reached within 24 weeks after beginning rescue OIT: 560 mg, 800 mg, or 1000 mg protein of the food

  A participant who reaches a Rescue OIT target maintenance dose of 560 mg, 800 mg, or 1000 mg of the food will return to the CRU two weeks after the end of the Build-Up Phase for their Initial Maintenance Dose Visit. The participant will be called or emailed at two and five weeks after the Initial Maintenance Dose Visit and will return to the CRU eight weeks after the Initial Maintenance Dose Visit for a Follow-Up Maintenance Dose Visit.

  If a participant does not tolerate the target maintenance dose during this eight week period, the participant will return to the clinic for dose adjustment and will continue daily home OIT dosing for 52 weeks after beginning rescue OIT (as described previously).

  If a participant tolerates the target maintenance dose during this eight week period, the participant will have an observed initial open feeding of the dietary food during a CRU visit. Open feedings to more than one dietary food may occur on the same day with a two-hour waiting period between each food. The amount of dietary food eaten at the open feeding will be based on the maximum quantity deemed to be safe, as determined by the participant's target maintenance dose (see Table 3.1.5.3e).

  Table 3.1.5.3e Minimum and Maximum Amounts of Protein Contained in a Single Food That Should Be Consumed by Participants at Open Feeding

Minimum Amount (mg protein of food)	Target Maintenance Dose (mg protein of food)	Maximum Amount (mg protein of food)
300	560	300
300	800	600
300	1000	1000

  If the participant tolerates ≥300 mg protein of the food during the open feeding(s), the participant will transition to dietary consumption of the food and will be provided with individualized instructions for inclusion of the food into their diet. Thereafter, the participant will be called or

emailed weekly for the first four weeks, every other week between six and sixteen weeks, and then every two months for safety follow-up. Starting at seven months of follow-up after the transition to Long term follow-up with dietary consumption, the participant will be called or emailed every month to complete monthly long-term follow-up phone calls/emails. In addition, the participant will be required to return to the CRU for a long-term follow-up visit every six months. Required phone calls/emails may be combined with other study visits in Stage 3.

If the participant continues to tolerate ≥300 mg protein of the food, via dietary consumption, until 52 weeks after beginning rescue OIT, the participant will complete an open OFC (see Table 3.1.5.3d) consisting of their specific rescue food to a cumulative dose of 8044 mg protein of the food. If a participant has dose-limiting symptoms at a single dose of ≤600 mg protein of the food, the participant will be considered a treatment failure for that food and will receive long-term follow-up with avoidance of the food. Otherwise, the participant will continue to receive long-term follow-up with dietary consumption of the food.

3.2 Primary Endpoint

The primary endpoint is consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1. Dose-limiting symptoms are defined in Appendix 1. A participant who meets this endpoint will be considered a 'success' while a participant who does not meet this endpoint will be considered a 'failure'.

3.3 Secondary Endpoints

Key secondary endpoints include:

Stage 1

1. Consumption of a single dose of ≥1000 mg of cashew protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.

2. Consumption of a single dose of ≥1000 mg of milk protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.

3. Consumption of a single dose of ≥1000 mg of egg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.

Stage 2

4. Consumption of ≥1 dose of 2000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2. This is the primary endpoint for Stage 2.

Other secondary endpoints include:

5. Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 (except those endpoints already defined by the primary and key secondary endpoints in Stage 1).

6. Number of foods consumed at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 1.

7. Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2 (except the endpoint already defined by the primary endpoint for Stage 2).

8. Number of foods consumed at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 2.

9. Number of weeks in each eight-week period during Stage 3 where ≥300 mg protein of each food is consumed at least twice per week.

10. Number of weeks in each eight-week period during Stage 3 where each food is not consumed.Safety endpoints include:

11. An AE related to study therapy regimen received during Stage 1.

12. An AE related to study therapy regimen received during Stage 1 OLE.

13. An AE related to study therapy regimen received during Stage 2.

14. An AE related to oral food intake received during Stage 3.

3.4 Exploratory Endpoints

Exploratory endpoints include:

1. Percent change in the maximum dose of food protein consumed without dose-limiting symptoms during the DBPCFC at the end of Stage 1 and during the DBPCFC at the end of Stage 2.

2. Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.

3. Number of foods consumed at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.

4. Change in quality of life between Week 0 in Stage 1 and the following times:

    - First DBPCFC Visit at the end of Stage 1;
    - For those participants who move to Stage 1 OLE:
        - First omalizumab injection visit in Stage 1 OLE;
        - First DBPCFC Visit at the end of Stage 1 OLE;
        - Last DBPCFC Visit at the end of Stage 1 OLE.
    - For those participants who move to Stage 2:
        - First omalizumab injection visit in Stage 2;

- First DBPCFC Visit at the end of Stage 2;
- Last DBPCFC Visit at the end of Stage 2.

- Six months after beginning Stage 3.

Quality of life is measured by the Food Allergy Quality of Life Questionnaire – Parent Form (FAQLQ-PF) for participants aged 0-12 years, Food Allergy Quality of Life Questionnaire – Child Form (FAQLQ-CF) for children/adolescents aged 8-12 years, Food Allergy Quality of Life Questionnaire – Teenager Form (FAQLQ-TF) for participants aged 13-17 years, and Food Allergy Quality of Life Questionnaire – Adult Form (FAQLQ-AF) for participants aged ≥18 years.

PK endpoints include:

5. Omalizumab trough concentration, measured at the following times:
   - First Screening DBPCFC Visit;
   - First DBPCFC Visit at the end of Stage 1;
   - First DBPCFC Visit at the end of Stage 1 OLE (for those participants who move to Stage 1 OLE);
   - IDE Visit during Stage 2 (for those participants who move to Stage 2); and
   - First DBPCFC Visit at the end of Stage 2 (for those participants who move to Stage 2).

Biomarkers include the following:

6. Total IgE
7. Total free IgE
8. Allergen-specific IgE
9. Allergen-specific immunoglobulin G4 (IgG4)
10. Allergen-specific immunoglobulin A (IgA)
11. IgG4/IgE ratio
12. Basophil activation
13. SPTs

Immune biomarkers will be measured at the following times:

- First Screening DBPCFC Visit;
- First DBPCFC Visit at the end of Stage 1;
- First DBPCFC Visit at the end of Stage 1 OLE (for those participants who move to Stage 1 OLE);

- IDE Visit during Stage 2, except the SPTs, total IgE, and allergen-specific IgE (for those participants who move to Stage 2);
- Initial Maintenance Dose Visit during Stage 2, except the SPTs, total IgE, and allergen-specific IgE (for those participants who move to Stage 2);
- First DBPCFC Visit at the end of Stage 2 (for those participants who move to Stage 2); and
- Six months after beginning Stage 3.

Mechanistic endpoints will be measured at the following times:

- First Screening DBPCFC Visit;
- First DBPCFC Visit at the end of Stage 1;
- IDE Visit during Stage 2 (for those participants who move to Stage 2);
- Initial Maintenance Dose Visit during Stage 2 (for those participants who move to Stage 2); and
- First DBPCFC Visit at the end of Stage 2 (for those participants who move to Stage 2).

3.5 Stratification, Randomization, and Blinding

Randomization will be accomplished through a password-protected, web-based, randomization system maintained by the Statistical and Clinical Coordinating Center (SACCC). The randomization schemes used in Screening DBPCFCs and Stages 1 and 2 of the study are as follows:

Screening DBPCFCs: A participant and/or parent/legal guardian who provides informed consent and/or assent and who meet initial eligibility criteria will undergo a Screening DBPCFC. The order of the blinded OFC to peanut in relation to the three other blinded OFCs during the Screening DBPCFC (i.e., first, second, third, or fourth) will be randomized using a 1:1:1:1 allocation ratio. Participants who do not experience dose-limiting symptoms to two non-peanut foods but who may be allergic to additional foods will receive an additional Screening DBPCFC consisting of up to two blinded OFCs to other non-peanut foods and one blinded OFC to placebo; the order of these blinded OFCs will be left to the discretion of the CRU dietitian/pharmacist.

Prior to randomization in Stage 1, the results of the Screening DBPCFC will be unblinded to determine eligibility.

Stage 1: Participants who meet the eligibility criteria will be randomized to receive omalizumab or placebo to omalizumab using a 2:1 allocation ratio and a permuted block randomization scheme stratified by <6 years of age at randomization and milk as a participant-specific food (yes/no). Additionally, the order of the blinded OFC to peanut in relation to the three other blinded OFCs during the DBPCFC (i.e., first, second, third, or fourth) at the end of Stage 1 will also be randomized using a 1:1:1:1 allocation ratio and a permuted block randomization scheme stratified by Stage 1 treatment arm. Randomization to treatment arm as well as the order of the blinded OFC to peanut during the DBPCFC will be conducted on the same day for each participant. Each participant and/or parent/legal guardian will remain blinded to the participant's treatment assignment in Stage 1 from the time of randomization to the time when all participants have completed Stage 3 and the database is locked. For those participants who move to Stage 1 OLE, the order of the blinded OFC to peanut in relation to the three other blinded OFCs during the DBPCFC at the end of the OLE will also be randomized using a 1:1:1:1 allocation ratio.

Stage 2: Participants who move to Stage 2 will be randomized to omalizumab-facilitated OIT or omalizumab + placebo OIT using a 1:1 allocation ratio and a permuted block randomization scheme stratified by Stage 1 treatment arm. Additionally, the order of the blinded OFC to peanut in relation to the three other blinded OFCs during the DBPCFC (i.e., first, second, third, or fourth) at the end of Stage 2 will also be randomized using a 1:1:1:1 allocation ratio and a permuted block randomization scheme stratified by Stage 2 treatment arm. Randomization to treatment arm as well as the order of the blinded OFC to peanut during the DBPCFC will be conducted on the same day for each participant. Each participant and/or parent/legal guardian will remain blinded to the participant's treatment assignment in Stage 2 from the time of randomization to the time when all participants have completed Stage 3 and the database is locked.

All investigational product (IP) will be distributed to the unblinded CRU pharmacist/pharmacy staff. The unblinded CRU pharmacist/pharmacy staff will dispense omalizumab and placebo for omalizumab to CRU staff who will administer injections. As it is expected that the CRU staff administering omalizumab and placebo for omalizumab will become unblinded because of differences (e.g., viscosity) between omalizumab and placebo for omalizumab, such staff will be considered unblinded and will not be involved in any other aspect of the study that would threaten blinding and/or that could be influenced by an unblinded CRU staff member performing the procedure. However, open label omalizumab may be administered by a blinded CRU staff member. The unblinded CRU pharmacist/pharmacy staff will dispense Multi-allergen OIT and placebo for Multi-allergen OIT to blinded CRU staff for OIT dosing. During all DBPCFCs, the participant and/or parent/legal guardian, as well as the CRU staff administering the blinded OFC, will not know which blinded OFC contains food protein or placebo.

Participants and blinded CRU staff will be unblinded to participants' treatment assignments in Stage 1 and 2 when all participants have completed Stage 3 and the database is locked. For each stage, laboratory staff will be blinded to participant treatment assignments until all participants have completed the stage, the database is frozen (Stage 1 or Stage 2) or locked (Stage 3), and processing and assaying of samples collected during the stage are completed.

SACCC statisticians will be unblinded to DBPCFC results at the end of Stage 1 when all participants have completed Stage 1 and the database is frozen. Participants, blinded CRU staff, and SACCC statisticians will be unblinded to DBPCFC results at the end of Stage 1 OLE and Stage 2 when each participant has completed each stage.

Stage 1 and Stage 1 OLE analyses will be conducted after all participants have completed Stage 1 and Stage 1 OLE (as appropriate), the database is frozen, and all SACCC statisticians are unblinded to Stage 1 treatment arm. Stage 2 analyses will be conducted after all participants have completed Stage 2 (as appropriate), the database is frozen, and all SACCC statisticians are unblinded to Stage 2 treatment arm. Stage 3 analyses will be conducted after all participants have completed Stage 3 and the database is locked.

Additional detail regarding the timing of the analyses, protection of the blind, and data sharing for each stage is given in Section 13.5.2 and in the Randomization Plan.

3.5.1 Procedure for Unblinding

Unblinding of treatment assignment or early unblinding of a DBPCFC result must be approved by the Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases (DAIT/NIAID) Medical Monitor unless an immediate life-threatening condition has developed and the DAIT/NIAID Medical Monitor is not accessible. The process for notifications of any unblinding event to study personnel is specified in the Manual of

Procedures (MOP). Unblinding events will also be reported to the NIAID Allergy and Asthma 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, the name of the individual who made the decision, and the names of the DAIT/NIAID Medical Monitor and others who were notified. The reasons for unblinding will be included in the final study report.

Unblinding due to an unplanned interim analysis of each stage, final analysis of each stage, or study termination will require written approval from the DAIT/NIAID Medical Monitor. Investigational New Drug (IND) Safety Reports will be reported to the FDA, NIAID Allergy and Asthma DSMB, and single Institutional Review Board (IRB) in an unblinded fashion.

4 Selection of Participants

4.1 Rationale for Study Population

This study will enroll children and adults from 1 year to less than 56 years of age at the Screening Visit with multi-food allergies. The rationale for choosing this study population is three-fold. First, the value of other treatment approaches that focus on a single food, such as OIT for peanut, are limited by the fact that many children and adults have multi-food allergies. In fact, between 30% and 70% of children and adults with peanut allergy have allergies to other foods.[3,4] Therefore, treatments that could provide relief for multiple foods are highly desirable and, if successful, would represent a major advance in the management of food allergy.

The second major rationale for this study population relates to age, with studies suggesting that treatment of peanut allergy with oral and/or epicutaneous immunotherapy (EPIT) may be more efficacious, and equally safe, when initiated in younger children.[13,19] This was clearly demonstrated in the DEVIL study of peanut OIT, which demonstrated high rates of both desensitization and sustained unresponsiveness in children 9 to 36 months of age, including dietary introduction of peanut after the OIT. This study will therefore expand our knowledge regarding the effects of OIT in children as young as age one, but this time focusing on patients with allergy to multiple other foods in addition to peanut. Further, it will provide a unique opportunity to study the effects of omalizumab, both as monotherapy and as an adjunct to OIT, which to date has only been studied down to four years of age.[13]

Third, while most treatment studies for food allergy are currently focused on children, there is a high burden of food allergy in adults as well.[2] This is especially the case for peanut and tree nut allergies, which persist into adulthood in 80-90% of patients, but is also highly relevant for the subset of approximately 20% of patients with severe milk, egg, and/or wheat allergies that persist into adulthood.[2]

4.2 Inclusion Criteria

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

1. Participant and/or parent/legal guardian must be able to understand and provide informed consent and/or assent, as applicable
2. Male or female, 1 year to less than 56 years of age at Screening
3. Peanut allergic; participant must meet all of the following criteria to minimize the chance that the participant will develop natural tolerance to peanut over the course of the study:
    a. Positive SPT (≥4 mm wheal greater than saline control) to peanut
    b. Positive peanut IgE (≥6 kUA/L) at Screening or within three months of Screening, determined by ImmunoCap

c. Positive blinded OFC to peanut during the Screening DBPCFC, defined as experiencing dose-limiting symptoms at a single dose of ≤100 mg of peanut protein

4. Allergic to at least two of the six other foods (milk, egg, wheat, cashew, hazelnut, walnut); allergy to milk and egg is defined as unable to tolerate both cooked and uncooked forms; each participant must meet all of the following criteria for at least two of the six other foods to minimize the chance that the participant will develop natural tolerance to at least two of the six other foods over the course of the study:
    a. Milk, egg, or wheat:
        i. Positive SPT (≥4 mm wheal greater than saline control) to food
        ii. Positive food specific IgE (≥6 kUA/L) at Screening or within three months of Screening, determined by ImmunoCap
        iii. Positive blinded OFC to food during the Screening DBPCFC, defined as experiencing dose-limiting symptoms at a single dose of ≤300 mg of food protein
    b. Cashew, hazelnut, or walnut:
        i. Positive SPT (≥4 mm wheal greater than saline control) to food or positive food specific IgE (≥6 kUA/L) at Screening or within three months of Screening, determined by ImmunoCap
        ii. Positive blinded OFC to food during the Screening DBPCFC, defined as experiencing dose-limiting symptoms at a single dose of ≤300 mg of food protein
5. With body weight (as measured at Screening) and total serum IgE level (as measured within three months of Screening) suitable for omalizumab dosing
6. If female of child-bearing potential, must have a negative urine or serum pregnancy test
7. For women of childbearing potential, must agree to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods (barrier methods or oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy) during the treatment period and for 60 days after the last dose of study drug.
8. Plan to remain in the study area of an OUtMATCH CRU during the trial
9. Be willing to be trained on the proper use of an epinephrine autoinjector and be willing to provide an epinephrine autoinjector for the duration of the study

4.3 Exclusion Criteria

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

1. Inability or unwillingness of a participant and/or parent/legal guardian to give written informed consent and/or assent or comply with the study protocol
2. Clinically significant laboratory abnormalities at Screening
3. Dose-limiting symptoms during the blinded OFC to placebo during the Screening DBPCFC
4. Sensitivity or suspected/known allergy to any ingredients (including excipients) of the active or placebo OFC material, Multi-allergen OIT, or drugs related to omalizumab (e.g., monoclonal antibodies, polyclonal gamma globulin). Guidance for determination of sensitivity to excipients will be detailed in the MOP.
5. Poorly controlled AD at Screening, per the PI's discretion
6. Poorly controlled or severe asthma/wheezing at Screening, defined by at least one of the following criteria:
    a. Global Initiative for Asthma (GINA) criteria regarding asthma control latest guidelines (see Appendix 3);
    b. History of two or more systemic corticosteroid courses within six months of Screening or one course of systemic corticosteroids within three months of Screening to treat asthma/wheezing;
    c. Prior intubation/mechanical ventilation for asthma/wheezing;
    d. One hospitalization or ED visit for asthma/wheezing within six months of Screening;

e. Forced expiratory volume in one second (FEV_1) <80% of predicted or FEV_1/forced vital capacity (FVC) <75%, with or without controller medications (only for participants who are aged seven years or older and are able to perform spirometry);
f. Inhaled corticosteroid (ICS) dosing of >500 mcg daily fluticasone (or equivalent ICS based on the CoFAR Inhaled Corticosteroid Equivalency Tables MOP).

7. History of severe anaphylaxis to participant-specific foods that will be used in this study, defined as neurological compromise or requiring intubation
8. Treatment with a burst of oral, intramuscular (IM), or intravenous (IV) steroids of more than two days for an indication other than asthma/wheezing within 30 days of Screening
9. Currently receiving oral, IM, or IV corticosteroids, tricyclic antidepressants, or β-blockers (oral or topical)
10. Past or current history of eosinophilic gastrointestinal (GI) disease within three years of Screening
11. Past or current history of cancer, or currently being investigated for possible cancer
12. Previous adverse reaction to omalizumab
13. Past or current history of any immunotherapy to any of the foods being treated in this study (e.g., OIT, sublingual immunotherapy [SLIT], EPIT) within 6 months of Screening
14. Treatment with monoclonal antibody therapy, such as omalizumab (Xolair®), dupilumab (Dupixent®), benralizumab (Fasenra™), mepolizumab (Nucala®), reslizumab (Cinqair®), or other immunomodulatory therapy within six months of Screening
15. Currently on "build-up phase" of inhalant allergen immunotherapy (i.e., has not reached maintenance dosing). Individuals tolerating maintenance allergen immunotherapy can be enrolled
16. Inability to discontinue antihistamines for the minimum wash-out periods required for SPTs or OFCs
17. Current participation in another therapeutic or interventional clinical trial or participation within 90 days of Screening
18. Use of investigational drugs within 24 weeks of Screening
19. Pregnant or breastfeeding, or intending to become pregnant during the study or within 60 days after the last dose of omalizumab or placebo for omalizumab
20. Has a first-degree relative already enrolled in the study
21. Past or current medical problems (e.g., severe latex allergy), history of other chronic diseases (other than asthma/wheezing, AD, or rhinitis) requiring therapy (e.g., heart disease, diabetes), findings from physical assessment, or abnormalities in clinical laboratory testing that are not listed above, which, in the opinion of the PI, 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

5.1.1 Omalizumab

As outlined in the current Investigator Brochure for Omalizumab (Xolair®), identified risks of omalizumab (causality has been established with omalizumab) include anaphylaxis, serum sickness, Eosinophilic Granulomatosis with Polyangiitis (EGPA or Churg-Strauss Syndrome), hypereosinophilic syndrome, and thrombocytopenia; potential risks of omalizumab include malignancies, arterial thrombotic events (ATEs), and antibody formation to omalizumab.

5.1.1.1 Anaphylaxis

Anaphylaxis has been reported to occur after administration of omalizumab in clinical trials and in post-marketing spontaneous reports. Anaphylactic reactions were rare in clinical trials (0.1%) and estimated as 0.2% from post-marketing reporting. The reported signs and symptoms included, but were not limited to, bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been reported as life threatening.

5.1.1.2 Serum Sickness

Serum sickness and serum sickness–like reactions, which are delayed allergic type III reactions, have rarely been seen in patients treated with humanized monoclonal antibodies including omalizumab in the post-approval use. The onset has typically been one to five days after administration of the first or subsequent injections, also after long duration of treatment. Symptoms suggestive of serum sickness include arthritis/arthralgia, rash (urticaria or other forms), fever, and lymphadenopathy.

5.1.1.3 EGPA (Churg-Strauss Syndrome) and Hypereosinophilic Syndrome

Patients with severe asthma may rarely present with systemic hypereosinophilic syndrome or EGPA (Churg-Strauss Syndrome). In rare cases, patients on therapy with anti-asthma medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. These events are commonly associated with the reduction of oral corticosteroid therapy and alerted to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, paranasal sinus abnormalities, cardiac complications, and/or neuropathy.

5.1.1.4 Thrombocytopenia

In nonclinical studies, a dose-dependent and reversible circulating platelet reduction was observed. In clinical studies, few patients experienced platelet counts below the lower limit of the normal laboratory range. None of these changes was associated with bleeding episodes or a decrease in hemoglobin.

5.1.1.5 Malignancies

During initial clinical trials in adults and adolescents 12 years of age and older with allergic asthma, there was a numerical imbalance in cancers arising in the active treatment group compared with the control group. The number of observed cases was uncommon (<1/100) in both the active and the control group. In a subsequent observational study (EXCELS) comparing 5007 omalizumab-treated patients and 2829 non omalizumab-treated patients followed for up to five years, the incidence rates of primary malignancies per 1000 patient years were 16.01 (295/18,426 patient years) and 19.07 (190/9963 patient years), respectively, which does not indicate an increased malignancy risk (rate ratio 0.84, 95% CI: 0.62-1.13). In a further analysis of randomized double-blind placebo-controlled clinical trials, including 4254 patients on omalizumab and 3178 patients on placebo, omalizumab treatment was not associated with an increased malignancy risk based on incidence rates per 1000 patient years of 4.14 for omalizumab-treated patients and 4.45 for placebo patients (rate ratio 0.93, 95% CI: 0.39-2.27). The overall observed incidence rate of malignancy in the omalizumab clinical trial program was comparable to that reported in the general population. There were no cases of malignancy in clinical trials in allergic asthma in the 6 to <12 years of age group with omalizumab; there were two cases of malignancy in the control group (medulloblastoma and nephroblastoma).

In the Phase III CIU program (733 patients enrolled and receiving at least one dose of omalizumab), there was one case of malignancy in the placebo group and one case in the omalizumab 300 mg group in a patient with a preexisting history.

5.1.1.6 Arterial Thrombotic Events

In controlled clinical trials in allergic asthma and during interim analyses of EXCELS (an observational study), a numerical imbalance of ATEs was observed. ATEs included stroke, transient ischemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause). The results from EXCELS revealed the rate of ATEs per 1,000 patient years was 7.52 (115/15,286 patient years) for omalizumab treated patients and 5.12 (51/9,963 patient years) for control patients. Although there was no consistent evidence of an association between omalizumab use and risk of ATEs, the 95% CIs were wide and could not definitively exclude an elevated risk.

5.1.1.7 Antibody Formation to Omalizumab

Omalizumab is a humanized monoclonal anti-IgE antibody. The formation of anti-drug antibodies (also called ADAs) after omalizumab administration is a rare event. There were three ADA-positive cases out of 23,375 serum samples tested in the Allergic Asthma and CIU programs following omalizumab administration. These cases were not associated with any severe AEs.

There was no case of drug-induced ADAs recorded across the entire CIU development program.

5.1.2 Multi-Allergen Oral Immunotherapy

Multi-allergen OIT in this study will consist of any of the following foods: peanut, milk, egg, wheat, cashew, hazelnut, and walnut. The major expected risks of Multi-allergen OIT are similar to the risks of single allergen OIT. Additionally, the risks are similar across each of the seven food allergens and can occur during build-up or maintenance. Specifically, the build-up and daily maintenance doses of OIT may cause allergic symptoms including sneezing, rhinorrhea, urticaria, angioedema, flushing, ocular, nasal, oral and/or throat pruritus, throat tightness without or with hoarseness, nausea, vomiting, abdominal pain and discomfort, stridor/laryngeal edema, cough, wheezing and/or shortness of breath, including symptoms of severe anaphylaxis such as severe stridor/laryngeal edema, bronchospasm/wheezing, hypotension, and altered mental status. Other allergy-associated AEs are flares of eczema and eosinophilic esophagitis (EoE).

In patients with food allergy, there have been many OIT studies performed using procedures and OIT dosing similar to those proposed in this study. The safety profile for OIT has been evaluated across the studies, and, approximately 80%, 15% and <1% of the participants are expected to have mild, moderate or severe symptoms, respectively, at some point in their dosing with the immunotherapy.[7] Most AEs have been allergy-related, predictable, and reversible. Of note, oral pruritus is a common local AE with single- or Multi-allergen OIT that is typically mild and resolves without treatment.[6,13,20]

The most common AE related to single and Multi-allergen OIT is abdominal pain.[6,21] OIT-related abdominal pain is most common during the Build-Up Phase, however, it could occur at any point during OIT therapy.[22] Often, abdominal pain ceases with treatment with antacids and/or antihistamines, or with a temporary reduction in dose. However, persistent GI symptoms (such as abdominal pain, nausea, heart-burn, and vomiting) might be symptoms of EoE.

EoE is a chronic immune disorder mediated by antigen exposure and is defined by clinical and histopathological criteria, in the absence of other causes. Clinical symptoms may include the following: reflux-like symptoms, abdominal pain and/or vomiting that is refractory to reflux treatment, dysphagia and/or food impaction. These symptoms occur in conjunction with histological evidence of dense eosinophilic infiltration of the mucosa [>15 eosinophils per high-power field (eos/hpf)]. A meta-analysis[23] and a recent retrospective review[24] estimated the incidence of EoE during OIT at rates of 2.7% and 5.1%, respectively. However, OIT-induced EoE-like symptoms resolve

with discontinuation of OIT in most affected patients, so that individuals do not undergo an esophagogastroduodenoscopy with esophageal biopsies. A definitive diagnosis of EoE cannot be made without histologic evidence.[25,26]

Symptoms related to severe anaphylaxis include:

- respiratory — stridor/laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea
- GI — significant severe abdominal pain/cramping/repetitive vomiting
- neurological — change in mental status
- circulatory — hypotension

5.1.2.1 Initial Dose Escalation and Dose Build-Up

The IDE Visit followed by the Build-Up Phase was developed based on published studies and the CoFAR CRU Investigators' previous experience with Multi-allergen OIT. Although there are few in number, previous Multi-allergen OIT studies have not reported significant clinical reactions during the Build-Up Phase of treatment.[6,7] The build-up and daily maintenance doses of Multi-allergen OIT may cause allergic symptoms including sneezing, rhinorrhea, urticaria, angioedema, flushing, flares of eczema, nausea, vomiting, abdominal discomfort, cough, wheezing, shortness of breath, ocular, nasal, oral, or throat pruritus, in addition to severe anaphylaxis. While a severe outcome of death is theoretically possible, this has not occurred during other dose escalations supervised by the PIs' participating in this study. The likelihood of a participant experiencing any allergic symptoms or severe reactions will be lessened by initiating OIT dosing at extremely small amounts of Multi-allergen OIT and by increasing doses during the Build-Up Phase under observation in a clinical setting until the maintenance dose is achieved. If a participant has an allergic reaction, they may need oral, IM, or IV medications. CRU staff trained in the diagnosis and treatment of allergic reactions and anaphylaxis, including a trained physician available within 60 seconds, as well as emergency medications and resuscitation equipment, will be available to treat any allergic reactions.

5.1.3 Multi-Allergen Oral Immunotherapy plus Omalizumab

In Phase 1 Multi-allergen OIT studies, participants who received omalizumab had similar symptoms to those participants who did not receive omalizumab; the frequency of the symptoms was less in the group who received omalizumab.[7] These results were validated in a recent Phase 2 pilot study of 48 children undergoing Multi-allergen OIT with or without omalizumab; those who received omalizumab-facilitated Multi-allergen desensitization had significantly fewer doses associated with an AE than those who had placebo for omalizumab (27% vs 68% when administered with Multi-allergen OIT) during build-up.[6] In particular, 22% of OIT doses in omalizumab participants and 54% of doses for placebo participants caused GI side effects; 0 and 1 percent of doses caused respiratory side effects in the omalizumab and placebo arms, respectively.

5.2 Risks of Other Protocol Specified Medications

Treatment of individual acute allergic reactions during Multi-allergen OIT therapy, OFCs, and open feedings should be with either an antihistamine and/or epinephrine, along with IV fluids, β-adrenergic agonist (e.g., albuterol), oxygen, and/or oral or topical steroids, as indicated. Risks of these common medications are summarized below:

- Antihistamines: drowsiness, dizziness, constipation, stomach upset, blurred vision, or dry mouth/nose/throat.

- Epinephrine: tachycardia, palpitations, nervousness, sweating, nausea, vomiting, trouble breathing, headache, dizziness, anxiety, tremors, or pale skin.
- β-adrenergic agonist: nervousness, shaking (tremor), headache, or dizziness.
- Oral steroids: nausea, vomiting, loss of appetite, heartburn, trouble sleeping, increased sweating, or acne.
- Topical steroids: itching, burning, erythema, skin hypopigmentation, skin thinning, striae, bruising, telangiectasias.

5.3 Risks of Study Procedures

5.3.1 Oral Food Challenges

OFCs (including DBPCFCs and open OFCs) may induce an allergic response regardless of the stage of the study during which they are conducted. Allergic reactions range from mild to severe and include life-threatening anaphylactic reactions and death; however, the risk of a severe allergic reaction is reduced by initiating the OFC with a very small amount of the food, gradually increasing the dose over a prolonged time period, and stopping the OFC at the first sign of a reaction. Symptoms usually are short-lived (less than two hours) and may include an itchy skin rash, nausea, abdominal discomfort, vomiting and/or diarrhea, stuffy "runny" nose, and sneezing and/or wheezing. Anaphylaxis, the most severe allergic reactions, may include respiratory symptoms (both laryngeal edema and bronchospasm/wheezing), circulatory symptoms (hypotension), and neurologic symptoms (altered mental status). While there has been one documented death of a child undergoing an OFC in a clinical setting, this has not occurred to date during medically supervised OFCs in highly trained research settings.[27] If a participant has an allergic reaction during an OFC, they may need oral, IM, or IV medications. CRU staff trained in the diagnosis and treatment of allergic reactions and anaphylaxis, including a trained physician available within 60 seconds, as well as emergency medications and resuscitation equipment, will be available throughout the OFC to treat any allergic reactions.

5.3.2 Open Feedings

While the amount of food given during an open feeding will be determined based on the amount consumed in the last OFC without dose-limiting symptoms, an open feeding still may induce an allergic response to food eaten. Allergic reactions range from mild to severe and include life-threatening anaphylactic reactions and death. Mild and moderate symptoms are usually short lived (less than two hours) and may include an itchy skin rash, nausea, abdominal discomfort, vomiting and/or diarrhea, stuffy "runny" nose, and sneezing and/or wheezing. Anaphylaxis, the most severe allergic reactions, may include respiratory symptoms (both laryngeal edema and bronchospasm/wheezing), circulatory symptoms (hypotension), and neurologic symptoms (altered mental status). If a participant has an allergic reaction during the open feeding, they may need oral, IM, or IV medications. CRU staff trained in the diagnosis and treatment of allergic reactions and anaphylaxis, including a trained physician available within 60 seconds, as well as emergency medications and resuscitation equipment, will be available throughout the open feeding to treat any allergic reactions.

5.3.3 Skin Prick Tests

Participants may experience mild to moderate pruritus or local discomfort at the sites of skin pricks with allergen and the positive control. Usually, the allergen-induced wheal and flare responses resolve within one to two hours, but rarely a participant may have local swelling that takes two to three days to clear entirely. Rarely skin testing will cause the participant being tested to have systemic allergic symptoms. These symptoms may include sneezing, ocular pruritus and tearing, rhinorrhea and/or generalized pruritus or urticaria. Treatment with oral antihistamines is available and is effective. Very rarely, some individuals with these types of symptoms may develop a serious,

systemic allergic reaction, but no deaths from prick skin testing using standard dosing techniques have been reported in 50 years. During the testing, a trained physician will be available within 60 seconds, along with the appropriate drugs and equipment, to provide treatment of anaphylactic reactions.

5.3.4 Blood Draw

The risks associated with drawing blood include discomfort, bleeding, bruising or swelling where the needle is inserted, local infection, and, in rare cases, syncope. A local skin anesthetic (i.e., topical lidocaine/prilocaine cream) may be placed on the skin before the blood draw to reduce the pain of the stick. Side effects from this agent (mainly skin rash) may occur, including allergic reactions. The National Institutes of Health (NIH) guidelines for blood collection (amount and frequency based on age and weight) will be followed.

5.3.5 Intravenous Insertion

Heparin/saline lock or IV may be inserted during an OFC, dose escalation, IDE, or dose build-up at the PI's discretion (e.g., participant at high risk of reaction or severe reaction based upon prior history and medical history). The risks associated with IV insertion include discomfort, bleeding, bruising or swelling where the IV is inserted, local infection, and, in rare cases, syncope. A local skin anesthetic (i.e., topical lidocaine/prilocaine cream) may be placed on the skin before the IV insertion to reduce the pain of the placement. Side effects from this agent (mainly skin rash) may occur, including allergic reactions.

5.3.6 Spirometry and Peak Expiratory Flow Measurements

Spirometry and Peak Expiratory Flow (PEF) measurements will be performed by trained and certified CRU staff according to American Thoracic Society standards as performed routinely in usual care as part of subspecialist management of asthma.

Spirometry and PEF measurements can cause coughing or presyncope, which will go away shortly after the test is finished.

For spirometry, participants may be asked to withhold their asthma medications for 8-24 hours before the procedures depending on the medication. Withholding of asthma medications before testing may cause a worsening of asthma symptoms. These medications and withholding instructions are specified in the MOP. Participants will be informed that they can take their asthma medications if needed. If participants do take their medications, the procedure will only be rescheduled, as described in the MOP.

5.3.7 Stool, Urine, and Saliva Sample Collection

There are no significant risks associated with stool, urine, and saliva sample collection.

5.3.8 Questionnaires

There is a possibility that the participant and/or parent/legal guardian may find questions too personal. A participant and/or parent/legal guardian may refuse to answer any questions that make them feel uncomfortable. There is also a possibility that answers may be read by others; however, participants' records are carefully protected so this is very unlikely. See Section 16.4 for more information on confidentiality.

5.4 Potential Benefits

The potential benefits of this study include the possibility that the treatments will:

- reduce sensitivity to peanut and other foods a study participant is allergic to;
- diminish allergic reactions following an accidental ingestion of foods a study participant is allergic to; and

- allow introduction of allergenic foods into the diet.

6 Investigational Agent/Intervention

6.1 Investigational Agents/Interventions

6.1.1 Investigational Agent #1: Omalizumab and Placebo for Omalizumab

6.1.1.1 Formulation, Packaging, and Labeling

Xolair® (omalizumab) is a recombinant humanized IgG1 monoclonal antibody that binds to the FcεR1 binding epitope of human IgE, preventing human IgE from binding to its specific high-affinity receptors on mast cells and basophils.

Fully blinded, packaged, and labeled Xolair® (omalizumab) liquid in pre-filled syringes (PFS) and placebo for omalizumab PFS will be provided to DAIT/NIAID by Genentech Inc.

PFS of omalizumab and placebo for omalizumab will be provided to each CRU as 75 mg and 150 mg dosage forms.

6.1.1.2 Dosage, Preparation, and Administration

Each participant's dose (for the duration of the study) will be calculated using the participant's weight at the Screening Visit and total IgE level (as measured at the Screening Visit or within three months of the Screening Visit and not the total IgE level that is drawn immediately before the first Screening DBPCFC Visit), according to the omalizumab dosing table (see Appendix 2). The proposed omalizumab dosing table in Appendix 2 differs from the dosing of omalizumab recommended in the current Investigator Brochure for Omalizumab (Xolair®) because of the differences in study population. The omalizumab dosing table presented in the current Investigator Brochure for Omalizumab (Xolair®) is intended for patients with asthma down to the age of 6 years. The target patient population for this study is younger and is anticipated to have body weight and baseline IgE combinations that are not covered in the current Investigator Brochure for Omalizumab (Xolair®). The proposed omalizumab dosing table is informed by an algorithm that targets 0.016 mg/kg/IgE/4 weeks while not exceeding a 20 mg/kg dose in a single administration and represents an extension of the asthma algorithm.

Omalizumab and placebo for omalizumab PFS will be blinded and identical in liquid content color, PFS type, and labeling; however, due to the different liquid viscosity between omalizumab and placebo for omalizumab, administration will be performed by CRU staff whom will not be involved in any other aspect of the study that would threaten blinding and/or that could be influenced by an unblinded CRU staff member performing the procedure.

A full description of the PFS for both omalizumab and placebo for omalizumab is provided in the OUtMATCH Pharmacy Manual – Omalizumab & Placebo for Omalizumab Pre-Filled Syringes (PFS) Investigational Product(s) Storage, Preparation, and Dispensing. If any abnormalities are noted with the PFS (either in appearance or in administration), such abnormalities should be reported to DAIT/NIAID as per the current OUtMATCH Pharmacy Manual – Omalizumab & Placebo for Omalizumab Pre-Filled Syringes (PFS) Investigational Product(s) Storage, Preparation, and Dispensing.

6.1.2 Investigational Agent #2: Multi-allergen Oral Immunotherapy and Placebo for Multi-allergen Oral Immunotherapy

6.1.2.1 Formulation, Packaging, and Labeling

Multi-allergen OIT will be any of the following drug products: peanut, milk, egg, wheat, cashew, hazelnut, and walnut (all food protein flours). Oat flour will be used for placebo for Multi-allergen OIT. Each dosage of each active drug product will be supplied to CRUs as measured flour packaged in one-ounce open label soufflé portion cups for the conduct of Protocol CoFAR-11. Each dosage of the placebo drug product will be supplied to CRUs as measured flour packaged in two-ounce open label soufflé portion cups. OIT products will be manufactured by the Sean N. Parker Center for Allergy & Asthma Research with Stanford University (Mountain View, CA) and provided to DAIT/NIAID for use in Protocol CoFAR-11. Each dosage of the final blinded OIT product (active/placebo) will be dispensed in a two-ounce blind labeled soufflé portion cup.

6.1.2.2 Dosage, Preparation, and Administration

CRU staff will prepare a prescription for each participant for the appropriate dose of each of the allergens. The unblinded CRU pharmacist/pharmacy staff or Sponsor-approved designated staff will compound the appropriate allergens and the unblinded CRU pharmacist/pharmacy staff will dispense the Multi-allergen OIT dose or placebo for Multi-allergen OIT dose in a blinded fashion (using the provided blinded labels for the study) to the PI (or designated CRU staff). OIT will be administered to the participant orally in an age-appropriate food vehicle, as described in the associated MOP. Dosage will be administered according to the protocol.

A full description of the Multi-allergen OIT/placebo for Multi-allergen OIT will be provided in the associated pharmacy manual. If any abnormalities are noted with these products (either in appearance or in administration), such abnormalities should be reported to DAIT/NIAID as per the associated pharmacy manual.

6.2 Drug Accountability

Under Title 21 of the Code of Federal Regulations (CFR) (21CFR §312.62), the PI will maintain adequate records in a chronological order of the disposition of the IP, 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.

The unblinded CRU pharmacist/pharmacy staff is to maintain records for receipt, storage, use, and disposition. An IP accountability log will be kept current for each participant. Additionally, an overall CRU inventory and accountability of the IP is to be maintained. This log will contain the identification of each participant and the date and quantity of drug dispensed.

All records regarding the disposition of the IP will be available for inspection by the study monitor.

6.3 Assessment of Participant Compliance with Investigational Agent

Omalizumab and placebo for omalizumab will be administered subcutaneously by CRU staff and adherence will be determined by the number of injections received over the expected number of injections based on the protocol.

Throughout Stage 2 and 3, each participant and/or parent/legal guardian will maintain diary logs to document daily OIT dosing (see Section 8.1.7). Additionally, each participant and/or parent/legal guardian will be instructed to return all used (empty packages) and unused Multi-allergen OIT/placebo for Multi-allergen OIT at each visit. Records of return, including open and unused product, will be recorded by the unblinded CRU pharmacist/pharmacy staff and CRU staff.

Assessment of participant compliance with administration of IP will be reviewed regularly.

6.4 Toxicity Prevention and Management

6.4.1 Omalizumab

6.4.1.1 Anaphylaxis

Anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of omalizumab. Anaphylaxis has occurred as early as after the first dose of omalizumab, but also has occurred beyond one year after beginning regularly administered treatment. The events were reported to occur predominantly within the first two hours post-dose, with few reports occurring as far as >36 hours post-dose.

The PI will be prepared to manage anaphylaxis that can be life-threatening; medications for the treatment of anaphylactic reactions will be available at the bedside. The American College of Allergy, Asthma, and Immunology guideline on the observation period after omalizumab administration[28] recommends two hours of monitoring in the clinic after the first three injections and 30 minutes or an appropriate time agreed upon by the individual patient and healthcare professional for subsequent injections. However, a delayed onset of symptoms and protracted progression of anaphylaxis should be taken into account when administering omalizumab.[29] Based on this guideline, participants will be observed for at least two hours after the first three doses and at least 30 minutes after subsequent doses in Stage 1, Stage 1 OLE as well as in Stage 2. Taking into account the time to onset of anaphylaxis seen in clinical trials and post-marketing spontaneous reports, some participants may require longer observation periods, depending on the PI's judgment. Participants will also be informed of the signs and symptoms of anaphylaxis and they will be instructed to seek immediate medical care should signs or symptoms occur.

6.4.1.2 Serum Sickness

Although rare, onset of serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, has been seen one to five days after administration of the first or subsequent injections, as well as after long duration of treatment. Symptoms suggestive of serum sickness include arthritis/arthralgia, rash (urticaria or other forms), fever, and lymphadenopathy. Antihistamines and corticosteroids may be useful for treating this disorder.

Participants will be informed and advised to report any suspected symptoms of serum sickness-like reactions. The PI may consider stopping omalizumab or placebo for omalizumab if a participant develops this constellation of signs and symptoms.

6.4.1.3 EPGA (Churg-Strauss Syndrome) and Hypereosinophilic Syndrome

Patients with severe asthma may rarely present systemic hypereosinophilic syndrome or EGPA (Churg-Strauss Syndrome). In rare cases, patients on therapy with anti-asthma medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. These events are commonly associated with the reduction of oral corticosteroid therapy and alerted to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, paranasal sinus abnormalities, cardiac complications, and/or neuropathy.

Abrupt discontinuation of systemic or ICS after initiation of omalizumab therapy is not recommended. Decreases in corticosteroids should be performed under the direct supervision of the PI and may need to be performed gradually.

6.4.1.4 Management of Drug Induced Liver Injuries

Large clinical trial and post marketing data did not reveal any hepatotoxic potential for omalizumab. Liver injury has not been described/listed as a risk associated with omalizumab. However, as a general precautionary measure 1) if the participant's aspartate aminotransferase (AST) or alanine aminotransferase (ALT) is >8 times the upper limit of normal (ULN), or 2) if the participant's AST or ALT is >3 times the ULN and total bilirubin >2 times the ULN, or clinical jaundice occurs, omalizumab or placebo for omalizumab will be held while liver tests are repeated. If the liver function test abnormality is confirmed, a referral for further evaluation for causes for the liver test abnormality will be initiated. During this evaluation, the participant's involvement in the study will be put on hold (no study drugs will be given or study procedures performed). If the abnormality is found to be unrelated to study drug or study procedure, has fully resolved, and is not expected to recur, the participant may restart the stage they were in when the event occurred. Otherwise, the participant will be withdrawn from the study. Guidelines for restarting the stage are provided in the OUtMATCH MOP.

6.4.1.5 Thrombocytopenia

Rare cases of thrombocytopenia have been reported in clinical studies and in post-marketing studies. As a general precautionary measure since the trial involves young children, a CBC will be obtained every three months to evaluate the platelet count. If clinically significant thrombocytopenia is observed, then omalizumab or placebo for omalizumab will be held while the platelet count is repeated. If clinically significant thrombocytopenia is confirmed, the participant will be withdrawn and a referral for further evaluation for thrombocytopenia will be initiated.

6.4.2 Multi-allergen Oral Immunotherapy

6.4.2.1 Reactions during Initial Dose Escalation

Participants may develop symptoms during IDE.

For *oropharyngeal pruritus*, the action should be to continue the normal IDE dosing in 15-30 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 continue the normal IDE dosing in 30-60 minutes or to discontinue IDE, depending on the PI'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 IDE should be discontinued and the appropriate rescue medications (see Section 7.4) administered.

For *severe symptoms*, defined as:

- respiratory —stridor/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 IDE should be discontinued and the appropriate rescue medications (see Section 7.4) administered.

If the participant requires treatment for symptoms with antihistamines on one occasion during IDE, then the rest of the IDE protocol may be followed. If the participant requires more than one medication (e.g., albuterol, diphenhydramine, epinephrine, or others) or multiple doses of antihistamines, the IDE should be discontinued and the participant will be considered an IDE failure if they did not tolerate the minimum total dose of 9 mg protein during the IDE in Stage 2 or the minimum dose of 3 mg protein of the food during the IDE in Stage 3.

The PI will be available for questions and decision making for any questions related to IDE dosing at all times.

All participants will be observed for a minimum of two hours following administration of the final dose and will be discharged only when deemed clinically stable by the PI.

6.4.2.2 Reactions during Build-Up or Maintenance Phase

To be eligible for a Dose Build-Up Visit, a participant cannot have active wheezing, peak flow <80% predicted, or a current flare of AD that contraindicates dose build-up in the clinical judgment of the PI. As needed, a participant will be maintained on their current dose until their flare of asthma or AD is resolved.

If a participant has a build-up dose in the CRU without symptoms, the action should be to continue per protocol with daily home OIT dosing at the tolerated dose with the next build-up visit two weeks later.

On the day of the Initial or Follow-Up Maintenance Dose Visit in the CRU, the participant may have the daily dose at home or in the CRU. If a participant has no symptoms, the action should be to continue per protocol with daily home OIT dosing at the tolerated dose with the next Follow-Up Maintenance Dose Visit eight weeks later. If the participant only experiences oropharyngeal pruritus during the administration of the daily dose, then the same dose can be repeated the next day at home and continued throughout the dose build-up or maintenance interval unless other symptoms begin to develop.

If the participant experiences mild symptoms (see Section 6.4.2.1) for 3-4 consecutive days, then the participant should return to the CRU for a 1-2 step dose reduction. If the dose is tolerated, the participant will remain on that dose for two weeks and then return to the CRU for dose build-up. If the dose is not tolerated, consultation with the PI is indicated.

If moderate symptoms (see Section 6.4.2.1) occur, the action should be to have the participant return to the CRU the next day (day 2) for OIT dosing with the same dose or a 1-2 step dose reduction, per PI discretion, under observation. If the dose on day 2 is tolerated in the CRU, the participant will continue on that daily home dose for the normal time interval per protocol. If the dose on day 2 is not tolerated in the

CRU, the participant should receive a 1-2 step dose reduction the next day (day 3) in the CRU. If the dose on day 3 is tolerated in the CRU, the participant will remain on that dose for two weeks and then return to the CRU for dose build-up. If the dose on day 3 is not tolerated in the CRU, the participant should receive a 1-2 step reduction the next day (day 4) in the CRU. If the dose of day 4 is tolerated in the CRU, the participant will remain on that dose for two weeks and then return to the CRU for dose build-up. If the dose on day 4 is not tolerated in the CRU, then a discussion with the PI will ensue to make a decision about whether to continue the participant on OIT in the study. If the participant is unable to return to the CRU for an observed dose on day 2 or 3 or 4, the PI will recommend that doses be skipped until the participant can be seen in the CRU.

If severe symptoms (see Section 6.4.2.1) occur, the action should be to treat the participant, and at the PI's discretion, either: 1) have them return to the CRU the next day (day 2) for OIT dosing with a 2-step dose reduction, or 2) discontinue OIT. If the participant tolerates the dose reduction, the participant will remain on that dose for two weeks and then return to the CRU for dose build-up. If the participant is unable to return to the CRU for an observed dose on day 2, the PI will recommend that doses be skipped until the participant can be seen in the CRU. A discussion with the PI may ensue to make a decision about whether to continue the participant on OIT in the study.

If a participant fails dose build-up after three consecutive (with 2-4 weeks between) attempts by Week 24, he/she will be considered a treatment failure.

For a completed dose build-up with no symptoms, participants should be observed for 30 minutes. For mild symptoms, participants should be observed for at least 30 minutes. For moderate to severe symptoms, the observation period should be based on symptoms and the treatment regimen needed to stabilize the participant, but at least 2 hours in length. Length of the observation period may be longer than the stated minimum times, per PI discretion.

If a participant has a severe allergic reaction 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, the participant will be withdrawn from the study (see Section 11.2).

For specific questions related to dose build-up or maintenance OIT dosing, the DAIT/NIAID Medical Monitor and the Protocol Chair(s) will be consulted.

6.5 Premature Discontinuation of Investigational Agent

Study therapy regimen may be prematurely discontinued for any participant for any of the reasons identified in Section 11.2. A participant who prematurely discontinues any of the investigational agents will follow end of study procedures as described in Section 11.4.

7 Other Medications

7.1 Concomitant Medications

7.1.1 Protocol-Mandated

Not applicable.

7.1.2 Other Permitted Concomitant Medications

Each participant may continue their usual medications, including those taken for asthma, allergic rhinitis and AD, during the study. However, each participant must be able to discontinue antihistamines prior to the SPTs and all OFCs. Regular topical steroid use is permitted at the time of a SPT.

7.2 Prophylactic Medications

No prophylactic medications are required; however, the investigator may choose to instruct the participant to take antihistamines prior to a dose of Multi-allergen OIT during study participation.

7.3 Prohibited Medications

Use of the following medications is prohibited during study participation:

1. Monoclonal antibodies except omalizumab, such as dupilumab (Dupixent®), benralizumab (Fasenra™), mepolizumab (Nucala®), reslizumab (Cinqair®), or other immunomodulatory therapy
2. Initiation of any immunotherapy such as OIT, SLIT, or EPIT (outside of that given to the participant for this study)
3. Oral β-blockers
4. Tricyclic antidepressants
5. Use of systemic cyclosporine, methotrexate, azathioprine, or mycophenolate and chronic use of systemic corticosteroids
6. Changes in aspirin desensitization therapy or initiation of new aspirin desensitization therapy
7. Investigational therapy other than study drug

A participant who uses prohibited medications during study participation will be withdrawn and will attend an Early Discontinuation Visit (see Section 8.9).

7.4 Rescue Medications

Participants must have epinephrine autoinjectors to use in the event of a severe reaction to one of the investigational agents because both Multi-allergen OIT and omalizumab (albeit rarely) may induce severe allergic reactions/anaphylaxis.

Life-threatening allergic reactions to food allergen may occur during OIT dosing, OFCs, and open feedings; epinephrine is used to treat these reactions. In addition, epinephrine has a unique use in food allergic reactions that are not life threatening. That is, injectable epinephrine is used early during allergic reactions to food allergens in order to prevent the progression of these allergic reactions (see Section 12.2.5).

A participant and/or parent/legal guardian must sign the Epinephrine Autoinjector Training Form and understand its use before the participant can receive the investigational agent.

Treatment of individual allergic reactions during Multi-allergen OIT therapy, SPT, and/or to local skin anesthetic (as applicable) used during the blood draw, will be with either an antihistamine and/or epinephrine, along with IV fluids, albuterol, and corticosteroids (including topicals), as indicated. All participants will be given a food allergy action plan to follow while in this study.

8 Study Procedures

8.1 Study Assessments

8.1.1 Vital Signs and Growth Parameters

The following vital signs and growth parameters will be collected at study visits prior to all study drug administrations unless otherwise noted:

- Weight
- Height
- Temperature
- Pulse Rate
- Respiratory Rate
- Blood Pressure (BP) – BP will only be collected for participants aged 2 years or older unless clinically indicated.

8.1.2 Medical History and Physical Examination

The participant's medical history will be obtained at the Screening Visit. Updates to the medical history (i.e., interim medical history) will be obtained at all subsequent visits.

The PI or licensed clinician on the CRU staff will perform a comprehensive physical examination at the Screening Visit, at the IDE Visit, and at each visit with an OFC or open feeding. The comprehensive exam will include skin, head, eyes, ears, nose, and throat (HEENT), respiratory, cardiovascular, GI, endocrine/metabolic, neurological, blood/lymphatic, and musculoskeletal evaluation. At all other visits, the PI or licensed clinician on the CRU staff will perform a limited physical examination, which will include skin, HEENT, respiratory, cardiovascular, GI evaluation, and a symptom assessment. A comprehensive or limited physical examination may be performed at an unscheduled visit as needed. Additional examinations may be completed at the PI's discretion.

Significant findings that are present prior to the start of the study must be included on the appropriate electronic case report form (eCRF). Significant findings that meet the definition of an AE must also be recorded on the AE eCRF.

8.1.3 Spirometry and Peak Expiratory Flow

Spirometry will be performed at the Screening Visit for participants who are age seven years or older and are able to perform spirometry. Spirometry will not be performed at any other visit. PEF will be performed at the Screening Visit for participants who are unable to perform spirometry, and at all OIT dosing visits, OFC visits, and unscheduled visits as needed. PEF will be attempted for participants aged four to six, but is not required if the participant is unable. PEF does not need to be attempted for participants younger than four and is not required.

8.1.4 SCORAD

The PI or certified CRU staff will assess the disease severity for participants with AD, as determined by the PI or licensed clinician on the CRU staff based on the current medical history and/or the physical exam, using SCORing Atopic Dermatitis (SCORAD), a standardized tool for assessing the extent or areas of the body affected by AD, disease intensity, and subjective symptoms of pruritus and sleep loss.

8.1.5 FAQLQ

The PI or CRU staff will assess quality of life using FAQLQ, a standardized and validated tool for assessing emotional impact, food anxiety, and social and dietary limitations in people with food allergy.

8.1.5.1 FAQLQ-PF

The PI or certified CRU staff will administer the FAQLQ-PF to parents/legal guardians of participants aged 0-12 years.

8.1.5.2 FAQLQ-CF

The PI or certified CRU staff will administer the FAQLQ-CF to children/adolescents aged 8-12 years with food allergy.

8.1.5.3 FAQLQ-TF

The PI or certified CRU staff will administer the FAQLQ-TF to adolescents aged 13-17 years.

8.1.5.4 FAQLQ-AF

The PI or certified CRU staff will administer the FAQLQ-AF to adults aged ≥18 years.

8.1.6 Questionnaires

The PI or certified CRU staff will administer questionnaires for the PI's assessment of inclusion/exclusion criteria and to collect participant information regarding:

1. Contact information
2. Demographics
3. Diet and food allergy history
4. GI symptoms[30]
5. Family history
6. Medication use
7. AEs
8. Stool Specimen Information
9. Monthly long-term follow-up questionnaires

8.1.7 Diaries

Each participant and/or parent/legal guardian will maintain electronic and/or paper diary logs throughout Stage 2, Stage 3 Rescue OIT, and for the first six months in Stage 3 Long-term follow-up with dietary consumption to collect OIT dosing, any reaction from at-home OIT dosing, use of concomitant medications, and food intake. CRU staff will have the capability to monitor participant compliance with diary completion.

8.1.8 Skin Prick Tests

Each participant will have SPTs performed to food and environmental allergens according to the MOP. Each participant will be required to withhold antihistamines for an appropriate length of time (five half-lives of the antihistamine being used) to limit interference with the results of the SPT. Positive (histamine) and negative (saline glycerin) controls will be placed to determine the validity of the test.

The following allergens will be tested:

- Food allergens: peanut, egg white, cow's milk, soy, wheat, sesame, tree nuts (cashew, English walnut, hazelnut, almond, pecan, pistachio, and Brazil nut)

- Environmental allergens: dust mite, cat, dog, Timothy grass, ragweed, oak, birch, Alternaria sp.

Oat will be tested by SPT for participants who have a suspected clinical reaction to oat since oat is used in the OFC material.

8.1.9 Oral Food Challenges: Double-Blind Placebo-Controlled Food Challenges and Open Oral Food Challenges

OFCs will be performed under direct medical supervision in the CRU or in an OFC area with emergency medications and CRU staff immediately available. OFCs will follow established study procedures. A dietitian will be available at each CRU to consult in providing an age-appropriate vehicle for the OFCs; OFC vehicles are not to be brought to the CRU by the participant and/or parent/legal guardian for use in the OFC.

OFC material consists of food protein flours (active) and oat flour (placebo) and will be prepared by the Manufacturing Facility for the Sean N. Parker Center for Allergy & Asthma Research with Stanford University and provided to DAIT/NIAID for use in Protocol CoFAR-11.

Prior to an OFC, each participant will withhold antihistamines for an appropriate length of time (five half-lives of the antihistamine being used) and each participant will be assessed as outlined in the CoFAR OFC Overview MOP to reduce risks and ensure a safe setting for conducting the OFC.

All OFCs at Screening and in Stages 1-2, including the OLE, will be DBPCFCs. In a DBPCFC, the participant and/or parent/legal guardian, as well as the CRU staff administering the OFC, will not know which OFC contains the food protein or the placebo. The blinded OFCs to food and placebo will be split and conducted on separate days. The Screening DBPCFC as well as all end of stage DBPCFCs may be conducted over four visits to accommodate OFCs to three foods and placebo; all blinded OFCs comprising each DBPCFC must occur within a maximum period of 28 days. If an additional Screening DBPCFC to other allergens is needed to identify one or two participant-specific foods, all blinded OFCs comprising the additional Screening DBPCFC must occur within a maximum period of 21 days after the fourth blinded OFC in the original Screening DBPCFC. Each participant will remain on the treatment assigned in a stage while completing the end of stage DBPCFC. A participant will not take a dose of Multi-allergen OIT/placebo for Multi-allergen OIT on the OFC days. Omalizumab or placebo for omalizumab injections may occur on the same day as an OFC as long as the injection occurs at least 30 minutes prior to the OFC to assess AEs.

Prior to randomization in Stage 1, the results of the Screening DBPCFC will be unblinded to determine eligibility.

The OFCs that are conducted in Stage 3 will be open OFCs. In an open OFC, placebo is not used and the participant and/or parent/legal guardian, as well as the CRU staff administering the open OFC, will know which food protein flour is used in each open OFC. The open OFCs will be conducted over a maximum of three visits to accommodate the three foods. A participant will not take a dose of rescue OIT or daily dietary consumption on the OFC days.

8.1.10 Open Feedings

Open feedings in Stage 3 will be performed under direct medical supervision in the CRU or in an OFC area with emergency medications and CRU staff immediately available. An open feeding will be performed if:

- a participant consumes a single dose of ≥600 mg protein of each food without dose-limiting symptoms during the participant's last OFC; or
- a participant has tolerated a target maintenance dose of ≥560 mg of protein for a food for eight weeks during the Maintenance Phase in rescue OIT.

The amount of food eaten at the open feeding will be based on the maximum quantity deemed to be safe, as determined by the participant's last OFC (see Table 3.1.5.1) or maintenance dose in rescue OIT (see Table 3.1.5.3e). During an open feeding, the participant will consume a portion of the food in a dietary form (e.g., two tablespoons of peanut butter) in an open setting in which all involved parties are aware of the identity of the food. The participant will be observed for a minimum of two hours after completing eating the food to assess if the food is tolerated. Open feedings to more than one food may occur on the same day with a two-hour waiting period between each food.

Participants who undergo long-term follow-up with dietary consumption of a food following completion of Stage 1 OLE or Stage 2 will remain on the treatment they were receiving until all open feedings are completed. Omalizumab or placebo for omalizumab injections may occur on the same day as an open feeding as long as the injection occurs at least 30 minutes prior to the open feeding to assess AEs. A participant will not take a dose of Multi-allergen OIT/placebo for Multi-allergen OIT/rescue OIT on the days the participant's open feedings are conducted.

8.2 Sample Collections

8.2.1 Blood Collection

Blood will be collected by peripheral venipuncture as per the schedule of events (Appendices 4-9) for:

1. Biomarkers assays
    a. Total IgE
    b. Total free IgE
    c. Allergen-specific IgE, IgG4, and IgA
    d. Basophil activation
2. PK sampling
3. Samples for mechanistic studies (see Section 9.2)

The blood collection should occur prior to initiating an OFC or IDE/up-dosing.

8.2.1.1 Blood Collection for Safety

Blood will be collected by peripheral venipuncture for safety at the Screening Visit and every three months during Stage 1, the OLE, Stage 2, and Stage 3 (only for participants still receiving omalizumab, placebo for omalizumab, or open label omalizumab from the previous stage) to assess:

1. CBC with differential
2. CMP

8.2.2 Stool Collection

Stool samples will be collected and stored for potential microbiome studies, specifically assessing the effects of the microbiome on OIT responses and/or the effects of OIT on the microbiome. Studies may also be conducted to assess other biologic outcomes that may be related to food allergy and the effects of the study's intervention.

A stool collection kit and specimen information questionnaire will be provided to the participant and/or parent/legal guardian at pre-specified visits. Instructions for sample collection, storage, and transportation will be provided in the MOP.

8.2.3 Urine Collection

Urine will be collected and stored for potential metabolomic studies to evaluate changes related to treatment with omalizumab and omalizumab-facilitated OIT. Instructions for the collection of urine samples will be provided in the MOP.

8.2.3.1 Urine Collection for Safety

8.2.3.1.1 Urinalysis

Urine for urinalysis will be collected at the Screening Visit and every three months during Stage 1, the OLE, Stage 2, and Stage 3 (only for participants still receiving omalizumab, placebo for omalizumab, or open label omalizumab from the previous stage).

8.2.3.1.2 Urine Pregnancy Testing

All females who have undergone menarche (or who undergo menarche during the study) will be required to have a urine pregnancy test at the Screening Visit and then routinely at study visits, as specified in the schedule of events for each stage of the study. If the result is positive, the participant will either not be eligible for enrollment or will be discontinued from the study. Additional urine pregnancy testing may be performed at the PI's discretion. Results of all pregnancy tests will be given to the caretaker (or participant if specified by IRB guidelines).

8.2.4 Saliva Collection

Saliva will be collected and stored for the possible assessment of food-specific IgA changes in relation to OIT. Instructions for the collection of saliva samples will be provided in the MOP.

8.3 Screening Visit

The research study will be explained in lay terms to the participant and/or parent/legal guardian of each potential participant. The participant or parent/legal guardian will sign an informed consent form before any study procedures are initiated; assent will be obtained as applicable. When the informed consent (and assent, if applicable) has been signed, the participant will be assigned a unique participant number.

The purpose of the Screening Visit is to confirm eligibility to enroll in the study.

The Screening Visit may occur over several days and the following procedures, assessments, and laboratory measures will be conducted to determine participant eligibility:

1. Informed Consent and assent, if applicable
2. Demographics
3. Vital Signs and Growth Parameters
4. Medical History
5. Comprehensive Physical Exam, including spirometry and PEF as applicable
6. Diet and Allergy Questionnaires
7. Concomitant Medications
8. SPT to food and environmental allergens
9. AEs
10. Blood Collection
    a. CBC with differential
    b. Total and allergen-specific IgE
    c. CMP
11. Urine Collection
    a. Urinalysis
    b. Urine Pregnancy Test (female participants of child-bearing potential)

A potential participant may rescreen at any time. Guidelines for rescreening participants are provided in the OUtMATCH MOP.

8.3.1 Screening Double-Blind Placebo-Controlled Food Challenge Visits

The Screening DBPCFC will be split and conducted on separate days. The Screening DBPCFC may be conducted over four visits to accommodate blinded OFCs to three foods and placebo; all blinded OFCs comprising the DBPCFC must occur within a maximum period of 28 days. The following procedures, assessments, and laboratory measures will be conducted to determine participant eligibility:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Comprehensive Physical Exam, including PEF
4. SCORAD for participants with AD (assessed on the first DBPCFC visit only)
5. Diet & Allergy Questionnaires
6. GI Symptoms Questionnaire
7. Concomitant Medications
8. Blinded OFC (see Table 3.1.1)
9. AEs

The following specimens will be collected prior to initiating the blinded OFC at the first Screening DBPCFC Visit.

10. Blood
    a. Total IgE
    b. Total free IgE
    c. Allergen-specific IgE, IgG4, and IgA
    d. Basophil activation
    e. PK sampling
    f. Samples for mechanistic studies

A stool collection kit and specimen information questionnaire will be given to the participant at the first Screening DBPCFC Visit. Participants will be instructed to return the stool collection kit and specimen information questionnaire no later than the Randomization Visit (Day 0).

In the event that a participant does not experience dose-limiting symptoms to two non-peanut foods and may be allergic to additional foods, such a participant may receive an additional DBPCFC consisting of up to two blinded OFCs to other non-peanut foods and one blinded OFC to placebo. The additional DBPCFC is only an option if the participant experienced dose-limiting symptoms to peanut and did not experience dose-limiting symptoms to placebo during the initial Screening DBPCFC. All blinded OFCs comprising this additional DBPCFC must occur within 21 days of the fourth blinded OFC in the original Screening DBPCFC.

A participant may be randomized once the assessment for all inclusion and exclusion criteria is complete and the participant is deemed eligible.

8.4 Stage 1

Appendix 4 provides the schedule of events for Stage 1.

Because the screening period may vary for each participant, the timing of blood and urine collections for safety during Stage 1 will based on the prior collection. Females who have undergone menarche (or who undergo menarche during the study) will have a urine pregnancy test monthly.

The following safety samples will be collected every three months:

1. Blood for Safety
    a. CBC with differential
    b. CMP
2. Urine for Safety
    a. Urinalysis

8.4.1 Randomization Visit (Day 0)

Each participant who demonstrates dose-limiting symptoms at a single dose of ≤100 mg of peanut protein and ≤300 mg protein of each of the two other foods during the Screening DBPCFC will be randomized 2:1 to receive omalizumab or placebo for omalizumab for 16-20 weeks.

The following procedures and assessments will be conducted at this visit:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Limited Physical Exam
4. Diet & Allergy Questionnaires
5. GI Symptoms Questionnaire
6. Family History Questionnaire
7. FAQLQ
8. Concomitant Medications
9. AEs
10. Randomization
11. Omalizumab or placebo for omalizumab administration

The following specimens will be collected:

12. Stool collection kit and specimen information questionnaire (if it has not been returned during the screening period)
13. Urine
14. Saliva

Participants will be observed in clinic for at least two hours after the first injection of omalizumab or placebo for omalizumab.

8.4.2 Omalizumab Injection Visits (Week 2 – Week 14)

Each participant will return to the CRU for omalizumab or placebo for omalizumab injections. Omalizumab injection visits may occur every two or four weeks, determined by the body weight in kilograms and total serum IgE level at the Screening Visit. Participants will be observed in clinic for at least two hours after the first three injections of omalizumab and at least 30 minutes for all subsequent injections in Stage 1.

The following procedures and assessments will be conducted at these visits:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Limited Physical Exam
4. Diet & Allergy Questionnaires
5. GI Symptoms Questionnaire
6. Concomitant Medications
7. AEs
8. Omalizumab or placebo for omalizumab administration

8.4.3 Double-Blind Placebo-Controlled Food Challenge Visits (Week 16 – Week 20)

At Week 16, each participant will complete a DBPCFC consisting of placebo and each of their three specific foods to a cumulative dose of 6044 mg protein of each food using the DBPCFC dosing schedule provided in Table 3.1.2. The DBPCFC may occur over four separate visits to accommodate OFCs to three foods and placebo; all blinded OFCs comprising the DBPCFC must occur within a maximum period of 28 days. Each participant will continue to receive omalizumab or placebo for omalizumab injections while all these blinded OFCs are completed. Omalizumab or placebo for omalizumab injections may occur on the same day as a blinded OFC as long as the injection occurs at least 30 minutes prior to the blinded OFC to assess AEs.

8.4.3.1 Initial Double-Blind Placebo-Controlled Food Challenge Visit (Week 16)

The following procedures and assessments will be conducted at the first DBPCFC Visit:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Comprehensive Physical Exam, including PEF
4. SCORAD for participants with AD
5. Diet & Allergy Questionnaires
6. GI Symptoms Questionnaire
7. FAQLQ
8. Concomitant Medications
9. SPT to peanut and two other food allergens
10. Blinded OFC (see Table 3.1.2)
11. AEs
12. Omalizumab or placebo for omalizumab administration (if needed)
13. Saliva Collection
14. Urine Collection
15. Blood Collection
    a. Total IgE
    b. Total free IgE
    c. Allergen-specific IgE, IgG4, and IgA
    d. Basophil activation
    e. PK sampling
    f. Samples for mechanistic studies

The blood and sample collection should occur prior to initiating the blinded OFC. If the blood collection for the safety labs coincides with the Week 16 blood collection, the priority, in terms of blood volume, is the safety labs.

8.4.3.2 Double-Blind Placebo-Controlled Food Challenge Visits (Week 17 – Week 20)

The following procedures and assessments will be conducted at the subsequent DBPCFC Visits:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Comprehensive Physical Exam, including PEF
4. Diet & Allergy Questionnaires
5. GI Symptoms Questionnaire
6. Concomitant Medications
7. Blinded OFC (see Table 3.1.2)
8. AEs
9. Omalizumab or placebo for omalizumab administration (if needed)

After the last DBPCFC Visit at Week 16-20, each participant will then continue to Stage 1 OLE or Stage 2 of the study.

8.5 Stage 1 Open Label Extension

Appendix 5 provides the schedule of events for Stage 1 OLE.

The timing of blood and urine collections for safety during Stage 1 OLE will be based on the prior collection. Females who have undergone menarche (or who undergo menarche during the study) will have a urine pregnancy test monthly.

The following safety samples will be collected every three months:

1. Blood for Safety
    a. CBC with differential
    b. CMP
2. Urine for Safety
    a. Urinalysis

8.5.1 Omalizumab Injection Visits (Stage 1 Open Label Extension Week 0 – Week 22)

Each participant will receive 24-28 weeks of treatment with open label omalizumab. The participant will continue to use the same omalizumab dosing frequency in the OLE as was used in Stage 1, which was determined by the body weight in kilograms and total serum IgE level at the Screening Visit. The first open label omalizumab injection visit in the OLE will be scheduled two or four weeks after the last omalizumab or placebo for omalizumab injection in Stage 1. Each participant will be observed in clinic for at least two hours after the first three injections of open label omalizumab in the OLE, and at least 30 minutes for all subsequent injections.

The following procedures and assessments will be conducted at each of the open label omalizumab injection visits:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Limited Physical Exam
4. Diet & Allergy Questionnaires
5. GI Symptoms Questionnaire
6. Interim Family History Questionnaire (Week 0 only)
7. FAQLQ (Week 0 only)
8. Concomitant Medications

9. AEs
10. Open label omalizumab administration

8.5.2 Double-Blind Placebo-Controlled Food Challenge Visits (Stage 1 Open Label Extension Week 24 – Week 28)

At Week 24, each participant will complete a DBPCFC consisting of placebo and each of their three specific foods to a cumulative dose of 8044 mg protein of each food using the DBPCFC dosing schedule provided in Table 3.1.2. The DBPCFC may occur over four separate visits to accommodate blinded OFCs to three foods and placebo; all blinded OFCs comprising the DBPCFC must occur within a maximum period of 28 days. Each participant will continue to receive open label omalizumab injections while all these blinded OFCs are completed. Omalizumab injections may occur on the same day as a blinded OFC with the injection occurring at least 30 minutes prior to the blinded OFC to assess AEs.

8.5.2.1 Initial Double-Blind Placebo-Controlled Food Challenge Visit (Stage 1 Open Label Extension Week 24)

The following procedures and assessments will be conducted at the first DBPCFC Visit:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Comprehensive Physical Exam, including PEF
4. SCORAD for participants with AD
5. Diet & Allergy Questionnaires
6. GI Symptoms Questionnaire
7. FAQLQ
8. Concomitant Medications
9. SPT to peanut and two other food allergens
10. Blinded OFC (see Table 3.1.2)
11. AEs
12. Open label omalizumab administration (if needed)
13. Blood Collection
    a. Total IgE
    b. Total free IgE
    c. Allergen-specific IgE, IgG4, and IgA
    d. Basophil activation
    e. PK sampling

The blood collection should occur prior to initiating the blinded OFC.

8.5.2.2 Double-Blind Placebo-Controlled Food Challenge Visits (Stage 1 Open Label Extension Week 25 – 28)

The following procedures and assessments will be conducted at the subsequent DBPCFC Visits:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Comprehensive Physical Exam, including PEF
4. Diet & Allergy Questionnaires
5. GI Symptoms Questionnaire
6. FAQLQ (conducted on the last DBPCFC Visit only)
7. Concomitant Medications
8. Blinded OFC (see Table 3.1.2)

9. AEs
10. Open label omalizumab administration (if needed)

Upon completion of the last DBPCFC Visit, each participant will be unblinded to the results of the DBPCFC at the end of Stage 1 OLE and will move to Stage 3 of the study.

8.6 Stage 2

Appendix 6 provides the schedule of events for Stage 2.

Open label omalizumab injections and omalizumab or placebo for omalizumab injections may occur on the same day as the IDE, Dose Build-Up, and Initial or Follow-Up Maintenance Dose Visits with an observation period between the injection and OIT dosing. The observation period will be at least two hours if the injection is one of the first three injections in Stage 2, and at least 30 minutes for all subsequent injections.

The timing of blood and urine collections for safety during Stage 2 will be based on the prior collection. Females who have undergone menarche (or who undergo menarche during the study) will have a urine pregnancy test monthly.

The following safety samples will be collected every three months:

1. Blood Collection for Safety
    a. CBC with differential
    b. CMP
2. Urine Collection for Safety
    a. Urinalysis

8.6.1 Omalizumab Injection Visits (Stage 2 Week 0 – 6)

Each participant will receive eight weeks of treatment with open label omalizumab. The participant will continue to use the same omalizumab dosing frequency in Stage 2 as was used in Stage 1, which was determined by the body weight in kilograms and total serum IgE level at the Screening Visit. The first open label omalizumab injection visit will be scheduled two or four weeks after the last omalizumab or placebo for omalizumab injection in Stage 1. Each participant will be observed in clinic for at least two hours after the first three injections of open label omalizumab in Stage 2, and at least 30 minutes for all subsequent injections.

The following procedures and assessments will be conducted at these visits:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Limited Physical Exam
4. Diet & Allergy Questionnaires
5. GI Symptoms Questionnaire
6. Interim Family History Questionnaire (Week 0 only; replacement participants who skip Stage 1 will be given the Family History Questionnaire used in Stage 1)
7. FAQLQ (Week 0 only)
8. Concomitant Medications
9. Open label omalizumab administration
10. AEs

A stool collection kit and specimen information questionnaire will be given to the participant at the last open label omalizumab injection visit before the IDE Visit. Participants will be instructed to return the stool collection kit and specimen information questionnaire no later than the IDE Visit.

8.6.2 Randomization

One week after starting Stage 2, participants will be randomized 1:1 to:

- Omalizumab-facilitated OIT: Open label omalizumab + Multi-allergen OIT for eight weeks, followed by placebo for omalizumab + Multi-allergen OIT for 44 weeks.
- Omalizumab + placebo OIT: Open label omalizumab + placebo for Multi-allergen OIT for eight weeks, followed by omalizumab + placebo for Multi-allergen OIT for 44 weeks.

8.6.3 Initial Dose Escalation Visit (Stage 2 Week 8)

Each participant randomized will receive daily oral therapy with Multi-allergen OIT or placebo for Multi-allergen OIT. During the IDE Visit, each randomized participant will be given Multi-allergen OIT or placebo for Multi-allergen OIT in incremental doses, increasing every 15 minutes, until a dose of 375 mg protein of Multi-allergen OIT for each allergen (1125 mg protein total food allergen dose) or placebo for Multi-allergen OIT is given (see Table 3.1.4a).

The following procedures and assessments will be conducted at this visit:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Comprehensive Physical Exam, including PEF
4. Diet & Allergy Questionnaires
5. GI Symptoms Questionnaire
6. Review Diaries
7. Concomitant Medications
8. Open label omalizumab administration (if needed)
9. Multi-allergen OIT or placebo for Multi-allergen OIT Dose Escalation (see Table 3.1.4a)
10. AEs
11. Collect stool collection kit and specimen information questionnaire (if it has not been returned before the IDE Visit)
12. Urine Collection
13. Saliva Collection
14. Blood Collection
    a. Total free IgE
    b. Allergen-specific IgG4 and IgA
    c. Basophil activation
    d. PK sampling
    e. Samples for mechanistic studies

The blood collection should occur prior to initiating the IDE. If the blood collection for the safety lab coincides with the Week 8 blood collection, the priority, in terms of blood volume, is the safety labs.

Each participant who tolerates a dose of at least 9 mg protein of Multi-allergen OIT or placebo for Multi-allergen OIT will remain in the study.

8.6.4 Initial Dose Build-Up Visit (Stage 2 Week 8 + 1 day)

The day after the IDE Visit, each participant will return to the CRU for an observed administration of Multi-allergen OIT or placebo for Multi-allergen OIT at the last dose the participant was able to tolerate on the IDE Visit.

The following procedures and assessments will be conducted at this visit:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Limited Physical Exam, including PEF
4. Diet & Allergy Questionnaires
5. GI Symptoms Questionnaire
6. Review Diaries
7. Concomitant Medications
8. Open label omalizumab administration (if needed)
9. Multi-allergen OIT or placebo for Multi-allergen OIT administration
10. AEs

If a participant cannot complete the Initial Dose Build-Up Visit within two days of the planned visit, he/she will be asked to repeat the IDE Visit. After completion of the Initial Dose Build-Up Visit, each participant will continue their daily OIT dosing at home over the next two weeks.

8.6.5 Dose Build-Up (Stage 2 Week 10 to Week 14 – Week 32)

Each participant will return to the CRU every two weeks for a dose escalation to a daily dose of 1000 mg protein of Multi-allergen OIT for each allergen (3000 mg protein total food dose) or equivalent placebo for Multi-allergen OIT (see Table 3.1.4b).

The following procedures and assessments will be conducted at each Dose Build-Up Visit:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Limited Physical Exam, including PEF
4. Diet & Allergy Questionnaires
5. GI Symptoms Questionnaire
6. Review Diaries
7. Concomitant Medications
8. Open label omalizumab or omalizumab/placebo for omalizumab administration (if needed)
9. Multi-allergen OIT or placebo for Multi-allergen OIT administration (see Table 3.1.4b)
10. AEs

A participant who does not tolerate a dose will be assessed for dose escalation (see Section 6.4.2). A participant who reaches a maximum tolerated daily dose of 1000 mg protein of Multi-allergen OIT for each allergen (3000 mg protein total food dose) or equivalent placebo for Multi-allergen OIT will take the same maintenance dose through Week 64. A participant who does not reach a maintenance dose of 250 mg protein of Multi-allergen OIT for each allergen (750 mg protein total food dose) during the Build-Up Phase will be considered a treatment failure and will be referred to an allergist for standard clinical care. A participant defined as a treatment failure will attend an Early Discontinuation Visit (see Section 8.9).

Each participant will complete a Build-Up Phase 8-24 weeks in length.

8.6.6 Initial Maintenance Dose Visit (Stage 2 Week 16 – Week 34)

Each participant will complete their Initial Maintenance Dose Visit two weeks after starting the maintenance dose during the Build-Up Phase.

The following procedures and assessments will be conducted at the Initial Maintenance Dose Visit:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Limited Physical Exam
4. PEF (only if OIT dosing occurs in clinic)
5. Diet & Allergy Questionnaires
6. GI Symptoms Questionnaire
7. Review Diaries
8. Concomitant Medications
9. Omalizumab or placebo for omalizumab administration (if needed)
10. Multi-allergen OIT or placebo for Multi-allergen OIT administration
11. AEs
12. Blood Collection
    a. Total free IgE
    b. Allergen-specific IgG4 and IgA
    c. Basophil activation
    d. Samples for mechanistic studies

If the blood collection for the safety lab coincides with the Initial Maintenance Dose Visit collection, the priority, in terms of blood volume, is the safety labs.

8.6.7 Follow-Up Maintenance Dose Visits (Stage 2 Week 24 – Week 58)

After the Initial Maintenance Dose Visit, the participant will return to the CRU every eight weeks for Follow-Up Maintenance Dose Visits. Because each participant will complete a Build-Up Phase 8-24 weeks in length, the number and timing of Follow-Up Maintenance Dose Visits may vary among participants.

The following procedures and assessments will be conducted at each Follow-Up Maintenance Dose Visit:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Limited Physical Exam
4. PEF (only if OIT dosing occurs in clinic)
5. Diet & Allergy Questionnaires
6. GI Symptoms Questionnaire
7. Review Diaries
8. Concomitant Medications
9. Omalizumab or placebo for omalizumab administration(if needed)
10. AEs

Multi-allergen OIT or placebo for Multi-allergen OIT administration may occur at a Follow-Up Maintenance Dose Visit, per PI discretion.

A stool collection kit and specimen information questionnaire will be given to the participant at the last visit before the first DBPCFC Visit at Week 60. Participants will be instructed to return the stool collection kit and specimen information questionnaire no later than the first DBPCFC Visit at Week 60.

The entire Maintenance Phase will comprise 26 to 44 weeks per participant.

8.6.8 Double-Blind Placebo-Controlled Food Challenge Visits (Stage 2 Week 60 – Week 64)

At Week 60, each participant will complete a DBPCFC consisting of placebo and each of their three specific foods to a cumulative dose of 8044 mg protein of each food using the DBPCFC dosing schedule provided in Table 3.1.2. The DBPCFC may occur over four separate visits to accommodate OFCs to three foods and placebo; all blinded OFCs comprising the DBPCFC must occur within a maximum period of 28 days. Each participant will continue to receive treatment as needed while all these blinded OFCs are completed. Omalizumab or placebo for omalizumab injections may occur on the same day as a blinded OFC as long as the injection occurs at least 30 minutes prior to the blinded OFC to assess AEs. Participants will be instructed to avoid taking their OIT dose on the same day as a blinded OFC.

8.6.8.1 First Double-Blind Placebo-Controlled Food Challenge Visit (Stage 2 Week 60)

The following procedures and assessments will be conducted at the first DBPCFC Visit:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Comprehensive Physical Exam, including PEF
4. SCORAD for participants with AD
5. Diet & Allergy Questionnaires
6. GI Symptoms Questionnaire
7. FAQLQ
8. Review Diaries
9. Concomitant Medications
10. Omalizumab or placebo for omalizumab administration (if needed)
11. SPT to peanut and two other food allergens
12. Blinded OFC (see Table 3.1.2)
13. AEs
14. Collect stool collection kit and specimen information questionnaire (if it has not been returned before the first DBPCFC Visit)
15. Saliva Collection
16. Urine Collection
17. Blood Collection
    a. Total IgE
    b. Total free IgE
    c. Allergen-specific IgE, IgG4, and IgA
    d. Basophil activation
    e. PK sampling
    f. Samples for mechanistic studies

The blood and sample collection should occur prior to initiating the blinded OFC. If the blood collection for the safety lab coincides with the Week 60 blood collection, the priority, in terms of blood volume, is the safety labs.

8.6.8.2 Double-Blind Placebo-Controlled Food Challenge Visits (Stage 2 Week 61 – Week 64)

The following procedures and assessments will be conducted at the subsequent DBPCFC Visits:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Comprehensive Physical Exam, including PEF
4. Diet & Allergy Questionnaires
5. GI Symptoms Questionnaire
6. FAQLQ (conducted on the last DBPCFC Visit only)
7. Review Diaries
8. Concomitant Medications
9. Omalizumab or placebo for omalizumab administration (if needed)
10. Blinded OFC (see Table 3.1.2)
11. AEs

Upon completion of the last DBPCFC Visit, each participant will be unblinded to the results of the DBPCFC at the end of Stage 2 and will move to Stage 3 of the study.

8.7 Stage 3 – Long-Term Follow-Up and Rescue Oral Immunotherapy

8.7.1 Long-Term Follow-Up with Dietary Consumption

Appendix 7 provides the schedule of events for long-term follow-up with dietary consumption of a food during Stage 3.

The timing of blood and urine collections for safety during Long-Term Follow-Up with Dietary Consumption will be based on the prior collection and is only needed for participants still receiving omalizumab, placebo for omalizumab, or open label omalizumab from the previous stage.

The following safety samples will be collected:

1. Blood for Safety
    a. CBC with differential
    b. CMP
2. Urine for Safety
    a. Urinalysis

Females who have undergone menarche (or who undergo menarche during the study) will have a monthly urine pregnancy test based on the prior collection until all open feedings are completed.

8.7.1.1 Open Feedings

Participants who start dietary consumption of a food in Stage 3 will undergo an open feeding of that food. Such participants will remain on the treatment they were receiving in Stage 1 OLE or Stage 2 until all open feedings are completed. If a participant is transitioning to dietary consumption from Stage 3 rescue OIT for more than one food allergen, refer to the OUtMATCH MOP for guidance on continuing the rescue OIT for the other rescue OIT food allergens. Open label omalizumab injections or omalizumab or placebo for omalizumab injections may occur on the same day as an open feeding as long as the injection occurs at least 30 minutes prior to the open feeding to assess AEs. A participant will not take a dose of Multi-allergen OIT/placebo for Multi-allergen OIT/rescue OIT on the days the participant's open feedings are conducted.

The following procedures and assessments will be completed during each open feeding:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Comprehensive Physical Exam (if there is more than one open feeding on a given day, a Limited Physical Exam will be performed prior to initiating each subsequent open feeding).
4. Diet & Allergy Questionnaires
5. GI Symptoms Questionnaire
6. Interim Family History Questionnaire (first open feeding only; do not collect if given on any other visit in Stage 3)
7. Review Diaries
8. Concomitant Medications
9. Open label omalizumab administration (if needed and participant was in Stage 1 OLE prior to the open feeding)
10. Omalizumab or placebo for omalizumab administration (if needed and participant was in Stage 2 prior to the open feeding)
11. Open Feeding
12. AEs

8.7.1.2 Safety Phone Calls or Emails During Long Term Follow-up with Dietary Consumption

All phone calls or emails may be combined with other study visits in Stage 3.

8.7.1.2.1 First 6 months in Long Term Follow-up with Dietary Consumption:

Following an observed initial open feeding of dietary food in the CRU, the participant will be called or emailed weekly for the first four weeks, every other week from six to sixteen weeks, and every two months until 6 months of Long-Term Follow-Up with Dietary Consumption has been completed. Additionally, if a participant is undergoing Rescue OIT and reaches the planned target maintenance dose allowing the transition to dietary consumption for the food, the participant will be called or emailed two and five weeks following the completion of the rescue OIT Initial Maintenance Dose Visit. The following procedures and assessments will be completed during each phone call or email:

1. Interim Medical History
2. Diet & Allergy Questionnaires
3. GI Symptoms Questionnaire
4. Review Diaries
5. Concomitant Medications
6. AEs

8.7.1.2.2 Month 7 and beyond of Long Term Follow-up with Dietary Consumption :

If a participant has been receiving long-term follow-up with dietary consumption for a food for over six months of follow-up in Stage 3, the participant will be contacted monthly by phone call or email. The following procedures and assessments will be completed during each monthly long-term follow-up phone call/email:

1. Interim Medical History

2. Monthly Long Term Follow-up Questionnaire
3. Diet & Allergy Questionnaires
4. GI Symptoms Questionnaire
5. Concomitant Medications
6. AEs

8.7.1.3 Long-Term Follow-Up Visits

The participant will return to the CRU every six months until they have a minimum of 12 months of follow-up in Stage 3 and will remain in Stage 3 until at least December 2022. The following procedures and assessments will be completed during each long-term follow-up visit:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Limited Physical Exam
4. SCORAD for participants with AD (first six-month visit only)
5. Diet & Allergy Questionnaires
6. GI Symptoms Questionnaire
7. FAQLQ (first six-month visit only)
8. Review Diaries (if needed)
9. Concomitant Medications
10. SPT to peanut and two other food allergens (first six-month visit and every 12 months thereafter)
11. AEs
12. Blood Collection (first six-month visit only)
    a. Total IgE
    b. Total free IgE
    c. Allergen-specific IgE, IgG4, and IgA
    d. Basophil activation

8.7.2 Long-Term Follow-Up with Avoidance

Appendix 8 provides the schedule of events for long-term follow-up with avoidance of a food during Stage 3.

Each participant who receives long-term follow-up with avoidance for a food will complete long-term follow-up visits every six months until the participant has completed a minimum of 12 months of follow-up in Stage 3 and will remain in Stage 3 until at least December 2022. Procedures and assessments that will be completed during each visit are the same as those given in Section 8.7.1.3. An interim family history questionnaire will be given on the first long-term follow-up visit if it has not been collected on any other visit in Stage 3.

If a participant is receiving long-term follow-up with avoidance for a food for over six months of follow-up in Stage 3, the participant will be contacted monthly by phone call or email. Procedures and assessments that will be completed during each phone call/email are the same as those given in Section 8.7.1.2.2. These phone calls/emails may be combined with other study visits in Stage 3.

8.7.3 Rescue Oral Immunotherapy

Appendix 9 provides the schedule of events for rescue OIT for a food during Stage 3.

The timing of blood and urine collections for safety during rescue OIT will be based on the prior collection and is only needed for participants still receiving omalizumab, placebo for omalizumab, or open label omalizumab from the previous stage. The following safety samples will be collected:

1. Blood for Safety
    a. CBC with differential
    b. CMP
2. Urine for Safety
    a. Urinalysis

Females who have undergone menarche (or who undergo menarche during the study) will have a urine pregnancy test routinely during rescue OIT (see Appendix 10 and 11 for scheduling details); the timing of the urine pregnancy test will be based on the prior collection.

8.7.3.1 Initial Dose Escalation, Dose Build-Up, and Initial and Follow-Up Maintenance Dose Visits

Participants who undergo an IDE Visit during rescue OIT for a food within 14 days of completing Stage 1 OLE or Stage 2 will remain on the treatment they were receiving until the IDE Visit is completed. Open label omalizumab injections or omalizumab or placebo for omalizumab injections may occur on the same day as the IDE Visit as long as the injection occurs at least 30 minutes prior to the IDE Visit to assess AEs. Participants from Stage 2 will be instructed to avoid taking their Multi-allergen OIT dose on the same day as the IDE Visit.

For the IDE Visit (if applicable), Initial Dose Build-Up Visit, Dose Build-Up, Initial Maintenance Dose Visit and Follow-Up Maintenance Dose Visits, each participant will complete procedures and assessments as outlined in Sections 8.6.3, 8.6.4, 8.6.5, 8.6.6, and 8.6.7, excluding stool, saliva, urine and blood sample collections. Additionally, an interim family history questionnaire will be asked at the IDE Visit (if it has not been collected on any other visit in Stage 3) and FAQLQ and blood will be collected at six months after the start of rescue OIT. Urine will be collected monthly during the IDE Visit and Dose Build-Up Visits, at the Initial Maintenance Dose Visit, and at each Follow-Up Maintenance Dose Visit.

If a participant cannot complete the Initial Dose Build-Up Visit within two days of the planned visit, he/she will be asked to repeat the IDE Visit.

Participants who reach a planned target maintenance dose of at least 560 mg protein of the food will complete the visits described above, however after the Initial Maintenance Dose Visit, the participant will be called or emailed at two and five weeks, as described in Section 8.7.1.2. After the Follow-Up Maintenance Visit, the participant will return to CRU to complete an open feeding for the food(s) as described in Section 8.7.1.1. If the participant tolerates ≥300 mg protein of the food during the open feeding(s), the participant will transition to dietary consumption of the food. Each participant will complete the procedures and assessments for the Safety Phone Calls or Emails and Long-Term Follow-Up Visits as described in Sections, 8.7.1.2 and 8.7.1.3.

If a participant is receiving rescue OIT doses for a food, the participant will complete daily diaries for that food.

Open Oral Food Challenge Visits

An open OFC will be completed approximately 52 weeks after the start of rescue OIT consisting of each of their three specific foods to a cumulative dose of 8044 mg protein of each food using the open OFC dosing schedule provided in Table 3.1.5.3d regardless of whether the participant has transitioned to dietary consumption for the food or has been maintained on rescue OIT doses . If rescue OIT is given at the same time for two or three foods, open OFCs may occur over separate visits to accommodate open OFCs to two or three foods respectively. Participants will be instructed to avoid taking their daily dietary consumption and/or OIT dose on the same day as an open OFC. The following procedures and assessments will occur during this visit:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Comprehensive Physical Exam, including PEF
4. SCORAD for participants with AD (prior to initiating the first open OFC only)
5. Diet & Allergy Questionnaires
6. GI Symptoms Questionnaire
7. FAQLQ (prior to initiating the first open OFC and after completing the last open OFC)
8. Review Diaries, as applicable
9. Concomitant Medications
10. SPT to peanut and two other food allergens
11. Open OFC (see Table 3.1.5.3d)
12. AEs
13. Urine Collection

8.8 Unscheduled Visits

Unscheduled visits may be performed at any time during the study to address study related issues or assess safety. The PI and CRU staff may determine if unscheduled visits are required for, but not limited to, the following reasons:

- Dose observation, if the participant has had symptoms with home OIT doses, missed consecutive OIT doses as a result of concurrent illnesses, or has had symptoms outside of the two-hour OIT dosing window.
- Receive an injection of omalizumab or placebo for omalizumab that could not be scheduled on the same day as another study visit.
- Provide additional samples for further biomarker or mechanistic studies, if samples are lost or destroyed, or if insufficient yields were obtained at a previous study visit.
- To assess a potential AE or clinically significant laboratory result.

The following procedures and assessments may be completed during this visit, per PI discretion:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Comprehensive or Limited Physical Exam with or without PEF
4. Diet & Allergy Questionnaires
5. GI Symptoms Questionnaire
6. Review Diaries (as applicable)

7. Monthly Long-Term Follow-Up Questionnaires (as applicable for the Stage)
8. Concomitant Medications
9. AEs
10. Omalizumab or placebo for omalizumab administration
11. Blood Collection for Safety
    a. CBC with differential
    b. CMP
12. Urine Collection for Safety
    a. Urine Pregnancy Test (female participants of child-bearing potential)
    b. Urinalysis
13. Additional sample collection, as appropriate

8.9 Early Discontinuation Visit

A participant who prematurely terminates the study due to withdrawal of consent or at the PI's discretion will attend an Early Discontinuation Visit.

The following procedures and assessments will be completed during this visit:

1. Vitals & Growth Parameters
2. Interim Medical History
3. Limited Physical Exam
4. Diet & Allergy Questionnaires
5. GI Symptoms Questionnaire
6. Review Diaries (as applicable for the Stage)
7. Monthly Long-Term Follow-Up Questionnaires (as applicable for the Stage)
8. Concomitant Medications
9. Urine Pregnancy Test (female participants of child-bearing potential)
10. AEs

If the following procedures and assessments have not been completed within the eight weeks preceding the Early Discontinuation Visit, they will be completed in addition to the procedures noted above:

11. SPT to peanut and two other food allergens
12. Blood Collection
    a. Total IgE
    b. Total free IgE
    c. Allergen-specific IgE, IgG4, and IgA
    d. Basophil activation
    e. CBC with differential
    f. CMP
13. Urinalysis

8.10 Visit Windows

Study visits must occur within the time limits specified below.

- Screening

- The first Screening DBPCFC must be completed no later than 8 weeks after the Screening Visit. For this Screening DBPCFC, the last DBPCFC Visit must occur no later than 28 days after the first DBPCFC Visit.
- If an additional Screening DBPCFC to other allergens is needed, it must be completed no later than 21 days after the fourth blinded OFC in the original Screening DBPCFC.
- The Screening Visit and Screening DBPCFC must be completed during a 15-week period.

- Stage 1
  - The first omalizumab injection visit (regardless of omalizumab dosing frequency) must occur between 1 and 21 days from the last Screening DBPCFC Visit.
  - Omalizumab injection visits for 2 week omalizumab dosing must occur between 4 days before and 7 days after the planned visit.
  - Omalizumab injection visits for 4 week omalizumab dosing must occur between 7 days before and 7 days after the planned visit.
  - The first DBPCFC Visit at the end of Stage 1 must occur no later than 2 weeks after the planned visit.
  - The last DBPCFC Visit at the end of Stage 1 must occur no later than 28 days after the first DBPCFC Visit at the end of Stage 1.

- Stage 1 OLE
  - Omalizumab injection visits for 2 week omalizumab dosing must occur between 4 days before and 7 days after the planned visit.
  - Omalizumab injection visits for 4 week omalizumab dosing must occur between 7 days before and 7 days after the planned visit.
  - The first DBPCFC Visit at the end of Stage 1 OLE must occur no later than 2 weeks after the planned visit.
  - The last DBPCFC Visit at the end of Stage 1 OLE must occur no later than 28 days after the first DBPCFC Visit at the end of Stage 1 OLE.

- Stage 2
  - The IDE Visit must occur no later than 14 days after the planned visit.
  - The Initial Dose Build-Up Visit must occur no later than 2 days after the planned visit.
  - Dose Build-Up Visits must occur between 4 days before and 7 days after the planned visit.
  - Initial Maintenance Dose Visit must occur between 4 days before and 7 days after the planned visit.
  - Follow-Up Maintenance Dose Visits must occur between 14 days before and 14 days after the planned visit.
  - Omalizumab injection visits for 2 week omalizumab dosing must occur between 4 days before and 7 days after the planned visit.
  - Omalizumab injection visits for 4 week omalizumab dosing must occur between 7 days before and 7 days after the planned visit.
  - The first DBPCFC Visit at the end of Stage 2 must occur no later than 2 weeks after the planned visit.
  - The last DBPCFC Visit at the end of Stage 2 must occur no later than 28 days after the first DBPCFC Visit at the end of Stage 2.

- Stage 3 – Long-term follow-up with dietary consumption of a food

- Omalizumab injection visits for 2 week omalizumab dosing must occur between 4 days before and 7 days after the planned visit.
- Omalizumab injection visits for 4 week omalizumab dosing must occur between 7 days before and 7 days after the planned visit.
- The first open feeding must occur no later than 14 days after the last DBPCFC visit in Stage 1 OLE or Stage 2.
- The last open feeding must occur no later than 21 days after the last DBPCFC visit in Stage 1 OLE or Stage 2.
- For participants who transition from rescue OIT, the open feeding for a food must occur no later than 14 days after the first Follow-Up Maintenance Dose Visit or the last open OFC in rescue OIT for a food (as applicable).
- Weekly and every two-week phone calls/emails must occur between 3 days before and 7 days after the planned phone call/email.
- Two-month phone calls/emails must occur between 2 weeks before and 2 weeks after the planned phone call/email.
- Monthly long-term follow-up phone calls/emails must occur between 7 days before and 7 days after the planned phone call/email.
- Long-term follow-up visits must occur between 1 month before and 1 month after the planned visit.

- Stage 3 – Long-term follow-up with avoidance of a food

  - Monthly long-term follow-up phone calls/emails must occur between 7 days before and 7 days after the planned phone call/email.
  - Long-term follow-up visits must occur between 1 month before and 1 month after the planned visit.

- Stage 3 – Rescue OIT for a food

  - For participants transitioning from Stage 1 OLE or Stage 2 who require an IDE Visit:
    - The IDE Visit must occur no later than 14 days after the last DBPCFC Visit in Stage 1 OLE or Stage 2.
    - The Initial Dose Build-Up Visit must occur no later than 2 days after the planned visit.
  - For participants transitioning from Stage 1 OLE or Stage 2 who do not require an IDE Visit:
    - The Initial Dose Build-Up Visit must occur no later than 14 days after the last DBPCFC Visit in Stage 1 OLE or Stage 2.
  - Omalizumab injection visits for 2 week omalizumab dosing must occur between 4 days before and 7 days after the planned visit.
  - Omalizumab injection visits for 4 week omalizumab dosing must occur between 7 days before and 7 days after the planned visit.
  - Dose Build-Up Visits must occur between 4 days before and 7 days after the planned visit.
  - Initial Maintenance Dose Visit must occur between 4 days before and 7 days after the planned visit.
  - For participants who reach a planned target dose of $\geq$560 mg of food protein allowing transition to dietary consumption, phone calls/emails at two and five weeks after the Initial Maintenance Dose Visit must occur between 3 days before and 7 days after the planned phone call/email.
  - Follow-Up Maintenance Dose Visits must occur between 14 days before and 14 days after the planned visit.

- For participants transitioning to dietary consumption for a food(s) after the first Follow-Up Maintenance Dose Visit, refer to the Visit Windows for Long-Term Follow-Up with Dietary Consumption of a Food.
- The Open OFC Visit at the end of rescue OIT must occur no later than 2 weeks after the planned visit.

- Safety Labs
  - For Stage 1/Stage 1 OLE and Stage 2, safety labs every 3 months must be obtained between 14 days before and 14 days after the planned visit.
  - For Stage 1/Stage 1 OLE, Stage 2, and Stage 3 – Rescue OIT (IDE Visit and Dose Build-Up Visits), urine pregnancy tests every month must be taken between 7 days before and 7 days after the planned visit.

9 Laboratory Research Assays

9.1 Biomarker Assays

9.1.1 Measurement of Food-Specific IgE, IgG4, and IgA

Food-specific IgE is a pre-requisite for food allergy. However, the presence of circulating food-specific IgE is not always a reliable marker of true food allergy and IgE antibodies (Abs) to specific allergen components are likely a more reliable indicator of food allergy.[31,32] In contrast to IgE, IgG4, and IgA Abs specific for food allergens may be protective. Food- and component-specific IgG, especially IgG4, Abs have been consistently shown to increase with OIT and there is evidence that the ratio of food allergen-specific IgG4:IgE may be a useful predictor of therapy outcome.[33-35] Food-specific IgA may also be a potentially useful biomarker of OIT success and is worthy of further investigation.[36] While the mechanisms of protection of IgG4 and IgA are incompletely understood, IgG inhibits basophil responses in vitro and may function as a protective "blocking antibody" in vivo.[37] Levels of food-specific IgE, IgG4, and IgA and, where relevant, component-specific Abs will be measured to determine their correlation with clinical and mechanistic outcomes following treatment with omalizumab or omalizumab-facilitated OIT.

The Central Biomarker Facility at the University of North Carolina at Chapel Hill (UNC-CH) will conduct the following assays on participants at specified timepoints for each stage of the protocol (the total free IgE assay will be conducted by Genentech):

- Total IgE
- Total free IgE
- Food allergen-specific IgE
- Food allergen-specific IgG4
- Food allergen-specific IgA
- IgG4/IgE ratios

9.1.2 Basophil Activation Test

Basophils are circulating CD203c+ CD123+ lineage marker (CD3, CD19, CD14, and CD41) negative granulocytes that can release histamine and other mediators of allergic inflammation. IgE binds to basophils via the FcεRI receptor and cross-linking of the IgE/FcεRI complex by allergen causes the basophil to degranulate. Several groups have used the basophil activation test (BAT) assay to show that basophil reactivity to allergen decreases during the course of

OIT[33,34,38,39] and therefore may be a useful biomarker of responsiveness to OIT. Also, in a small study of omalizumab treatment for peanut allergy, basophil activation and high peanut to total IgE ratio were associated with treatment success.[10,40] BAT assays capture functional information about the level of IgE and the activation potential of these circulating effector cells. BAT assays are predictive of clinical reactivity to peanut (allergic versus sensitized)[41] and are predictive of various features of clinical response such as threshold, severity, and response to baked egg or milk.[42-45]

Basophil activation is typically studied in whole blood BAT assays with several doses of allergen (1000 ng/mL, 100 ng/mL, 10 ng/mL, and 1 ng/mL) and positive and negative controls and is quantitated by measuring the increased surface expression of CD63 and CD203c. For BAT assays, blood will be shipped overnight from the CRUs to the designated laboratory. Results of the BAT assays will be correlated with clinical and mechanistic study outcomes, where appropriate.

9.2 Mechanistic Studies

9.2.1 Predicting the Response to Omalizumab through High Dimensional Profiling of Basophil Activation (Stage 1 and Stage 2, Peanut Response)

Rationale: As described above, BAT assays are typically performed using flow cytometry with two markers of activation, CD63 and CD203c. However, basophils are heterogeneous[46,47] and it is hypothesized that a higher resolution analysis of their activation will be more predictive/informative of clinical response in the context of food allergy. Mass cytometry by time of flight (CyTOF) has been used to profile the peripheral blood response to peanut.[48] A combination of surface markers (CD63, CD203c, CD164, and HLA-DR) and intracellular signaling molecules (MAP kinases, CREB, mTOR, and STAT signaling pathways) can identify cells activated in peripheral blood in response to allergen or IgE cross-linking. Basophils demonstrate a range of activation, including signaling in the absence of surface degranulation. Studies will be performed using samples from Stage 1 and Stage 2 participants to test the hypothesis that high dimensional analysis of peanut-specific and IgE-induced basophil activation will be predictive of the clinical response to omalizumab or omalizumab-facilitated OIT.

Approach: Heparinized peripheral blood will be used for CyTOF analysis of basophils. Whole blood will be collected at the following times:

- First Screening DBPCFC Visit;
- First DBPCFC Visit at the end of Stage 1;
- IDE Visit during Stage 2;
- Initial Maintenance Dose Visit during Stage 2; and
- First DBPCFC Visit at the end of Stage 2.

For each stage and at each CRU, lyophilized tubes containing a range of peanut antigen doses (a combination of purified Ara h 1, Ara h 2, and Ara h 3 at 100, 10, or 1 ng/mL) or anti-IgE doses (1, 0.2 µg) together with anti-CD63, -CD203c, and -CD164 Abs will be used to do novel two-step BAT assays. Details can be found in the MOP.

9.2.2 Assessment of the Impact of Omalizumab Treatment in Stages 1 and 2 on Dendritic Cells and Peanut-Specific CD4+T Cells

Rationale: Preliminary studies using high dimensional mass cytometry to assess immune response suggest a dampening of the Th2 response in successfully desensitized study participants. While the effects of OIT on allergen-specific CD4+ T cells have been studied extensively and while it is known that omalizumab reduces the number of

FcεRI on dendritic cells (DCs),[49] relatively little is known about the effects of omalizumab therapy alone or omalizumab-facilitated OIT on DC subsets and their interactions with CD4+ T cells. The hypothesis to be tested in this study is that omalizumab treatment will downregulate additional Th2-polarizing molecules, including OX40L and TIM-4, on DC subsets and increase expression of FcγRIIb, which in turn will result in a dampened Th2 response, as assessed through downregulation of interleukin-4 and interleukin-9 production and an increased allergen-specific IgG4:IgE ratio. DC subset-T cell cross talk will be compared in participants treated with omalizumab versus placebo (Stage 1) and omalizumab-facilitated OIT vs omalizumab monotherapy (Stage 2).

Approach: High dimensional mass cytometry and functional assays with a focus on the response to peanut will be performed. Whole blood from participants will be collected at the following times:

- First Screening DBPCFC Visit;
- First DBPCFC Visit at the end of Stage 1;
- IDE Visit during Stage 2;
- Initial Maintenance Dose Visit during Stage 2; and
- First DBPCFC Visit at the end of Stage 2.

Peripheral blood mononuclear cells (PBMCs) and plasma will be isolated and stored frozen. Thawed PBMCs will be analyzed to assess any changes in frequency and/or function of DC and T cell subsets over the course of therapy. Statistically significant findings from mass cytometry will be validated through functional assays involving DC-T effector cell-Treg coculture.

9.3 Other Biosamples/Assays

Blood for PK sampling will be collected to evaluate serum omalizumab concentrations during treatment with omalizumab and omalizumab-facilitated OIT.

Stool samples will be collected and stored for future analysis aiming at, but not limited to, assessing the effects of the gut microbiome on OIT responses and/or the effects of OIT on the microbiome. Studies may also be conducted to assess other biologic outcomes that may be related to food allergy and the effects of the study's interventions.

Urine samples will be collected and stored for future analysis aiming at, but not limited to, assessing metabolomic changes related to treatment with omalizumab and omalizumab-facilitated OIT.

Saliva will be collected and stored for future analysis aiming at, but not limited to, assessing food-specific IgA changes in relation to OIT.

SPT will be performed in order to assess changes in wheal size related to treatment with omalizumab and omalizumab-facilitated OIT.

10 Biospecimen Storage

During the consent process, a participant and/or parent/legal guardian will be asked to give permission for long-term storage and future use of samples. All samples will be stored at the Central Biomarker Facility at UNC-CH. The following specimens will be stored:

- Serum

- Plasma
- PBMCs
- Stool
- Urine
- Saliva

Plasma and PBMCs will also be stored at Stanford University.

Instructions for sample preparation, handling, storage, and shipping will be defined in the MOP. The PI will be responsible for knowing about and observing all the regulations for classification, packaging and labeling, permits and authorizations, personnel training for shipment of biological and hazardous materials required for the conduct of this study.

11 Criteria for Participant and Study Completion and Premature Study Termination

11.1 Participant Completion

A participant will be considered to have completed:

- Stage 1 when the participant has completed all four blinded OFCs comprising the DBPCFC at the end of Stage 1.
- Stage 1 OLE when the participant has completed all four blinded OFCs comprising the DBPCFC at the end of Stage 1 OLE.
- Stage 2 when the participant has completed all four blinded OFCs comprising the DBPCFC at the end of Stage 2.
- Stage 3 when the participant has completed the first six-month visit in Stage 3.

11.2 Participant Stopping Rules and Withdrawal Criteria

11.2.1 Automatic Stopping Rules

A participant will be prematurely terminated from the study for the following reasons:

1. The participant and/or parent/legal guardian elects to withdraw consent/assent from all future study activities, including follow-up.
2. The participant is “lost to follow-up” as defined in the MOP (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
3. The participant dies.
4. The participant becomes pregnant.
5. The participant experiences one CoFAR Grade 4 allergic reaction related to omalizumab/placebo for omalizumab or Multi-allergen OIT/placebo for Multi-allergen OIT (see Table 12.4.1.2).
6. The participant develops biopsy-documented EoE.
7. The participant is an IDE failure or treatment failure in Stage 2.
8. The participant does not complete all four blinded OFCs comprising the DBPCFC at the end of Stage 1.
9. The participant does not complete all four blinded OFCs comprising the DBPCFC at the end of Stage 1 OLE.
10. The participant does not complete all four blinded OFCs comprising the DBPCFC at the end of Stage 2.

11. The participant develops a confirmed clinically significant laboratory abnormality (i.e., transaminitis [see Section 6.4.1.4], thrombocytopenia [see Section 6.4.1.5]) related to study drug or study procedure.
12. The participant's continued participation in the study is assessed by the PI to no longer be in the best interest of the participant or to jeopardize the safe conduct of the study.

11.2.2 Discretionary Stopping Rules Requiring DSMB Review

Per the PI's discretion and in conjunction with the Protocol Chair(s) and DAIT/NIAID Medical Monitor, a participant may be prematurely terminated from the study if:

1. The participant experiences a CoFAR Grade 4 AE (see Table 12.4.1.2) related to an OFC.

However, in the circumstance that the PI, Protocol Chair(s), and DAIT/NIAID Medical Monitor deem it appropriate for the affected participant to continue in the study, the CoFAR Grade 4 AE will be reviewed by the NIAID Allergy and Asthma DSMB prior to the final participant disposition determination.

11.2.3 Discretionary Stopping Rules

Per the PI's discretion and in conjunction with the Protocol Chair(s) and DAIT/NIAID Medical Monitor, a participant may be prematurely terminated from the study for the following reasons:

1. One occasion in which the participant experiences a Grade 4 AE (see Section 12.4.1.1 or Table 12.4.1.2).
2. The participant experiences recurrent symptoms that may or may not require medical intervention but prevent the participant from tolerating the study therapy regimen.
3. The participant develops poor control or persistent activation of secondary atopic disease (e.g., AD, asthma).
4. The participant starts taking a prohibited medication (see Section 7.3), with no alternative medications available per the prescribing doctor.
5. The participant misses more than two consecutive doses of omalizumab or placebo for omalizumab in any stage of the study.
6. Non-adherence (non-compliance) with home OIT dosing, as indicated by missing >8 consecutive days of OIT dosing on any one occasion, or three consecutive days of OIT dosing on five or more occasions that was not directed by the PI for clinically indicated reasons.
7. Medically indicated circumstances (e.g., as part of the treatment for intercurrent AEs) that require the participant to miss OIT dosing for >8 consecutive days.

11.3 Participant Replacement

A participant less than 18 years of age at randomization in Stage 1 who withdraws or is withdrawn at any time during Stage 1 of the study will not be replaced until the first 60 participants have entered Stage 1 OLE and a minimum of 22 participants have withdrawn in Stage 1. At that time, a participant less than 18 years of age at randomization in Stage 1 who withdraws or is withdrawn at any time during Stage 1 will be replaced to ensure that a minimum of 128 participants less than 18 years of age meet the criteria that define the full analysis set in Stage 2 (see Section 13.5.1.2). A participant who replaces a withdrawn participant will complete the Screening Visit (see Section 8.3), skip all visits in Stage 1 of the study, and will begin the study in Stage 2.

11.4 Follow-up after Early Study Withdrawal

A participant who withdraws or is withdrawn at any time in the study will attend an Early Discontinuation Visit (see Section 8.9). If a participant refuses to come to the CRU for an Early Discontinuation Visit, assessments that do not require in-person evaluation may be conducted by phone. To the extent possible, a participant will be monitored for

safety until they come back for their Early Discontinuation Visit and for at least 30 days after the Early Discontinuation Visit.

11.5 Study Stopping Rules

If any of the stopping rules listed below are met, study enrollment will be suspended, IDE Visits will be suspended, and dose escalation of OIT during Stage 2 and 3 will be stopped pending expedited review of all pertinent data by the NIAID Allergy and Asthma DSMB. Depending on the stopping rule, additional study procedures (as outlined below) will also be suspended pending expedited review of all pertinent data.

- Any death related to OIT dosing, an OFC, omalizumab, or placebo for omalizumab: If this stopping rule is met, all OIT maintenance visits, all OFCs, all open feedings, and all omalizumab or placebo for omalizumab injections will be suspended.

- More than three participants requiring more than two injections of epinephrine during a single OIT dosing: If this stopping rule is met, no additional study procedures aside from those outlined above will be suspended and all omalizumab or placebo for omalizumab injections will continue to be received.

- More than one participant requiring more than two injections of epinephrine during a single omalizumab/placebo for omalizumab injection: If this stopping rule is met, all omalizumab or placebo for omalizumab injections will be suspended.

- More than one participant with more than one CoFAR Grade 4 AE related to OIT dosing (see Table 12.4.1.2): If this stopping rule is met, all OFCs and all open feedings will be suspended but all OIT maintenance visits and all omalizumab or placebo for omalizumab injections will continue to be received.

- More than three CoFAR Grade 4 AEs related to an OFC (see Table 12.4.1.2): If this stopping rule is met, all OFCs and all open feedings will be suspended but all OIT maintenance visits and all omalizumab or placebo for omalizumab injections will continue to be received.

- 5% or more of the randomized participants have been diagnosed with biopsy-proven EoE, as assessed on a rolling basis during regular AE reviews, and the total number of cases of EoE is at least five: If this stopping rule is met, no additional study procedures aside from those outlined above will be suspended and all omalizumab or placebo for omalizumab injections will continue to be received.

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. AEs that are classified as serious according to the definition of health authorities must be reported promptly (see Section 12.6.1) to the IND Sponsor, DAIT/NIAID. Appropriate notifications will also be made to PIs, IRB, and health authorities, as needed.

Information in this section complies with International Conference on Harmonisation (ICH) Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice (GCP), 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

12.2 Definitions

12.2.1 Adverse Event

Any untoward or unfavorable medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related (see 21 CFR 312.32(a)).

An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use or in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Pre-existing diseases or conditions present or detected during the first time an assessment or laboratory measurement is done during the Screening Visit will be considered AEs only if they change in severity of grade from that timepoint. Vitals or laboratory measurements repeated for confirmation of the pre-existing disease or condition are not considered a different timepoint.

All symptoms or events, with the exception of oropharyngeal pruritus, that occur within two hours and that are expected according to the Protocol and related to administration of Multi-allergen OIT/placebo for Multi-allergen OIT will be recorded as an AE and will also be identified as an OIT dosing reaction on the AE eCRF. Any symptom or event, with the exception of oropharyngeal pruritus, that occurs more than two hours after Multi-allergen OIT/placebo for Multi-allergen OIT dosing will be recorded as an AE but will not be identified as an OIT dosing reaction on the AE eCRF. Since oropharyngeal pruritus (including lip pruritus) is expected in many participants and is not considered clinically significant, it will not be captured as an AE unless it is bothersome enough to require treatment with more than antihistamines; however, oropharyngeal pruritus will be documented on the eCRF as an OIT dosing reaction if it occurs within two hours of administration of Multi-allergen OIT/placebo for Multi-allergen OIT.

For the study-mandated procedures/requirements below, only the signs and symptoms listed under each procedure will be considered outside normal range and will be recorded as an AE. For all other study-mandated procedures/requirements, all AEs will be recorded.

Skin Prick Test

The following events related to SPT will be considered AEs if they occur within 48 hours of the SPT:

- Prolonged (>24 hours) pruritus at the SPT site
- Induration/swelling at the SPT site larger than 10 mm in diameter and lasting more than 24 hours
- Allergic or anaphylactic reaction that requires the use of rescue medications, detailed in Section 7.4

Blood Draw

The following events related to a blood draw procedure will be considered AEs:

- Syncope/vasovagal events
- Bruising at the puncture site larger than 2 cm diameter
- Bleeding from the puncture site lasting more than 30 minutes

- Induration/swelling at the puncture site larger than 2 cm diameter
- Allergic reaction to local skin anesthetic that requires rescue medications
- Infection at the puncture site

Laboratory Results

An abnormal laboratory value will only be considered an AE if the value is clinically significant (i.e., changes in therapy or monitoring are implemented as a result of the event).

Oral Food Challenge

The following events related to an OFC will be considered AEs:

- Severe dose-limiting symptoms as defined by Appendix 1

As moderate dose-limiting symptoms as defined by Appendix 1 is the usual threshold at which an OFC will be considered positive to the food, almost every positive OFC will be recorded as an AE, which will dilute the true incidence of AEs for this trial. To avoid artificially increasing the AE incidence from OFCs, only severe dose-limiting symptoms as defined by Appendix 1 will be considered AEs. However, all reactions that occur during an OFC will be captured in the appropriate eCRF.

Stage 3 Dosing with Dietary Food Equivalents

The following events related to reactions following ingestion of food equivalents will be considered AEs:

- Symptoms or events, with the exception of oropharyngeal pruritus, that are bothersome enough to require treatment with more than antihistamines. Oropharyngeal pruritus will not be considered an AE.

12.2.2 Adverse Event of Special Interest

Adverse Event of Special Interest (AESI) is an AE (serious or nonserious) that is one of scientific and medical concern specific to the IND Sponsor's product or program, for which ongoing monitoring and rapid communication by the PI to the IND Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., regulators) might also be warranted (based on CIOMS VI and ICH E2F).

For Xolair® (omalizumab), AESIs have been identified and will be recorded by the CRUs and reported to the IND Sponsor, DAIT/NIAID. PIs should use their clinical judgment to identify the following events:

- Suspected anaphylactic reactions to Xolair® (omalizumab), identified based on Sampson's criteria (see Appendix 11)
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law or Section 6.4.1.4
- Suspected transmission of an infectious agent by the study drug, as defined below:
    - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate

an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- Any occurrences of overdose, medication errors, drug abuse and drug misuse related to IP administration.

12.2.3 Suspected Adverse Reaction

Any AE for which there is a reasonable possibility that the investigational drugs (Xolair® (omalizumab) and/or Multi-allergen OIT) or investigational study therapy regimen caused the AE. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A Suspected Adverse Reaction (SAR) implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug (21 CFR 312.32(a)).

12.2.4 Unexpected Adverse Event

An "Unexpected AE" or "Unexpected SAR" means an AE or SAR which is considered "unexpected" because it is not listed in the Reference Safety Information or in the Investigator Brochure or is not listed at the specificity or severity that has been observed or is not consistent with the risk information described in the general investigational plan, protocol, or elsewhere in the current application. Unexpected AEs or Unexpected SARs are further defined in 21 CFR 312.32.

12.2.5 Serious Adverse Event

An AE or SAR is considered "serious" if, in the view of the PI or Sponsor, DAIT/NIAID, it results in any of the following outcomes (see 21 CFR 312.32(a)):

- Death.
- A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the PI or Sponsor, DAIT/NIAID, its occurrence places the participant 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.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly or birth defect.
- 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 participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective or pre-planned hospitalizations for a pre-existing condition or hospital admissions for the purposes of conducting protocol mandated procedures are not considered to be a Serious Adverse Event (SAE) unless prolonged due to complications.

Injectable epinephrine may be used for both life threatening and non-life threatening allergic reactions. The use of epinephrine will not be considered an SAE if it is used to prevent the progression of non-life-threatening allergic reactions that occur during OFCs (see Section 7.4). The use of epinephrine will be considered an SAE if used for an allergic reaction that occurs during OIT dosing, omalizumab dosing, or an open feeding.

12.3 Pregnancy Reporting

The PI shall be informed immediately of any pregnancy in a study participant or a partner of a study participant during the study. A pregnant participant shall be instructed to stop taking all study products. The PI shall counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy.

The PI shall report to the IND Sponsor, DAIT/NIAID, all pregnancies within 24 hours of becoming aware of the event using the Pregnancy eCRF. The pregnancy should not be reported on the Adverse Event eCRF. All pregnancies identified during the study shall be followed to conclusion. Follow-up information detailing the outcome of the pregnancy should be entered into the electronic data capture (EDC) system, reported to the IND Sponsor, DAIT/NIAID, it becomes available. When possible, similar information shall be obtained for a pregnancy occurring in a partner of a study participant.

- 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

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons must be reported as an SAE to the IND Sponsor as described in Section 12.6.1. In addition, if the pregnancy results in a congenital abnormality or birth defect, a separate SAE report must be submitted to the IND Sponsor, DAIT/NIAID, using the SAE reporting procedures described above.

12.4 Grading and Attribution of Adverse Events

Baseline-emergent and treatment-emergent AEs for each stage of the study will be defined in the Statistical Analysis Plan (SAP).

12.4.1 Grading Criteria

12.4.1.1 Grading of Non-Allergic Adverse Events

The PI will grade the severity of all non-allergic AEs experienced by the study participants according to the Grading Table for Non-Allergic Adverse Events Version 2.0 (see Appendix 12). This grading table was based on the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials and adapted to make it applicable for the population under study. The modifications were drawn from grading scales from NIAID's Division of AIDS and Division of Microbiology and Infectious Diseases, the CTCAE Version 5.0, and the 2017 AAP updated Clinical Practice Guideline for Screening and Management of High Blood pressure in Children and Adolescents.[50-55]

AEs will be graded on a scale from 1 to 5 according to the Grading Table for Non-Allergic Adverse Events Version 2.0:

Grade 1 = Mild

Grade 2 = Moderate

Grade 3 = Severe

Grade 4 = Life-Threatening

Grade 5 = Death

Abnormal laboratory evaluations should only be captured as an AE if the abnormal result is considered clinically significant (i.e., changes in therapy or monitoring are implemented as a result of the abnormal result).

For clinically significant abnormal laboratory values, use the Grading Table for Non-Allergic Adverse Events Version 2.0. If a specific abnormal value is not listed in the table, the events should be graded using the general grading scale at the end of the table in Appendix 12.

12.4.1.2 Grading of Systemic Allergic Reactions other than Local Reactions to Skin Prick Testing

The PI will grade severity of systemic allergic reactions, other than local reactions to SPT, experienced by the study participants according to the criteria set forth in the CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0 defined in Table 12.4.1.2.

Table 12.4.1.2 CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Reaction involving **one of the following organ systems in which the symptoms are mild**: <u>Cutaneous</u> Generalized pruritus, generalized urticaria, flushing, angioedema <u>Upper respiratory</u> Rhinitis, cough unrelated to laryngeal edema or bronchospasm <u>Conjunctival</u> Injection/redness, itching, tearing <u>GI</u> Nausea, abdominal pain (no change in activity level), single episode of vomiting and/or single episode of diarrhea	Reaction involving **two or more of the following organ systems in which the symptoms are mild**: <u>Cutaneous</u> Generalized pruritus, generalized urticaria, flushing, angioedema <u>Upper respiratory</u> Rhinitis, cough unrelated to laryngeal edema or bronchospasm <u>Conjunctival</u> Injection/redness, itching, tearing <u>GI</u> Nausea, abdominal pain (no change in activity level), single episode of vomiting, and/or single episode of diarrhea	Reaction involving **one or more of the following organ systems**: <u>Lower respiratory</u> Throat tightness, wheezing, chest tightness, dyspnea, cough that respond to short-acting bronchodilator treatment (including IM epinephrine) with or without supplemental oxygen <u>GI</u> Severe abdominal pain, more than two episodes of vomiting and/or diarrhea	**Life-threatening reaction** involving **one or more of the following organ systems** with or without other symptoms listed in Grades 1 to 3: <u>Lower respiratory</u> Throat tightness with stridor, wheezing, chest tightness, dyspnea, or cough associated with a requirement for supplemental oxygen and refractoriness to short-acting bronchodilator treatment (including IM epinephrine)[1] **OR**	Death

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	OR Reaction involving **at least one of the following organ systems in which the symptoms are moderate:** <u>Cutaneous</u> Generalized pruritus, generalized urticaria, flushing, angioedema <u>Upper respiratory</u> Rhinitis, cough unrelated to laryngeal edema or bronchospasm <u>Conjunctival</u> Injection/redness, itching, tearing <u>GI</u> Nausea, abdominal pain (with change in activity level), two episodes of vomiting and/or diarrhea		Respiratory compromise requiring mechanical support <u>Cardiovascular</u> Reduced BP with associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope) defined as: • Children: low systolic BP (age specific[2]) or >30% decrease in systolic BP • Adults: systolic BP of less than 90 mmHg or >30% decrease from baseline	

1. Examples of refractoriness could include continuous albuterol nebulizer or epinephrine IV infusion or more than three IM epinephrine injections.
2. Low systolic BP for children is defined as: less than 70 mmHg from 1 month to 1 year of age, less than (70 mmHg + [2 x age]) from 1 to 10 years of age, and less than 90 mmHg from 11 to 17 years of age.

12.4.1.3 Grading of Local Reactions to Skin Prick Testing

Local reactions to skin prick testing will be graded by the criteria set forth in the Grading Scale for Local Reactions to Skin Prick Testing Version 1.0 defined in Table 12.4.1.3.

Table 12.4.1.3 Grading Scale for Local Reactions to Skin Prick Testing Version 1.0[1]

Grade 1	Grade 2	Grade 3
Meets the minimum criteria listed in Section 12.2.1, but requiring no medication other than topical corticosteroids or antihistamines.	Interfering with usual daily activities or sleep and requiring oral steroids.	Requiring a visit to a health care provider for treatment

1. All systemic reactions due to skin prick testing that meet the minimum criteria outlined in Section 12.2.1 should be graded according to Table 12.4.1.2 CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0.

12.4.2 Attribution Definitions

The relationship, or attribution, of an AE to the study therapy regimen or study procedures will initially be determined by the PI and recorded on the appropriate AE/SAE eCRF. Final determination of attribution for safety reporting will be determined by Sponsor, DAIT/NIAID. The relationship of an AE to study therapy regimen or procedures will be determined using the descriptors and definitions provided in Table 12.4.2.

Table 12.4.2 Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
UNRELATED CATEGORY		
1	Not Related	The AE is clearly not related; there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possibly Related	The AE has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Related	The AE is clearly related.

12.5 Collection and Recording of Adverse Events

12.5.1 Collection Period

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

12.5.2 Collecting Adverse Events

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

- Observing the participant
- Interviewing the participant (e.g., using a checklist, structured questioning, diary, etc.)
- Receiving an unsolicited complaint from the participant
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an AE, as defined in Section 12.4

12.5.3 Recording Adverse Events

Throughout the study, the PI will record all AEs and SAEs as described previously (Section 12.2) on the appropriate AE/SAE eCRF 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 the end of study participation, or until at least 30 days after the participant prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever is clinically appropriate.

12.6 Reporting of Adverse Events, Serious Adverse Events, and Pregnancies

12.6.1 Reporting of Serious Adverse Events, Adverse Events of Special Interest, and Pregnancies to the IND Sponsor

This section describes the responsibilities of the PI to report SAEs, AESIs, and pregnancies to the IND Sponsor, DAIT/NIAID. Timely reporting of AEs is required by 21 CFR and ICH E6 guidelines.

The PI shall report all pregnancies within 24 hours of becoming aware of the event as per the reporting process described in Section 12.3.

PIs will report all SAEs and/or AESIs (see Sections 12.2), regardless of relationship or expectedness, within 24 hours of discovering the event.

For SAEs and AESIs, all requested information on the AESI/SAE eCRF will be provided. However, unavailable details of the event will not delay submission of the known information. Initial AESI/SAE eCRFs should include as much information as possible, but at a minimum must include the following:

- AE term
- Relationship to IP and whether "OIT dosing reaction."
- Relationship to study procedure
- Reason why the event is serious or AESI
- Supplementary eCRF pages that are current at the time of AESI/SAE reporting: medical history, concomitant medications, demographics, IP administration

As additional details become available, the AESI/SAE eCRF will be updated and submitted. Every time the AESI/SAE eCRF is submitted, it should be electronically signed by the PI.

12.6.2 Reporting to the FDA

After an AE requiring 24-hour reporting (see Section 12.6.1) or pregnancy is submitted by the PI and assessed by the IND Sponsor, DAIT/NIAID, the IND Sponsor must report the event to the FDA using one of two categories.

12.6.2.1 Expedited Safety Reporting

This category applies if the safety event is classified as one of the following:

- **Serious and Unexpected Suspected Adverse Reaction [SUSAR]** (see Sections 12.2.3 and 12.2.4 and 21 CFR 312.32I(1)).

  The IND Sponsor, DAIT/NIAID, shall report any SAR that is both serious and unexpected. The IND Sponsor, DAIT/NIAID, shall report an AE as a SAR only if there is evidence to suggest a causal relationship between the study drug and the AE, such as:

  1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
  2. 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
  3. An aggregate analysis of specific 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 studies that suggests a significant human risk**

  The IND Sponsor, DAIT/NIAID, shall report any findings from other clinical, epidemiological studies, pooled analysis of multiple studies, or any finding from 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, package insert, or other aspects of the overall conduct of the study.

- **AESI of anaphylaxis associated with Xolair® (omalizumab)**

  The IND Sponsor, DAIT/NIAID, shall report any suspected reactions to Xolair® (omalizumab).

The IND Sponsor, DAIT/NIAID, shall notify the FDA of the fatal or life-threatening SUSAR(s) and IND Safety Reports within 7 and 15 calendar days of IND Sponsor awareness, respectively. The IND Sponsor will provide the IND Safety Reports to the Investigational Drug Product Manufacturers and all participating PIs.

12.6.2.2 Standard Reporting (report in the IND Annual Report)

All AEs as per 21 CFR 312.33, as well as all pregnancies and use of epinephrine for both life-threatening and non-life threatening reactions, will be recorded by the CRUs, reported to the IND Sponsor, and included in the IND Annual Report submitted to the FDA by the IND Sponsor.

12.6.3 Reporting of Adverse Events to IRBs

All investigators shall report AEs and SAEs in a timely fashion to their local and single IRB in accordance with applicable regulations and guidelines.

12.6.4 Reporting of Other Safety Information

A PI shall promptly notify the IND Sponsor, DAIT/NIAID, and the DAIT SACCC via email when an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an AE.

12.7 Review of Safety Information

12.7.1 Medical Monitor Review

The DAIT/NIAID Medical Monitor shall receive monthly reports from the DAIT SACCC compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the CRUs on appropriate eCRFs.

In addition, the DAIT/NIAID Medical Monitor shall review and make decisions on the disposition of the SAE and pregnancy reports received by the SACCC (see Sections 12.6.1 and 12.3).

12.7.2 DSMB Review

12.7.2.1 Planned DSMB Reviews

The NIAID Allergy and Asthma DSMB shall review safety data twice per year during planned DSMB Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs that is created by the DAIT SACCC.

12.7.2.2 Ad hoc DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the NIAID Allergy and Asthma DSMB may be called upon for ad hoc reviews when an event occurs that is of sufficient concern to the DAIT/NIAID Medical Monitor and/or Protocol Chair or Co-Chair to warrant a DSMB review. The DSMB will be notified within 24-48 hours by the DAIT/NIAID Medical Monitor and will promptly review

any event that potentially impacts safety at the request of the Protocol Chair or Co-Chair or DAIT/NIAID Medical Monitor or any occurrence that meets the definition of the participant stopping rules requiring DSMB review defined in Section 11.2 or study stopping rules defined in Section 11.5. After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

The DSMB will also review each Xolair® (omalizumab)-associated anaphylactic reaction as identified by the PIs to confirm that the event: a) satisfies the criteria for anaphylactic reaction, and b) is associated with Xolair® (omalizumab).

12.7.2.2.1 Temporary Suspension of Trial for Ad hoc DSMB Review for Reasons Other than a Stopping Rule

The DAIT/NIAID Medical Monitor may temporarily suspend the trial at any time at his/her discretion. The DAIT/NIAID Medical Monitor will determine if a temporary halt in screening, enrollment and/or drug dosing/updosing should be implemented pending the review.

For rules regarding the temporary suspension of the trial due to a stopping rule, please refer to Section 11.5.

13 Statistical Considerations and Analytical Plan

13.1 Overview

The efficacy and safety of omalizumab as monotherapy and as an adjunct therapy to Multi-allergen OIT will be studied using a Phase III, randomized, double-blind, placebo-controlled, multi-site, and multi-stage trial of omalizumab and Multi-allergen OIT in children and adults, ages 1 year to less than 56 years, with multi-food allergy. All analyses specified in this document will be performed for participants aged less than 18 years and repeated in all participants aged 1 year to less than 56 years. Detailed specifications of the statistical methods will be described in the SAP. The SAP will be reviewed by health authorities and finalized prior to database lock. To allow for incorporation of health authority input, the statistical methods in the SAP may differ from and will supersede those described in this document.

13.2 Endpoints

Please refer to Section 3.2, 3.3, and 3.4 which provide definitions of the primary, secondary, and exploratory endpoints.

For endpoints based on the results of DBPCFCs, if a participant has dose-limiting symptoms to any dose during the blinded OFC to placebo, the participant will be considered a ‘failure’ at every dose of the blinded OFCs to peanut and two other participant-specific foods comprising the rest of the DBPCFC.

Appendix 13 provides a mapping of the endpoints that will be used to address each of the objectives given in Section 2.2, 2.3, and 2.4 as well.

13.3 Missing Data

If a participant does not complete a DBPCFC at the end of Stage 1, Stage 1 OLE, or Stage 2 because the participant is withdrawn from the study prior to the DBPCFC (see Section 11.2) or the participant misses the visit where a blinded OFC would be performed, the participant will be considered a ‘failure’ for all efficacy endpoints based on the blinded OFCs that were missed. For these participants, the maximum tolerated dose without dose-limiting symptoms will also be set to 0 mg.

If a participant stops an OFC before consuming the final dose and does not have dose-limiting symptoms on the last dose consumed, the participant will be considered a:

- 'Success' if the participant consumed the dose that is used to define the efficacy endpoint; or
- 'Failure' if the participant did not consume the dose that is used to define the efficacy endpoint.

For example, a participant consumes a single dose of 600 mg of peanut protein without dose-limiting symptoms during the blinded OFC to peanut at the end of Stage 1, but then refuses to continue with the rest of the blinded OFC to peanut. In this case, the participant will be assumed to have met the primary endpoint but will be marked as a failure for efficacy endpoints defined by consumption of a single dose of ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.

Imputation of missing DBPCFC data in this way assumes that the data is missing-not-at-random (MNAR). To assess the impact of the MNAR assumption, a sensitivity analysis of the primary endpoint will be performed (see Section 13.5.4).

For FAQLQ and immune biomarker endpoints, any missing data will be assumed MAR and no explicit imputation will be performed.

A participant will only be included in analyses of OFC endpoints for peanut and the two other participant-specific foods.

13.4 Measures to Minimize Bias

Bias will be minimized in the following ways:

- The randomization scheme used for treatment arms in Stage 1 (see Section 3.5) will be stratified to ensure that the distribution of <6 years of age and milk as a participant-specific food (yes/no) is balanced across the treatment arms in Stage 1.
- The randomization scheme used for treatment arms in Stage 2 (see Section 3.5) will be stratified to ensure that the distribution of treatment arms in Stage 1 is balanced across the treatment arms in Stage 2.
- The randomization scheme used for the order of the blinded OFC to peanut in relation to the other three blinded OFCs during the DBPCFC (first, second, third, or fourth) at the end of Stage 1 will be stratified to ensure that the distribution of the Stage 1 treatment arm is balanced across the four orderings in Stage 1. A similar stratified randomization scheme will be used for the order of the blinded OFC to peanut during the DBPCFC at the end of Stage 2 to ensure that the distribution of the Stage 2 treatment arm is balanced across the four orderings in Stage 2. The order of the blinded OFC to peanut in relation to the other three blinded OFCs during the Screening DBPCFC as well as the DBPCFC at the end of Stage 1 OLE will also be randomized.
- For each participant, randomization of the order of the blinded OFC to peanut during the DBPCFC at the end of Stage 1, Stage 2, or Stage 1 OLE will be performed immediately after randomization of the Stage 1 or Stage 2 treatment arm or immediately after entering Stage 1 OLE respectively.
- Each participant, CRU staff (excluding the unblinded CRU pharmacist/pharmacy staff and a CRU staff member who will administer omalizumab or placebo for omalizumab injections), and laboratory staff will be blinded to treatment assignments until unblinding occurs (see Section 3.5).
- During all DBPCFCs, the participant and/or parent/legal guardian, as well as the CRU staff administering the blinded OFC, will not know which OFC contains food protein or placebo.

13.5 Analysis Plan

13.5.1 Analysis Populations

13.5.1.1 Stage 1 Analysis Populations

Pediatric Full Analysis Set (FA-S1): All participants aged less than 18 years who have been randomized to receive either omalizumab or placebo for omalizumab in Stage 1. Participants will be analyzed according to the treatment arm to which they were randomized in Stage 1, regardless of the treatment they actually received in Stage 1.

Full Analysis Set (FFA-S1): All participants who have been randomized to receive either omalizumab or placebo for omalizumab in Stage 1. Participants will be analyzed according to the treatment arm to which they were randomized in Stage 1, regardless of the treatment they actually received in Stage 1.

Pediatric Per-Protocol Set (PP-S1): All participants in the FA-S1 population who have completed at least 75% of scheduled injections with either omalizumab or placebo for omalizumab in Stage 1 and have completed the blinded OFC to peanut during the DBPCFC at the end of Stage 1. The PP-S1 set will only include participants who receive the correct treatment according to their randomization assignment and correct omalizumab dosing frequency in Stage 1. Participants with major protocol deviations that could be expected to materially affect efficacy or safety during Stage 1 as specified in the SAP will also be excluded from PP-S1.

Pediatric Pre-Randomization Safety Set (SS1-S1): All randomized participants aged less than 18 years at randomization and all participants who are enrolled but never randomized aged less than 18 years at the Screening Visit.

Pediatric Safety Set (SS2-S1): All randomized participants aged less than 18 years at randomization who have received at least one dose of omalizumab or placebo for omalizumab in Stage 1 and all participants who are enrolled, never randomized, aged less than 18 years at the Screening Visit, and have received at least one dose of omalizumab or placebo for omalizumab in Stage 1. Participants will be analyzed according to the treatment they actually received in Stage 1, defined as “omalizumab” if a participant received any dose (including a partial single dose) of omalizumab during Stage 1 and “placebo for omalizumab” otherwise, regardless of the treatment arm to which they were randomized in Stage 1.

Full Safety Set (FSS-S1): All participants who have received at least one dose of omalizumab or placebo for omalizumab in Stage 1. Participants will be analyzed according to the treatment they actually received in Stage 1, defined as “omalizumab” if a participant received any dose (including a partial single dose) of omalizumab during Stage 1 and “placebo for omalizumab” otherwise, regardless of the treatment arm to which they were randomized in Stage 1.

13.5.1.2 Stage 1 Open Label Extension Analysis Populations

Pediatric Full Analysis Set (FA-S1OLE): All participants aged less than 18 years at Stage 1 randomization who have moved to Stage 1 OLE, grouped according to treatment arm to which they were randomized in Stage 1.

Full Analysis Set (FFA-S1OLE): All participants who have moved to Stage 1 OLE, grouped according to treatment arm to which they were randomized in Stage 1.

Pediatric Safety Set (SS-S1OLE): All participants in the FA-S1OLE population who have received any dose (including a partial single dose) of open label omalizumab during Stage 1 OLE, grouped according to the treatment received in Stage 1 defined as “omalizumab” if a participant received any dose (including a partial single dose) of omalizumab during Stage 1 and “placebo for omalizumab” otherwise.

Full Safety Set (FSS-S1OLE): All participants who have moved to Stage 1 OLE and received any dose (including a partial single dose) of open label omalizumab during Stage 1 OLE, grouped according to the treatment received in Stage 1 defined as “omalizumab” if a participant received any dose (including a partial single dose) of omalizumab during Stage 1 and “placebo for omalizumab” otherwise.

13.5.1.3 Stage 2 Analysis Populations

Pediatric Full Analysis Set (FA-S2): All participants aged less than 18 years at the beginning of Stage 2 who have been randomized in Stage 2 and have received at least one open label omalizumab injection as a part of their randomized Stage 2 treatment arm or attempted an OIT dose as a part of their randomized Stage 2 treatment arm. An OIT dose is defined as a partial or single dose of Multi-allergen OIT or placebo for Multi-allergen OIT. Participants who have only received treatment during the first 8 weeks of open-label omalizumab will not be included in this set. Participants will be analyzed according to the treatment arm to which they were randomized in Stage 2, regardless of the treatment they actually received in Stage 2.

Full Analysis Set (FFA-S2): All participants who have been randomized in Stage 2 and have received at least one open label omalizumab injection as a part of their randomized Stage 2 treatment arm or attempted an OIT dose as a part of their randomized Stage 2 treatment arm. Participants who have only received treatment during the first 8 weeks of open-label omalizumab will not be included in this set. Participants will be analyzed according to the treatment arm to which they were randomized in Stage 2, regardless of the treatment they actually received in Stage 2.

Pediatric Per-Protocol Set (PP-S2): All participants in the FA-S2 population who have completed at least 75% of scheduled injections with either omalizumab or placebo for omalizumab in Stage 2, have completed at least 80% of scheduled daily Multi-allergen OIT or placebo for Multi-allergen OIT doses in Stage 2 and have completed Stage 2. The PP-S2 set will only include participants who receive the correct treatment according to their randomization assignment and correct omalizumab dosing frequency in Stage 2. Participants with major protocol deviations that could be expected to materially affect efficacy or safety during Stage 2 as specified in the SAP will also be excluded from PP-S2.

Pediatric Pre-Randomization Safety Set (SS1-S2): All participants aged less than 18 years at the beginning of Stage 2 who receive an injection of open label omalizumab prior to receiving treatment in one of the two treatment arms in Stage 2.

Full Pre-Randomization Safety Set (FSS1-S2): All participants who receive an injection of open label omalizumab prior to receiving treatment in one of the two treatment arms in Stage 2.

Pediatric Safety Set (SS2-S2): All participants aged less than 18 years at the beginning of Stage 2 who have received at least one open label omalizumab injection as a part of their randomized Stage 2 treatment arm or attempted an OIT dose as a part of their randomized Stage 2 treatment arm. Participants who have only received treatment during the first 8 weeks of open-label omalizumab will not be included in this set. Participants will be analyzed according to the treatment they actually received in Stage 2, regardless of the treatment arm to which they were randomized in Stage 2. Treatment will be defined as omalizumab-

facilitated OIT if the participant attempted a partial or single dose of Multi-allergen OIT during Stage 2 or omalizumab + placebo OIT otherwise.

Full Safety Set (FSS2-S2): All participants who have received at least one open label omalizumab injection as a part of their randomized Stage 2 treatment arm or attempted an OIT dose as a part of their randomized Stage 2 treatment arm. Participants who have only received treatment during the first 8 weeks of open-label omalizumab will not be included in this set. Participants will be analyzed according to the treatment they actually received in Stage 2, regardless of the treatment arm to which they were randomized in Stage 2. Treatment will be defined as omalizumab-facilitated OIT if the participant attempted a partial or single dose of Multi-allergen OIT during Stage 2 or omalizumab + placebo OIT otherwise.

13.5.1.4 Stage 3 Analysis Populations

Pediatric Full Analysis Set (FA-S3): All participants aged less than 18 years at the start of Stage 3 who completed Stage 2 (see Section 11.1) and moved to Stage 3. Participants will be analyzed according to the treatment arm to which they were randomized in Stage 2, regardless of the treatment they actually received in Stage 2.

Full Analysis Set (FFA-S3): All participants who completed Stage 2 (see Section 11.1) and moved to Stage 3. Participants will be analyzed according to the treatment arm to which they were randomized in Stage 2, regardless of the treatment they actually received in Stage 2.

Pediatric Per-Protocol Set (PP-S3): All FA-S3 participants who receive the correct treatment according to their randomization assignment and correct omalizumab dosing frequency in Stage 2. Participants with major protocol deviations that could be expected to materially affect efficacy or safety during Stage 3 as specified in the SAP will also be excluded from PP-S3.

Pediatric Safety Set (SS-S3): All FA-S3 participants. Participants will be analyzed according to the treatment they actually received in Stage 2, defined as omalizumab-facilitated OIT if the participant received any dose (including a partial single dose) of OIT during Stage 2 and omalizumab + placebo OIT otherwise, regardless of the treatment arm to which they were assigned in Stage 2.

Full Safety Set (FSS-S3): All FFA-S3 participants. Participants will be analyzed according to the treatment they actually received in Stage 2, defined as omalizumab-facilitated OIT if the participant received any dose (including a partial single dose) of OIT during Stage 2 and omalizumab + placebo OIT otherwise, regardless of the treatment arm to which they were assigned in Stage 2.

Separate Stage 3 analysis populations for Stage 1 OLE participants are further defined in the SAP.

13.5.2 Timing of Analyses

Due to the multi-stage nature of the study design, analyses of the primary, secondary, and selected exploratory endpoints measured in each stage of the study will be conducted when all participants have completed that stage of the study (see Section 11.1) or have withdrawn from the study (see Section 11.2) and all data collected during that stage of the study are frozen (Stage 1/Stage 1 OLE and Stage 2) or locked (Stage 3). For instance, analyses of the primary, secondary, and selected exploratory endpoints measured in Stage 1/Stage 1 OLE of the study will be analyzed when all participants have withdrawn or completed Stage 1/Stage 1 OLE of the study (as applicable) and all data collected during Stage 1/Stage 1 OLE are frozen. Analyses of exploratory endpoints for Stage 1/Stage 1 OLE may be conducted at a later time. Appendix 13 provides a mapping of the endpoints in each stage that will be used to address each of the objectives in each stage.

13.5.3 Primary Analysis of Primary Endpoint

Using participants included in the FA-S1 set, the primary analysis of the primary endpoint will use a logistic regression model to estimate the odds ratio (and associated 95% Wald confidence interval) comparing consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 between the omalizumab and placebo for omalizumab arms. Fixed effects will only include treatment arm, age at randomized (<6 years versus ≥6 years), milk as a participant-specific food (yes/no), and the order of the blinded OFC to peanut during the DBPCFC. A two-sided significance level of 0.05 will be used. Further details of this analysis (including modifications to the planned analysis if the model does not converge) will be provided in the SAP.

13.5.4 Supportive Analyses of the Primary Endpoint

Sensitivity analyses of the primary endpoint will include:

- Cochran-Mantel-Haenszel test adjusting for age at Stage 1 randomization (<6 years versus ≥6 years) and milk as a participant-specific food (yes/no), using the FA-S1 population.
- Replication of the primary analysis of the primary endpoint, using the PP-S1 population.
- Replication of the primary analysis of the primary endpoint, using the FFA-S1 population.
- A tipping point analysis of the primary endpoint will also be performed to assess sensitivity of results to the MNAR assumption (see SAP for more details).

Supportive analyses of the primary endpoint will include:

- Separate subgroup analyses, using the FA-S1 population. Each analysis will fit a logistic regression model in each subgroup, similar to that described in Section 13.5.3. Subgroups will be defined by: 1) age at Stage 1 randomization (<6, 6 to <12, 12 to <18); 2) order of blinded OFC to peanut during the DBPCFC at the end of Stage 1; 3) race; 4) ethnicity; 5) sex; 6) CRU; 7) dose consumed during the Screening DBPCFC with dose-limiting symptoms (a single dose of ≤30 mg or 100 mg of peanut protein); and 8) omalizumab dosing frequency (2 or 4 weeks).
- A predictive model will also be developed to predict the probability of consuming a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 using each immune biomarker measured at the first Screening DBPCFC Visit. Only Stage 1 treatment arm, age at randomization (<6 years versus ≥6 years), milk as a participant-specific food (yes/no), and the order of the blinded OFC to peanut during the DBPCFC at the end of Stage 1 will be forced into the model as covariates. All immune biomarker levels measured at the first Screening DBPCFC Visit as well as the interaction between each immune biomarker and Stage 1 treatment arm will be included as possible covariates. Covariates will be log transformed, as appropriate.

13.5.5 Analyses of Secondary Endpoints

13.5.5.1 Key Secondary Endpoints

Using participants in the FA-S1 population who have cashew, milk, or egg as a participant-specific food and the results of the DBPCFCs at the end of Stage 1, consumption of a single dose of ≥1000 mg protein of cashew, milk, or egg without dose-limiting symptoms will be evaluated by applying a separate logistic regression model (similar to Section 13.5.3) to each Stage 1 key secondary endpoint. The significance level

used for each of these analyses will be adjusted to ensure that the overall family-wise error rate of the primary and Stage 1 key secondary endpoints is below 5% (see Section 13.5.5.2).

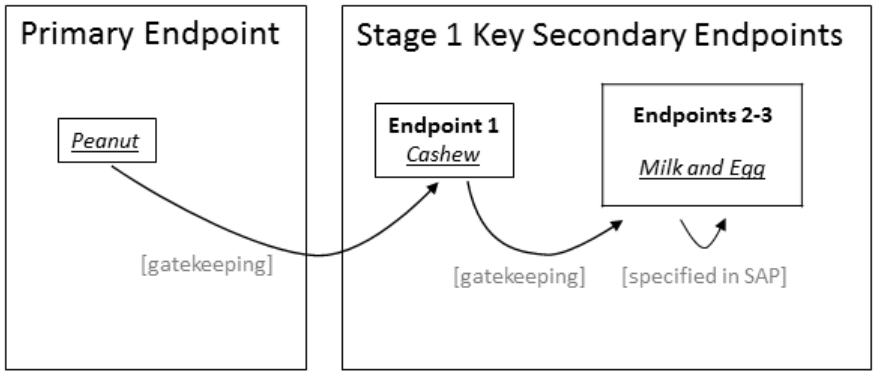
Using the FA-S2 population and the results of the DBPCFCs at the end of Stage 2, consumption of ≥1 dose of 2000 mg protein of all three foods without dose-limiting symptoms (Key Secondary Endpoint 4) will be evaluated by applying a logistic regression model to estimate the odds ratio (and associated 95% Wald confidence interval) between the omalizumab-facilitated OIT and omalizumab + placebo OIT arms. Fixed effects will only include Stage 1 treatment arm, Stage 2 treatment arm, an interaction between Stage 1 and Stage 2 treatment arm, age at Stage 1 randomization (<6 years versus ≥6 years), milk as a participant-specific food, and the order of the blinded OFC to peanut during the DBPCFC at the end of Stage 2. A two-sided significance level of 0.05 will be used without any further Type I error control.

13.5.5.2 Type I Error Control

To control the inflation of Type I error that arises when multiple tests of comparison are performed within and across multiple families of endpoints (i.e., the primary endpoint as well as Stage 1 key secondary endpoints), both gatekeeping and multiple testing strategies will be performed to ensure the overall family-wise error rate is below 5%. All hypotheses testing under Type I error control will be performed in the FA-S1 population.

As shown in Figure 13.5.5.2, a gatekeeping procedure will be used to sequentially test the primary endpoint and Stage 1 key secondary endpoints. Gatekeeping will not proceed if a hypothesis is rejected in the wrong direction (i.e., placebo for omalizumab arm has a higher proportion of participants who consume without dose-limiting symptoms than the omalizumab arm).

Figure 13.5.5.2 Gatekeeping and multiple testing strategies



First, the primary endpoint will be tested using a two-sided significance level of 0.05. If the null hypothesis corresponding to the primary endpoint is not rejected, the key secondary endpoints will be analyzed as exploratory without further Type I error control and all p-values will be considered nominal. But, if the null hypothesis corresponding to the primary endpoint is rejected, the key secondary endpoint corresponding to consumption of a single dose of ≥1000 mg of cashew protein without dose-limiting symptoms will then be tested using a two-sided significance level of 0.05.

If the null hypothesis corresponding to consumption of a single dose of ≥1000 mg of cashew protein without dose-limiting symptoms is rejected, the key secondary endpoints corresponding to the consumption of a single dose of ≥1000 mg of milk and egg protein without dose-limiting symptoms will be

tested. Details for the Type I error control procedure within these two endpoints will be specified in the SAP.

No Type I error control will be implemented for testing Key Secondary Endpoint 4.

13.5.5.3 Other Secondary Endpoints

The analyses of all secondary endpoints that are not key secondary endpoints are summarized in Table 13.5.5.3. 95% confidence intervals will also be reported of all applicable endpoint estimates. A two-sided significance level of 0.05 will be used for superiority tests and a one-sided significance level of 0.025 will be used for the non-inferiority test. Endpoints will be log-transformed, as appropriate.

Table 13.5.5.3 Other Secondary Endpoints

Stage	Secondary Endpoint		Analysis Population	Type of Test	Model	Fixed Effects	Endpoint Estimate (95% CI reported)
1	5	Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 (except those endpoints already defined by the primary and key secondary endpoints)	FA-S1	Superiority	Logistic Regression Model	Stage 1 treatment arm, age (<6 years versus ≥6 years), milk as a participant-specific food (yes/no), and the order of the blinded OFC to peanut during the DBPCFC at the end of Stage 1	Odds ratio between omalizumab and placebo for omalizumab arms
	6	Number of foods consumed at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 1			Ordinal Logistic Regression Model		Odds ratio comparing consumption of a higher number of foods without dose-limiting symptoms between the omalizumab and placebo for omalizumab arms
2	7	Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2 (except the endpoint already defined by the primary endpoint for Stage 2)	FA-S2	Superiority	Logistic Regression Model	Stage 1 treatment arm, Stage 2 treatment arm, interaction between Stage 1 and Stage 2 treatment arm, age at Stage 1 randomization (<6 years versus ≥6 years), milk as a participant-specific food, and the order of the blinded OFC to peanut during the DBPCFC at the end of Stage 2	Odds ratio between the omalizumab-facilitated OIT and omalizumab + placebo OIT arms
	7*	Consumption of a single dose of ≥600 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2		Non-Inferiority	Logistic Regression Model		Odds ratio between the omalizumab-facilitated OIT and omalizumab + placebo OIT arms
	8	Number of foods consumed at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food without dose-		Superiority	Ordinal Logistic Regression Model		Odds ratio comparing consumption of a higher number of foods without dose-limiting symptoms between the omalizumab-facilitated OIT and

Stage	Secondary Endpoint		Analysis Population	Type of Test	Model	Fixed Effects	Endpoint Estimate (95% CI reported)
		limiting symptoms during the DBPCFC at the end of Stage 2					omalizumab + placebo OIT arms
3	9	Number of weeks in each eight-week period during Stage 3 where ≥300 mg protein of each food is consumed at least twice per week[1]	FA-S3	Superiority	Generalized Estimating Equation	Stage 1 treatment arm, Stage 2 treatment arm, interaction between Stage 1 and Stage 2 treatment arm, age at Stage 1 randomization (<6 years versus ≥6 years), milk as a participant-specific food, and the eight-week period during which the endpoint was measured	The ratio of the rate of consumption of each food at least twice per week in each eight-week period between the omalizumab-facilitated OIT and omalizumab + placebo OIT arms in Stage 2
	10	Number of weeks in each eight-week period during Stage 3 where each food is not consumed[1]			Generalized Estimating Equation		The ratio of the rate of not consuming each food in each eight-week period between the omalizumab-facilitated OIT and omalizumab + placebo OIT arms in Stage 2

1. For each individual food endpoint other than peanut, participants in the FA-S1, FA-S2, or FA-S3 population with the food designated as a participant-specific food will be included in the analysis.
2. These endpoints will also be summarized in participants in the FA-S1OLE population who enter Stage 3.

To test that omalizumab + placebo OIT is not inferior to omalizumab-facilitated OIT, a non-inferiority test based on a one-sided significance level of 0.025 and a non-inferiority margin for the odds ratio of 0.35 will be performed when estimating the odds ratio of a participant consuming a single dose of ≥600 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2 between the omalizumab-facilitated OIT and omalizumab + placebo OIT arms in the FA-S2 population (i.e., Secondary Endpoint 7*). A non-inferiority margin for the odds ratio of 0.35 was selected because:

1. Any difference in the proportion of participants meeting this endpoint between the arms smaller than 18% is not clinically significant.
2. Unpublished data from MAP-X,[56] a previous Phase 2 study, showed that approximately 85% of participants in an arm similar to omalizumab-facilitated OIT consumed a single dose of ≥600 mg protein of all three foods without dose-limiting symptoms. Assuming 10% of participants on a non-active placebo would be expected to meet this endpoint, a non-inferiority margin of 18% would be equivalent to 24% of an expected 75% effect size between omalizumab-facilitated OIT and non-active placebo. Under this scenario, a 18% non-inferiority margin in the difference in proportion equates to a non-inferiority margin for the odds ratio of 0.35.

In the case that participants in the omalizumab + placebo OIT arm have significantly higher odds of consuming a single dose of ≥600 mg protein of all three foods without dose-limiting symptoms than participants in the omalizumab-facilitated OIT arm, superiority will be concluded.

13.5.5.4 Supportive Analyses of Secondary Endpoints

Supportive analyses of secondary endpoints will include:

- For each food other than peanut, a predictive model will be developed to predict the probability of consuming a single dose of ≥1000 mg protein of the food without dose-limiting symptoms during

the DBPCFC at the end of Stage 1 using each immune biomarker measured at the first Screening DBPCFC Visit. Only Stage 1 treatment arm, age (<6 years versus ≥6 years), milk as a participant-specific food (yes/no), and the order of the blinded OFC to peanut during the DBPCFC at the end of Stage 1 will be forced into the model as covariates. All immune biomarker levels measured at the first Screening DBPCFC Visit as well as the interaction between each immune biomarker and Stage 1 treatment arm will be included as possible covariates. Covariates will be log transformed, as appropriate.

- A separate analysis of each secondary endpoint measured in Stage 2 will be performed in each of the following two subgroups: participants who do not respond to 16-20 weeks of treatment with omalizumab in Stage 1 and participants who respond to 16-20 weeks of treatment with omalizumab in Stage 1. A responder will be defined as a participant who consumes a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1. These analyses will be based on a logistic regression model and will estimate the odds ratio comparing consumption of each food protein without dose-limiting symptoms during the DBPCFC at the end of Stage 2 between omalizumab-facilitated OIT and omalizumab + placebo OIT arms.

- A predictive model will be developed to predict the probability of consuming ≥1 dose of 2000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2 using each immune biomarker measured at the first DBPCFC Visit at the end of Stage 1. Only Stage 1 treatment arm, Stage 2 treatment arm, and the order of the blinded OFC to peanut during the DBPCFC at the end of Stage 2 will be forced into the model as covariates. All immune biomarker levels measured at the first DBPCFC Visit at the end of Stage 1 and the interaction between each immune biomarker and Stage 2 treatment arm will be included as possible covariates. Covariates will be log transformed, as appropriate.

- Using the FA-S3 population and each sub-group defined by Stage 1 treatment arm, a generalized estimating equation will also be used to estimate the rate ratio comparing the mean rate each food is consumed at least twice per week in each eight-week period during Stage 3 between the two arms in Stage 2.

13.5.5.5 Safety Endpoints

Using the pediatric safety sets in Stage 1, 1 OLE, 2, and 3 (see Section 13.5.1), the number of AEs related to the study therapy regimen will be summarized by treatment arm, AE grade, and AE severity. The number and proportion of participants experiencing at least one AE related to the study therapy regimen will also be summarized by treatment arm, AE grade, and AE severity. Separate summaries will be generated for SAEs, deaths, AESIs (defined in Section 12.2.2), and AEs leading to discontinuation of study drug.

Descriptive summaries of laboratory values at baseline and throughout the study will be generated for selected parameters. For these selected parameters, changes from baseline and the proportion of participants experiencing clinically significant changes relative to baseline will be compared between randomized treatment arms.

Similar analyses for Stage 3 AEs will be conducted for SS-S1OLE participants who enter Stage 3.

13.5.6 Analyses of Exploratory Endpoints

Exploratory endpoints measured in Stage 1, Stage 1 OLE, Stage 2, and Stage 3 will be analyzed using the participants included in the FA-S1, FA-S1OLE, FA-S2, and FA-S3 sets respectively. For each individual food endpoint other than peanut, participants in the FA-S1, FA-S1OLE, FA-S2, or FA-S3 population with the food designated as a participant-specific food will be included in the analysis. All analyses will be based on a two-sided significance level of 0.05; 95% confidence intervals of the appropriate endpoint estimate will also be reported.

Exploratory Endpoint 1: For each food, an ordinal logistic regression model will be used to analyze the percent change in the maximum dose of food protein consumed without dose-limiting symptoms during the DBPCFC at the end of Stage 1 and during the DBPCFC at the end of Stage 2. Fixed effects will only include Stage 1 treatment arm, Stage 2 treatment arm, age (<6 years versus ≥6 years), an interaction between Stage 1 and Stage 2 treatment arms, milk as a participant-specific food (yes/no), and the order of the blinded OFC to peanut during the DBPCFC at the end of Stage 1 and Stage 2. This model will estimate the ratio of the odds that a higher maximum dose of food protein was consumed without dose-limiting symptoms during the DBPCFC at the end of Stage 2 compared to the DBPCFC at the end of Stage 1 between the omalizumab-facilitated OIT and omalizumab + placebo OIT arms. Should the distribution of this endpoint not meet the assumptions of an ordinal logistic regression model, other models may be considered, as further specified in the SAP.

Exploratory Endpoint 2: The proportion of participants consuming a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE will be summarized.

Exploratory Endpoint 3: The proportion of participants consuming 0, 1, 2, or 3 foods at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE will be summarized.

Exploratory Endpoint 4: Linear mixed models will be used to estimate the change over time (relative to Week 0 in Stage 1) in quality of life (total score as well as each sub-domain). For Stage 1 analyses, the change over time in quality of life measured in Stage 1 will be compared between treatment arms in Stage 1 using a model that includes a random intercept and fixed effects for treatment arms in Stage 1, age (<6 years versus ≥6 years), milk as a participant-specific food (yes/no), time of measurement, and an interaction term between treatment arms in Stage 1 and time of measurement. For Stage 2 analyses, the change over time in quality of life measured in Stage 1 and Stage 2 will be compared between treatment arms in Stage 2 using a linear mixed model that includes a random intercept and fixed effects for Stage 1 treatment arm, Stage 2 treatment arm, an interaction between Stage 1 and Stage 2 treatment arms, age (<6 years versus ≥6 years), milk as a participant-specific food, time of measurement, and an interaction term between Stage 1 treatment arm, Stage 2 treatment arm, and time of measurement. For Stage 3 analyses, a similar model will be used to compare the change over time in quality of life measured in Stage 1, Stage 2, and Stage 3 between treatment arms in Stage 2.

The mean difference in quality of life between Week 0 in Stage 1 and the first DBPCFC Visit at the end of Stage 1, the first omalizumab injection visit in Stage 1 OLE, and the first and last DBPCFC Visit at the end of Stage 1 OLE will be summarized in FA-S1OLE participants. The mean difference in quality of life between Week 0 in Stage 1 and the first DBPCFC Visit at the end of Stage 1, the first omalizumab injection visit in Stage 1 OLE, the first and last DBPCFC Visit at the end of Stage 1 OLE, and six months after the beginning of Stage 3 will be summarized in FA-S1OLE participants who enter Stage 3.

Exploratory Endpoint 5: Omalizumab trough concentration measured at the first Screening DBPCFC Visit and in Stage 1, Stage 1 OLE, and Stage 2 will be summarized at each time point and each omalizumab dosing regimen, as appropriate.

Exploratory Endpoints 6-12: Linear (or nonlinear, if appropriate) mixed models will be used to estimate the geometric mean ratio over time (relative to the first Screening DBPCFC Visit) of each immune biomarker. Models will be similar to that described for Exploratory Endpoint 4.

The change in the immune biomarkers between the first Screening DBPCFC Visit, the first DBPCFC Visit at the end of Stage 1, and the first DBPCFC Visit at the end of Stage 1 OLE will be summarized in FA-S1OLE participants. The change in the immune biomarkers between the first Screening DBPCFC Visit, the first DBPCFC Visit at the end of Stage 1, the first DBPCFC Visit at the end of Stage 1 OLE, and six months after beginning Stage 3 will be summarized in FA-S1OLE participants who enter Stage 3.

Ratios between immune biomarkers (other than IgG4/IgE) may be evaluated by applying similar approaches to that described above.

Exploratory Endpoint 13: Linear mixed models will be used to estimate the mean difference in the SPT wheal size to each food over time (relative to the SPT wheal size at the Screening Visit). Models will be similar to that described for Exploratory Endpoints 4.

The mean difference in SPT wheal size between the Screening Visit, the first DBPCFC Visit at the end of Stage 1, and the first DBPCFC Visit at the end of Stage 1 OLE will be summarized in FA-S1OLE participants. The mean difference in SPT wheal size between the Screening Visit, the first DBPCFC Visit at the end of Stage 1, the first DBPCFC Visit at the end of Stage 1 OLE, and six months after the beginning of Stage 3 will be summarized in FA-S1OLE participants who enter Stage 3.

13.5.7 Descriptive Analyses

Descriptive analyses will be reported separately for randomized study therapy regimens in each stage separately. Continuous variables will be reported using the mean, standard deviation, minimum, maximum, median, first and third quartiles, and sample size. Categorical variables will be reported as frequencies and percentages.

13.6 Statistical Hypotheses

Most analyses of primary and secondary endpoints will be based on two-sided superiority tests. For example, the null and alternative hypotheses for the primary endpoint are:

Null hypothesis: The odds of a participant consuming a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 in omalizumab and placebo for omalizumab arms are equal.

Alternate hypothesis: The odds of a participant consuming a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 in omalizumab and placebo for omalizumab arms are not equal.

The endpoint measuring consumption of a single dose of ≥600 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2 will be based on a one-sided non-inferiority test. The null and alternative hypotheses for this endpoint are:

Null hypothesis: The odds ratio of a participant consuming a single dose of ≥600 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2 between the omalizumab + placebo OIT arm and omalizumab-facilitated OIT arm is less than 0.35. This hypothesis implies that omalizumab + placebo OIT is inferior to omalizumab-facilitated OIT.

Alternative hypothesis: The odds ratio of a participant consuming a single dose of ≥600 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2 between the omalizumab + placebo OIT arm and omalizumab-facilitated OIT arm is greater than 0.35. This hypothesis implies that omalizumab + placebo OIT is not inferior to omalizumab-facilitated OIT within the 0.35 non-inferiority margin.

13.7 Sample Size Considerations

All power calculations were performed using SAS version 9.4.

13.7.1 Stage 1

A total of 225 participants (150 omalizumab and 75 placebo for omalizumab) will be randomized in Stage 1 of this study. 210 of those participants are expected to be younger than 18 years of age, with at least 50 aged 1 year to less than 6 years.

Primary Endpoint: Table 13.7.1a provides the estimated power to detect an odds ratio of consuming a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 between the omalizumab and placebo for omalizumab arms. Power calculations for this endpoint were performed using Fisher's exact tests with a two-sided Type I error rate of 5%. For example, assuming 10% of participants randomized to placebo for omalizumab in Stage 1 and 70% of participants randomized to omalizumab in Stage 1 consume a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1, a sample size of 210 participants (140 omalizumab and 70 placebo) will provide more than 99% power to detect the odds ratio of 21.0. Alternatively, this sample size will allow us to detect an odds ratio of 3.3-3.8 between the two arms in Stage 1 with 80%-90% power if 10% of participants randomized to placebo for omalizumab in Stage 1 and 27%-30% of participants randomized to omalizumab in Stage 1 consume a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.

Table 13.7.1a Power Justification of the Primary Endpoint

Sample Size	Per Arm (Omalizumab:Placebo)	Proportion of Participants who Consume a Single Dose of ≥600 mg of Peanut Protein without Dose-Limiting Symptoms During the DBPCFC at the End of Stage 1		Odds Ratio	Power
		Omalizumab	Placebo for omalizumab		
210	140:70	70%	10%	21.0	>99%
210	140:70	60%	10%	13.5	>99%
210	140:70	50%	10%	9.0	>99%
210	140:70	30%	10%	3.8	90%
210	140:70	27%	10%	3.3	80%

Stage 1 Key Secondary Endpoints: For Secondary Endpoint 1-3, it is assumed that cashew, milk, and egg allergies will have a prevalence of 59%, 30%, and 27% respectively (based on unpublished data obtained from M-TAX[57] and MAP-X[56]). Power calculations are based on a Fisher's exact test and a significance level of 0.05 (i.e., no correction for Type I error control). Under this assumption, Table 13.7.1b provides the minimum odds ratio of consuming a single dose of ≥1000 mg protein of each food without dose-limiting symptoms between omalizumab versus placebo for omalizumab arms that can be detected to achieve 80% and 90% power under the assumption that 10% of participants randomized to placebo for omalizumab consume a single dose of ≥1000 mg protein of each food without dose-limiting symptoms. For example, if 59% of participants have an allergy to cashew and 10% of participants in the placebo arm consume a single dose of ≥1000 mg of cashew protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1, this study will be able to detect an odds ratio of consuming a single dose of ≥1000 mg cashew protein without dose-limiting symptoms of 5.3 between omalizumab and placebo for omalizumab arms with 90% power and a 5% Type I error rate.

Table 13.7.1b Minimum Odds Ratio to Achieve 80% and 90% Power in Consumption of a Single Dose of ≥1000 mg protein of Cashew, Milk, and Egg without Dose-Limiting Symptoms during the DBPCFC at the End of Stage 1 between Arms

Food	Prevalence of Food Allergy	Total Expected Sample Size (Omalizumab:Placebo)	Minimum Odds Ratio to Achieve 80% Power[1]	Minimum Odds Ratio to Achieve 90% Power[1]
Cashew	59%	123 (82:41)	4.5	5.3
Egg	30%	63 (42:21)	7.5	9.5
Milk	27%	57 (38:19)	8.3	10.6

1. Assuming 10% of participants randomized to placebo for omalizumab consume a single dose of ≥1000 mg protein of each food without dose-limiting symptoms.

13.7.2 Stage 2

Participants must complete Stage 1 (see Section 11.1) to move to Stage 2. Assuming approximately 10% of the 210 participants aged less than 18 years do not complete Stage 1 and 60 participants aged less than 18 years move into Stage 1 OLE, it is expected that 128 participants aged less than 18 years will be randomized in Stage 2. The assumption that all 60 participants in Stage 1 OLE would be aged less than 18 years provides the minimum possible sample size for Stage 2. The justification for this expected sample size is provided using the following two endpoints measured in Stage 2.

- Stage 2 Primary Endpoint (Key Secondary Endpoint 4): Consumption of ≥1 dose of 2000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2: Using a two-sided Fisher's exact test with a Type I error rate of 5% and assuming 60% of participants randomized to omalizumab + placebo OIT and 85% of participants randomized to omalizumab-facilitated OIT consume a dose of ≥1 dose of 2000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2 (resulting in an odds ratio of 3.8), a sample size of 128 (64 per arm) will provide 86% power to detect this odds ratio.

- Stage 2 Secondary Endpoint: Consumption of a single dose of ≥600 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2: Using a binomial non-inferiority test with a one-sided Type I error rate of 2.5%, a non-inferiority margin for the odds ratio of 0.35, and assuming that

86% of participants in both the omalizumab-facilitated OIT and omalizumab + placebo OIT arms consume a single dose of ≥600 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2, a sample size 128 (64 per arm) will provide 84% power to detect non-inferiority of omalizumab + placebo OIT to omalizumab-facilitated OIT.

14 Identification and Access to Source Data

14.1 Source Data

Source documents and source data are considered to be the original documentation where participant information, visits consultations, examinations 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.

14.2 Access to Source Data

The PI and CRU staff will make all source data available to the Sponsor (DAIT/NIAID), Genentech, Novartis, as well as to relevant health authorities. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

15 Protocol Deviations

15.1 Protocol Deviation Definitions

Protocol Deviation – The PIs and CRU 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 CRU and implemented promptly where appropriate.

Major Protocol Deviation (Protocol Violation) – A Protocol Violation is a deviation from the IRB approved protocol that may affect the participant's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human participant 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. Examples of Major Protocol Deviations will be defined in the MOP.

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 participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

15.2 Reporting and Managing Protocol Deviations

The PI has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor, DAIT/NIAID. However, protocol deviations may also be identified during CRU monitoring visits or during other forms of study conduct review.

Upon determination that a protocol deviation has occurred, CRU staff will: a) notify the PI, b) notify the SACCC, and c) complete a Protocol Deviation form. The Protocol Deviation form will document at minimum the date the deviation occurred, the date it was identified, a description of the event, whether the deviation resulted in an SAE/AE, PI signature, single IRB reporting requirement, and documentation of a corrective action plan. The Sponsor, DAIT/NIAID, may request discussion with the PI to determine the effect of the protocol deviation on the overall study and corrective

actions. The PI will sign the paper source Protocol Deviation CRF, electronically sign Major Deviations in the EDC system, and submit the deviation to the single IRB and local IRB/ethics committee per IRB regulations. Major protocol deviations will be reported to the NIAID Allergy and Asthma DSMB by the DAIT/NIAID Medical Monitor at the medical monitor's discretion.

16 Ethical Considerations and Compliance with Good Clinical Practice

16.1 Quality Control and Quality Assurance

The PI is required to keep accurate records to ensure that the conduct of the study is fully documented. The PI is required to ensure that all CRFs are completed for every participant entered in the trial.

The Sponsor, DAIT/NIAID, is responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

The eCRFs will be completed online via a web-based EDC system that has been validated and is compliant with Part 11 Title 21 of the CFR. CRU staff at the CRU will enter information into the eCRFs, and the data will be stored remotely at a central database. Data quality will be ensured through the EDC system's continuous monitoring of data and real-time detection and correction of errors. All elements of data entry (i.e., time, date, verbatim text, and the name of the person performing the data entry) will be recorded in an electronic audit trail to allow all changes in the database to be monitored and maintained in accordance with federal regulations.

Per 21CFR 312.62(c), the clinical research records must be retained for a minimum of two years after the marketing application is approved for the drug for the indication for which it was being investigated. Alternatively, if no application will be filed or if the application is not approved for the requested indication, the records must be retained for a minimum of two years after the investigation is discontinued and FDA is notified. Documents may also be retained for a longer period, if required by the applicable regulatory, the institution's requirements or by an agreement with the Sponsor.

16.2 Statement of Compliance

This clinical study will be conducted using 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, informed consent/assent materials, and any information given to the participant will be reviewed and approved by the single IRB. Any amendments to the protocol, informed consent/assent materials, or any information given to the participant will also be approved by the single IRB before they are implemented.

16.3 Informed Consent/Assent Process

The consent process will provide information about the study to each prospective participant and/or parent/legal guardian and will allow adequate time for review and discussion prior to his/her decision. The PI or designee listed on the FDA 1572 will review the consent and answer questions as needed. Consent designees must be listed on the CRU delegation of responsibilities log and have demonstrated knowledge of the protocol and study procedures. The participant and/or parent/legal guardian will be told that being in the trial is voluntary and that the participant may withdraw from the study at any time, for any reason. All participants and/or parents/legal guardians will be asked to read, sign, and date a consent form before the participant enters the study, takes study drug, or undergoes any study-specific procedures. Each participant will also sign an assent, as appropriate. Consent materials will be presented in the participant's and/or parent's/legal guardian's primary language. A copy of the signed consent form will be given to the participant or parent/legal guardian as well.

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.

16.4 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 all participant information. CRU staff will not transmit documents containing protected health information to the Sponsor, DAIT/NIAID, or their representatives.

17 Publication Policy

The CoFAR policy on the publication of study results will apply to this trial.

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Appendix 1: Definition of Dose-Limiting Symptoms

OFCs will be considered positive with the occurrence of any dose-limiting symptoms during a single dose, which in the view of the PI indicate a true allergic reaction which should preclude the administration of any further doses. As defined below, mild symptoms are not usually considered dose-limiting, although a combination of mild symptoms during a single dose might lead to the cessation of an OFC at the discretion of the PI. All moderate and severe symptoms as defined below are considered dose-limiting.

Mild:

- Skin – limited (few) or localized hives, swelling (e.g., mild lip edema), skin flushing (e.g., few areas of faint erythema) or mild pruritus (e.g., occasional scratching)
- Respiratory – rhinorrhea (e.g., occasional sniffling or sneezing), nasal congestion, occasional cough, throat discomfort
- GI – mild abdominal discomfort (including mild nausea with or without decreased activity), isolated emesis thought to be secondary to gag

Moderate:

- Skin – systemic hives (e.g., numerous or widespread hives), swelling (e.g., significant lip or face edema), pruritus causing protracted scratching, more than a few areas of erythema or pronounced erythema
- Respiratory – throat tightness without hoarseness, persistent cough, wheezing without dyspnea
- GI – persistent moderate abdominal pain/cramping/nausea with decreased activity, vomiting

Severe:

- Skin – severe generalized urticaria/angioedema/erythema
- Respiratory – laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea, stridor
- GI – severe abdominal pain/cramping/repetitive vomiting
- Neurological – change in mental status
- Circulatory – clinically significant hypotension

Appendix 2: Omalizumab Dosing Table

	Body Weight (kg)												
Baseline IgE (IU/mL)	≥10-12	> 12-15	>15-20	>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30-100	75	75	75	75	75	75	150	150	150	150	150	300	300
>100-200	75	75	75	150	150	150	300	300	300	300	300	450	600
>200-300	75	75	150	150	150	225	300	300	450	450	450	600	375
>300-400	150	150	150	225	225	300	450	450	450	600	600	450	525
>400-500	150	150	225	225	300	450	450	600	600	375	375	525	600
>500-600	150	150	225	300	300	450	600	600	375	450	450	600	
>600-700	150	150	225	300	225	450	600	375	450	450	525		
>700-800	150	150	150	225	225	300	375	450	450	525	600		
>800-900	150	150	150	225	225	300	375	450	525	600			
>900-1000	150	150	225	225	300	375	450	525	600				
>1000-1100	150	150	225	225	300	375	450	600					
>1100-1200	150	150	225	300	300	450	525	600					
>1200-1300	150	225	225	300	375	450	525						
>1300-1500	150	225	300	300	375	525	600						
>1500-1850		225	300	375	450	600							

DO NOT DOSE

Dosing frequency:

	Dose every 4 weeks
	Dose every 2 weeks
	Do not dose

Appendix 3: Evaluation of Asthma Control

The evaluation of asthma control will be assessed using the GINA Guidelines updated in 2018 as described in the table below.

Asthma symptom control				
In the past 4 weeks, has the patient had:		**Well controlled**	**Partly controlled**	**Uncontrolled**
Daytime asthma symptoms more than twice/week?	Yes ☐ No ☐			
Any night waking due to asthma?	Yes ☐ No ☐			
Reliever needed for symptoms* more than twice/week?	Yes ☐ No ☐	None of these	1-2 of these	3-4 of these
Any activity limitation due to asthma?	Yes ☐ No ☐			

Individuals who meet the criteria of Uncontrolled are not eligible for enrollment as study participants.

Appendix 4: Schedule of Events for Screening and Stage 1

	Screen	Screening DBPCFC	Omalizumab Injection[1]		DBPCFC		UV[2]	Early Discontinuation[3]
Week During Stage 1	**-15 weeks[4]**		**0**	**2-14**	**16**	**17-20**		
Study Assessments								
ICF	X							
Demographics	X							
Vitals & Growth Parameters	X	X	X	X	X	X	X	X
Medical History	X	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
Physical Exam	X	X	X[6]	X[6]	X	X	X[7]	X[6]
Spirometry and PEF	X[8]	X[9]			X[9]	X[9]	X[10]	
SCORAD[11]		X[12]			X			
Diet & Allergy Questionnaire	X	X	X	X	X	X	X	X
GI Symptoms Questionnaire		X	X	X	X	X	X	X
Family History Questionnaire			X					
FAQLQ			X		X			
Review Diaries							X[13]	X[13]
Monthly Long-Term Follow-Up Questionnaires							X[22]	X[22]
Epinephrine Autoinjector Training Form and Food Allergy Action Plan	X							
Concomitant Medications	X	X	X	X	X	X	X	X
SPT	X[14]				X[15]			X[15, 16]
Blinded OFC		X			X	X		
AEs	X	X	X	X	X	X	X	X
Randomization			X					
Omalizumab or placebo for omalizumab administration			X	X	X	X	X	
Sample Collections								
Blood[17]								
Total IgE	X	X[18]			X			X[16]
Total Free IgE		X[18]			X			X[16]
Allergen-Specific IgE	X	X[18]			X			X[16]
Allergen-Specific IgG4 and IgA		X[18]			X			X[16]
Basophil Activation		X[18]			X			X[16]
PK Sampling		X[18]			X			
Samples for Mechanistic Studies		X[18]			X			
Provide Stool Collection Kit and Specimen Information Questionnaire		X[19]						
Collect Stool Collection Kit and Specimen Information Questionnaire		X[20]	X[20]					
Urine			X		X			
Saliva			X		X			
Safety Sample Collections								
Blood								
CBC With Differential	X	Every 3 months					X	X[16]
CMP	X	Every 3 months					X	X[16]
Urine								
Urinalysis	X	Every 3 months					X	X[16]
Urine Pregnancy Test[21]	X	Monthly					X	X

1. Omalizumab injection visits may occur every two or four weeks, determined by the body weight in kilograms and total serum IgE level at the Screening Visit.
2. Unscheduled Visits (UV) may occur at any time during the study.
3. Early Discontinuation Visits may occur at any time during the study.
4. Screening may take up to 15 weeks.
5. An interim medical history will be collected.
6. A limited physical exam will be performed.
7. A comprehensive or limited physical exam will be performed, as needed.
8. Spirometry will be performed for participants who are age seven years or older and are able to perform spirometry; peak flow will be performed for participants who are unable to perform spirometry.
9. Peak flow only.
10. Peak flow, as needed.
11. SCORAD will be performed for participants with AD. AD is determined by the PI or licensed clinician based on the current medical history and/or the physical exam.
12. SCORAD will only be assessed prior to initiating the blinded OFC at the first Screening DBPCFC Visit.
13. Only performed if participant is in Stage 2, Stage 3 Rescue OIT, or if participant has less than or equal to six months of Long-term follow-up with dietary consumption in Stage 3.
14. SPT to food and environmental allergens.
15. SPT to peanut and two other foods.
16. Only applicable if has not been completed within the eight weeks preceding the Early Discontinuation Visit.
17. If safety labs coincide with the bioassay/mechanistic blood collection, the priority, in terms of blood volume, is the safety labs.

18. Samples will be collected prior to initiating the blinded OFC at the first Screening DBPCFC Visit.
19. Provide stool collection kit and specimen information questionnaire at the first Screening DBPCFC Visit.
20. Collect stool collection kit and specimen information questionnaire at any time prior to the first injection visit in Stage 1 (or Stage 2 for replacement participants).
21. Only needed for female participants of child-bearing potential
22. Monthly questionnaires only completed if participant has more than six months of follow-up in Stage 3 with dietary consumption or avoidance .

Appendix 5: Schedule of Events for Stage 1 Open Label Extension

	Omalizumab Injection[1]		DBPCFC	
Week During Stage 1 OLE	**0**	**2-22**	**24**	**25-28**
Study Assessments				
Vitals & Growth Parameters	X	X	X	X
Interim Medical History	X	X	X	X
Physical Exam	X[2]	X[2]	X	X
PEF			X	X
SCORAD[3]			X	
Diet & Allergy Questionnaire	X	X	X	X
GI Symptoms Questionnaire	X	X	X	X
Family History Questionnaire	X[4]			
FAQLQ	X		X[5]	X[5]
Concomitant Medications	X	X	X	X
SPT			X[6]	
Blinded OFC			X	X
AEs	X	X	X	X
Open label omalizumab administration	X	X	X	X
Unblinding to DBPCFC Results				X[7]
Sample Collections				
Blood				
Total IgE			X	
Total Free IgE			X	
Allergen-Specific IgE, IgG4, IgA			X	
Basophil Activation			X	
PK Sampling			X	
Safety Sample Collections				
Blood				
CBC With Differential	Every 3 months			
CMP	Every 3 months			
Urine				
Urinalysis	Every 3 months			
Urine Pregnancy Test[7]	Monthly			

1. Omalizumab injection visits may occur every two or four weeks, determined by the body weight in kilograms and total serum IgE level at the Screening Visit.
2. A limited physical exam will be performed.
3. SCORAD will be performed for participants with AD. AD is determined by the PI or licensed clinician based on the current medical history and/or the physical exam.
4. An interim family history questionnaire will be collected.
5. FAQLQ will be collected prior to initiating the first blinded OFC and after completing the last blinded OFC in the OLE.
6. SPT to peanut and two other foods.
7. Unblind each participant to OFC results after completing the last blinded OFC in the OLE.
8. Only needed for female participants of child-bearing potential.

Appendix 6: Schedule of Events for Stage 2

	Omalizumab Injection		IDE	Build-Up[1]	Build-Up and/or Maintenance[1,2]	Maintenance[2]		DBPCFC	
Week During Stage 2	**0**	**2-6**	**8**	**8+1 day[3]**	**10-14**	**16-up to 32**	**34-60**	**60**	**61-64**
Study Assessments									
Vitals & Growth Parameters	X	X	X	X	X	X	X	X	X
Interim Medical History	X	X	X	X	X	X	X	X	X
Physical Exam	X[4]	X[4]	X	X[4]	X[4]	X[4]	X[4]	X	X
PEF			X	X	X[20]	X[20]	X[20]	X	X
SCORAD[5]								X	
Diet & Allergy Questionnaire	X	X	X	X	X	X	X	X	X
GI Symptoms Questionnaire	X	X	X	X	X	X	X	X	X
Family History Questionnaire	X[6]								
FAQLQ	X							X[7]	X[7]
Review Diaries			X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
SPT								X[8]	
Blinded OFC								X	X
AEs	X	X	X	X	X	X	X	X	X
Open label omalizumab administration	X[9]	X[9]	X[10]	X[10]	X[11]				
Randomization		X[12]							
Omalizumab or placebo for omalizumab administration						X[9,11]	X[9]	X[9]	X[9]
Multi-allergen OIT or placebo for Multi-allergen OIT			X	X	X	X	X		
Unblinding to DBPCFC Results									X[13]
Sample Collections									
Blood[14]									
Total IgE								X	
Total Free IgE			X			X[15]		X	
Allergen-Specific IgE								X	
Allergen-Specific IgG4 and IgA			X			X[15]		X	
Basophil Activation			X			X[15]		X	
PK Sampling			X					X	
Samples for Mechanistic Studies			X			X[15]		X	
Provide Stool Collection Kit and Specimen Information Questionnaire		X[16]					X[17]		
Collect Stool Collection Kit and Specimen Information Questionnaire	X[18]		X					X	
Urine	X[18]		X					X	
Saliva	X[18]		X					X	
Safety Sample Collections									
Blood									
CBC with Differential	Every 3 months								
CMP	Every 3 months								
Urine									
Urinalysis	Every 3 months								
Urine Pregnancy Test[19]	Monthly								

1. Participants may reach their maintenance dose at different times during the Build-Up Phase. The Initial Maintenance Dose Visit will occur two weeks after each participant reaches their maintenance dose during the Build-Up Phase.
2. Because participants may reach their maintenance dose at different times during the Build-Up Phase, each participant will only attend Follow-Up Maintenance Dose Visits that are eight weeks apart.
3. Participants will return to the CRU the day after the IDE Visit for an observed dose administration of Multi-allergen OIT or placebo for Multi-allergen OIT at the last dose the participant was able to tolerate on the IDE Visit.
4. A limited physical exam will be performed.
5. SCORAD will be performed for participants with AD. AD is determined by the PI or licensed clinician based on the current medical history and/or the physical exam.
6. An interim family history questionnaire will be collected for all participants who complete Stage 1. Replacement participants who skip Stage 1 will be given the family history questionnaire used in Stage 1.
7. FAQLQ will be collected prior to initiating the first blinded OFC and after completing the last blinded OFC during the DBPCFC at the end of Stage 2.
8. A SPT to peanut and two other foods.
9. Omalizumab injection visits may occur every two or four weeks, determined by the body weight in kilograms and total serum IgE level at the Screening Visit.
10. Open label omalizumab may occur on IDE or the Initial Dose Build-Up Visit.

11. Open label omalizumab and omalizumab or placebo for omalizumab may occur at Dose Build-Up Visits or may be a separate visit.
12. Randomization will occur one week after beginning Stage 2.
13. Unblind each participant to OFC results after completing the last blinded OFC during the DBPCFC at the end of Stage 2.
14. If safety labs coincide with the bioassay/mechanistic blood collection, the priority, in terms of blood volume, is the safety labs.
15. Initial Maintenance Dose Visit only.
16. Provide stool collection kit and specimen information questionnaire at the last visit before the IDE Visit.
17. Provide stool collection kit and specimen information questionnaire at the last visit before the first DBPCFC Visit.
18. Sample will only be collected at this visit for replacement participants.
19. Only needed for female participants of child-bearing potential.
20. PEF is not required if an OIT dose is not given during an in clinic Initial or Follow-Up Maintenance Dose Visit.

Appendix 7: Schedule of Events for Stage 3 – Long-Term Follow-Up with Dietary Consumption of a Food

Visit	Open Feeding	Safety Phone Calls[1]	Long-Term Follow-Up Visits[2]
Study Assessments			
Vitals & Growth Parameters	X		X
Interim Medical History	X	X	X
Physical Exam	X[3]		X[4]
SCORAD[5]			X[6]
Diet & Allergy Questionnaire	X	X	X
GI Symptoms Questionnaire	X	X	X
Family History Questionnaire	X[7]		
FAQLQ			X[8]
Open Feeding	X		
ReviewDiaries	X	X[15]	X[15]
Monthly Long-Term Follow-Up Questionnaires		X[16]	
Concomitant Medications	X	X	X
SPT			X[9]
AEs	X	X	X
Open label omalizumab administration	X[10]		
Omalizumab or placebo for omalizumab administration	X[11]		
Sample Collections			
Blood			
Total IgE			X[12]
Total Free IgE			X[12]
Allergen-Specific IgE, IgG4, and IgA			X[12]
Basophil Activation			X[12]
Safety Sample Collections			
Blood			
CBC with Differential	Every 3 months[13]		
CMP	Every 3 months[13]		
Urine			
Urinalysis	Every 3 months[13]		
Urine Pregnancy Test	Monthly[14]		

1. The open feeding will be followed by weekly phone visits for the first four weeks, every other week from 6 to 16 weeks, and then every two months for safety follow-up until the participant has completed 6 months in Stage 3 Long-Term Follow-Up with Dietary Consumption.
2. The participant will return to the CRU every six months for up to two years.
3. A comprehensive physical exam will be performed prior to initiating the open feeding. If there is more than one open feeding on a given day, a limited physical exam will be performed prior to initiating each subsequent open feeding.
4. A limited physical exam will be performed.
5. SCORAD will be performed for participants with AD. AD is determined by the PI or licensed clinician based on the current medical history and/or the physical exam.
6. SCORAD will be collected at the first six-month visit.
7. An interim family history questionnaire will only be collected once at the beginning of Stage 3.
8. FAQLQ will be collected at the first six-month visit.
9. A SPT to peanut and two other foods will be completed at the first six-month clinic visit and yearly thereafter.
10. A participant who receives long-term follow-up with dietary consumption of a food(s) within seven days of completing Stage 1 OLE will receive open label omalizumab until all open feedings are completed.
11. A participant who receives long-term follow-up with dietary consumption of a food(s) within seven days of completing Stage 2 will receive the treatment they were assigned to in Stage 2 until all open feedings are completed.
12. A venous blood sample will be collected at the first six-month visit.
13. Only perform safety sample collection if it has been more than three months since the last safety sample collection and the participant is still receiving omalizumab, placebo for omalizumab, or open label omalizumab from the previous stage.
14. Only perform a urine pregnancy test if it has been more than one month since the last urine pregnancy test and the participant is still receiving study drug from Stage 2 or rescue OIT from Stage 3.
15. Diaries are only required during the first six months of follow-up in Stage 3 Long term follow-up with dietary consumption
16. Monthly Long-Term Follow-Up Questionnaires are collected after the participant has completed six months of follow-up in Stage 3 Long term follow-up with dietary consumptions.

Appendix 8: Schedule of Events for Stage 3 – Long-Term Follow-Up with Avoidance of a Food

Visit	Long-Term Follow-Up Visits[1]	Monthly Long-Term Follow-Up Phone Calls/Emails
Study Assessments		
Vitals & Growth Parameters	X	
Interim Medical History	X	X
Physical Exam	X[2]	
SCORAD[3]	X[4]	
Diet & Allergy Questionnaire	X	X
GI Symptoms Questionnaire	X	X
Family History Questionnaire	X[5]	
FAQLQ	X[6]	
Review Diaries	X[9]	
Concomitant Medications	X	X
SPT	X[7]	
AEs	X	X
Monthly Long-Term Follow-Up Questionnaires		X[10]
Sample Collections		
Blood		
Total IgE	X[8]	
Total Free IgE	X[8]	
Allergen-Specific IgE, IgG4, and IgA	X[8]	
Basophil Activation	X[8]	

1. The participant will return to the CRU every six months for up to two years.
2. A limited physical exam will be performed.
3. SCORAD will be performed for participants with AD. AD is determined by the PI or licensed clinician based on the current medical history and/or the physical exam.
4. SCORAD will be collected at the first six-month visit.
5. An interim family history questionnaire will only be collected once at the beginning of Stage 3.
6. FAQLQ will be collected at the first six-month visit.
7. A SPT to peanut and two other foods will be completed at the first six-month clinic visit and yearly thereafter.
8. A venous blood sample will be collected at the first six-month visit.
9. Diaries are only required during the first six months of follow-up in Stage 3 (inclusive).
10. Monthly Long-Term Follow-Up Questionnaires are collected after the participant has completed six months of follow-up in Stage 3.

Appendix 9: Schedule of Events for Stage 3 – Rescue Oral Immunotherapy for a Food[1]

Visit	IDE[2]	Build-Up[3]	Maintenance[4]	Open OFC
Study Assessments				
Vitals & Growth Parameters	X	X	X	X
Interim Medical History	X	X	X	X
Physical Exam	X	X[5]	X[5]	X
PEF	X	X	X[17]	X
SCORAD[6]				X[7]
Diet & Allergy Questionnaire	X	X	X	X
GI Symptoms Questionnaire	X	X	X	X
Family History Questionnaire	X[8]			
FAQLQ		X[9]		X[9]
Open Feeding				
Review Diaries	X	X	X	X
Concomitant Medications	X	X	X	X
SPT				X[10]
AEs	X	X	X	X
Rescue OIT	X	X	X	
Open label omalizumab administration	X[11]			
Omalizumab or placebo for omalizumab administration	X[12]			
Open OFC				X
Sample Collections				
Blood				
Total IgE		X[13]	X[13]	
Total Free IgE		X[13]	X[13]	
Allergen-Specific IgE, IgG4, and IgA		X[13]	X[13]	
Basophil Activation		X[13]	X[13]	
Safety Sample Collections				
Blood				
CBC with Differential	Every 3 months[14]			
CMP	Every 3 months[14]			
Urine				
Urinalysis	Every 3 months[14]			
Urine Pregnancy Test[15]	Monthly[16]		X[16]	X[16]

1. Participants who reach a maintenance dose of <560 mg protein of a food within 24 weeks after beginning rescue OIT stay on the rescue OIT treatment plan.
2. The participant will attend an IDE Visit if the participant has dose-limiting symptoms to a single dose of ≤100 mg protein of the food during the DBPCFC at the end of Stage 1 OLE or 2. The day after the IDE Visit, each participant who attends an IDE Visit will return to the CRU for an observed dose administration of the last dose of OIT the participant was able to tolerate on the IDE Visit.
3. Participants may reach their maintenance dose at different times during the Build-Up Phase. The Initial Maintenance Dose Visit will occur two weeks after each participant reaches their maintenance dose during the Build-Up Phase.
4. Each participant may reach their maintenance dose at different times during the Build-Up Phase. Each participant will only attend Follow-Up Maintenance Dose Visits every eight weeks after the participant reaches their maintenance dose.
5. A limited physical exam will be performed.
6. SCORAD will be performed for participants with AD. AD is determined by the PI or licensed clinician based on the current medical history and/or the physical exam.
7. SCORAD will be collected prior to initiating the first Open OFC.
8. An interim family history questionnaire will only be collected once at the beginning of Stage 3.
9. FAQLQ will be collected at six months after the start of rescue OIT, prior to initiating the first open OFC and after completing the last open OFC in rescue OIT.
10. A SPT to peanut and two other foods will be completed at the first Open OFC Visit.
11. A participant who receives rescue OIT within 14 days of completing Stage 1 OLE will receive open label omalizumab until the IDE Visit is completed.

12. A participant who receives rescue OIT within 14 days of completing Stage 2 will receive the treatment they were assigned to in Stage 2 until the IDE Visit is completed.
13. A venous blood sample will be collected at six months after the start of rescue OIT.
14. Only perform safety sample collection if it has been more than three months since the last safety sample collection and the participant is still receiving omalizumab, placebo for omalizumab, or open label omalizumab from the previous stage.
15. Only needed for female participants of child-bearing potential.
16. Urine pregnancy tests will be performed monthly during the IDE Visit and Dose Build-Up Visits. If a pregnancy test has not been performed in the last month, urine pregnancy tests will also be performed at the Initial Maintenance Dose Visit, at each Follow-Up Maintenance Dose Visit, and at the Open OFC Visit.
17. PEF is not required if an OIT dose is not given during an in clinic Initial or Follow-Up Maintenance Dose Visit.

Appendix 10: Schedule of Events for Stage 3 – Rescue Oral Immunotherapy for a Food With Long-Term Follow-Up with Dietary Consumption[1]

Visit	IDE[2]	Build-Up[3]	Maintenance[3]	Safety Phone Calls[4]	Open Feeding	Long-Term Follow-Up Visits[5]	Open OFC
Study Assessments							
Vitals & Growth Parameters	X	X	X		X	X	X
Interim Medical History	X	X	X	X	X	X	X
Physical Exam	X	X[6]	X[6]		X[7]	X[6]	X
PEF	X	X	X[19]				X
SCORAD[8]						X[9]	X[9]
Diet & Allergy Questionnaire	X	X	X	X	X	X	X
GI Symptoms Questionnaire	X	X	X	X	X	X	X
Family History Questionnaire	X[10]						
FAQLQ		X[11]					X[11]
Open Feeding					X		
Review Diaries	X[20]	X[20]	X[20]	X[20]	X[20]	X[20]	
Monthly Long-Term Follow-Up Questionnaires				X[21]		X[21]	
Concomitant Medications	X	X	X	X	X	X	X
SPT						X[12]	X[12]
AEs	X	X	X	X	X	X	X
Rescue OIT	X	X	X				
Open label omalizumab administration	X[13]						
Omalizumab or placebo for omalizumab administration	X[14]						
Open OFC							X
Sample Collections							
Blood							
Total IgE		X[15]	X[15]				
Total Free IgE		X[15]	X[15]				
Allergen-Specific IgE, IgG4, and IgA		X[15]	X[15]				
Basophil Activation		X[15]	X[15]				
Safety Sample Collections							
Blood							
CBC with Differential	Every 3 months[16]						
CMP	Every 3 months[16]						
Urine							
Urinalysis	Every 3 months[16]						
Urine Pregnancy Test[17]	Monthly[18]		X[18]		X[18]		X[18]

1. Participants who reach a target maintenance dose of 560 mg, 800 mg, or 1000 mg of protein of the food within 24 weeks of entering rescue OIT and tolerate this dose for eight weeks after starting the Maintenance Phase will transition to Long-Term Follow-Up with Dietary Consumption of the food if the participant tolerates ≥300 mg protein of the food at the open feeding.
2. The participant will attend an IDE Visit if the participant has dose-limiting symptoms to a single dose of ≤100 mg protein of the food during the DBPCFC at the end of Stage 1 OLE or 2. The day after the IDE Visit, each participant who attends an IDE Visit will return to the CRU for an observed dose administration of the last dose of OIT the participant was able to tolerate on the IDE Visit.
3. Each participant may reach their maintenance dose at different times during the Build-Up Phase. Participants who reach a target maintenance dose of 560 mg, 800 mg, or 1000 mg of the food will return to the CRU two weeks after the end of the Build-Up Phase for the Initial Maintenance Dose Visit. Participants will return eight weeks after the Initial Maintenance Dose for a Follow-Up Maintenance Dose. If the participant does not tolerate the target maintenance dose during the eight week period, the participant will return to the clinic for dose adjustment and will continue daily home OIT dosing 52 weeks after beginning rescue OIT (See Appendix 9).
4. Each participant will be called or emailed at two and five weeks after the Initial Maintenance Dose Visit. The Open Feeding will be followed by weekly phone visits for the first four weeks, every other week from 6 to 16 weeks, and then every two months for safety follow-up until they have completed 6 months of Stage 3 Long-Term Follow-Up with Dietary Consumption.

5. The participant will return to the CRU every six months for up to two years.
6. A limited physical exam will be performed.
7. A comprehensive physical exam will be performed prior to initiating the open feeding. If there is more than one open feeding on a given day, a limited physical exam will be performed prior to initiating each subsequent open feeding.
8. SCORAD will be performed for participants with AD. AD is determined by the PI or licensed clinician based on the current medical history and/or the physical exam.
9. SCORAD will be collected at the first six-month visit and prior to initiating the first Open OFC.
10. An interim family history questionnaire will only be collected once at the beginning of Stage 3.
11. FAQLQ will be collected at six months after the start of rescue OIT, prior to initiating the first open OFC, and after completing the last open OFC in rescue OIT.
12. A SPT to peanut and two other foods will be completed at the Open OFC Visit, at the first six-month visit, and yearly thereafter.
13. A participant who receives rescue OIT within 14 days of completing Stage 1 OLE will receive open label omalizumab until the IDE Visit is completed. If the Open OFC visit is within 3 months of the first six-month visit, the SPT will only be completed at the Open OFC Visit.
14. A participant who receives rescue OIT within 14 days of completing Stage 2 will receive the treatment they were assigned to in Stage 2 until the IDE Visit is completed.
15. A venous blood sample will be collected at six months after the start of rescue OIT. If the participant has reached dietary consumption and does not have clinic visits scheduled, bring the participant in for an Unscheduled Visit to collect the blood.
16. Only perform safety sample collection if it has been more than three months since the last safety sample collection and the participant is still receiving omalizumab, placebo for omalizumab, or open label omalizumab from the previous stage.
17. Only needed for female participants of child-bearing potential.
18. Urine pregnancy tests will be performed monthly during the IDE Visit and Dose Build-Up Visits. If a pregnancy test has not been performed in the last month, urine pregnancy tests will also be performed at the Initial Maintenance Dose Visit, at the Follow-Up Maintenance Dose Visit, at the Open Feeding(s), and at the Open OFC Visit.
19. PEF is not required if an OIT dose is not given during an in clinic Initial or Follow-Up Maintenance Dose Visit.
20. Diaries are only required during the first six months of follow-up in Stage 3 Long-term follow-up with dietary consumption.
21. Monthly Long-Term Follow-Up Questionnaires are collected after the participant has completed six months of follow-up in Stage 3 Long term follow-up with dietary consumption..

Appendix 11: Sampson's Criteria for Diagnosing Potential Cases of Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria[58] is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent GI symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP∗
   b. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

* Low systolic BP for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 × age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years

Appendix 12: Grading Table for Non-Allergic Adverse Events Version 2.0

Note: In addition, all deaths related to an AE are to be classified as Grade 5.

Local Reaction to Injections and Infusions	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Injection Site Pain or Tenderness[50,51]	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb OR Repeated use of non-narcotic pain reliever >24 hours	Pain or tenderness causing inability to perform usual social & functional activities OR any use of narcotic pain reliever	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema, Redness, Induration, or Swelling[51]				
>15 years of age	2.5 to <5 cm in diameter OR 6.25 to <25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥5 to <10 cm in diameter OR ≥25 to <100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥10 cm in diameter OR ≥100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤15 years of age	≤2.5 cm in diameter	>2.5 cm in diameter with <50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

Note: In addition, all deaths related to an AE are to be classified as Grade 5.

Vital Signs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever[50] (oral temperature; no recent hot or cold beverages or smoking)	38.0 – 38.4°C (100.4 – 101.1°F)	38.5.0 – 38.9°C (101.2 – 102.0°F)	39.0 – 40°C (102.1 – 104°F)	>40.0°C (>104.0°F)
Tachyarrhythmia[54]	Asymptomatic, intervention not indicated	Symptomatic; non-urgent medical intervention indicated	Urgent medical intervention indicated	Life-threatening consequences
Bradyarrhythmia[54]	Asymptomatic, intervention not indicated	Symptomatic, intervention not indicated; change in medication initiated	Symptomatic, intervention indicated	Life-threatening consequences; urgent intervention indicated
Hypertension[54,55] (at least two values should be obtained for confirmation)	**Adult (≥18 years of age):** Systolic BP 120 – 139 mmHg or diastolic BP 80 – 89 mmHg; **1 to <13 years of age:** SBP and/or DBP ≥90th percentile but <95th percentile, or 120/80 mmHg to <95th percentile (whichever is lower); **13 – 17 years of age:** SBP between 120 and 129 with a DBP <80 mmHg	**Adult:** Systolic BP 140 – 159 mmHg or diastolic BP 90 – 99 mmHg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (≥24 hours); symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg; monotherapy indicated initiated; **1 to <13 years of age:** Recurrent or persistent (≥24 hours) BP >ULN; monotherapy indicated; SBP and/or DBP ≥95th percentile to <95th percentile + 12 mmHg, or 130/80 to 139/89 mmHg (whichever is lower); **13 – 17 years of age**: Recurrent or persistent (≥24 hours) BP >ULN;	**Adult:** Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated; **1 to <13 years of age**: SBP and/or DBP ≥95th percentile + 12 mmHg, or ≥140/90 mmHg (whichever is lower); **13 – 17 years of age**: BP ≥140/90 mmHg	**Adult and Pediatric:** Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated

Vital Signs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
		monotherapy indicated; systolic between 130 – 139 or diastolic between 80 – 89		
Hypotension[50,54]	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Urgent Medical intervention indicated	Life-threatening consequences and urgent intervention indicated; hospitalization indicated
Dyspnea or Respiratory Distress[51]	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to <95%*	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry <90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

* O_2 saturation ranges provided in this table serves as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Note: In addition, all deaths related to an AE are to be classified as Grade 5.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/Vomiting[50,51]	No interference with activity or 1 – 2 episodes / 24 hours	Some interference with activity or >2 episodes / 24 hours	Prevents daily activity, requires outpatient IV hydration	Hospitalization or Life-threatening consequences (e.g., hypotensive shock)
Diarrhea[50]	2 – 3 loose stools or <400 gm / 24 hours	4 – 5 stools or 400 – 800 gm / 24 hours	6 or more watery stools or >800 gm / 24 hours or requires outpatient IV hydration	Hospitalization or Life-threatening consequences
Headache[50]	No interference with activity	Repeated use of nonnarcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Hospitalization or Life-threatening consequences
Fatigue[50]	No interference with activity	Some interference with activity	Significant; prevents daily activity	Hospitalization or Life-threatening consequences
Myalgia[50]	No interference with activity	Some interference with activity	Significant; prevents daily activity	Hospitalization or Life-threatening consequences

Note: In addition, all deaths related to an AE are to be classified as Grade 5.

Other Clinical	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Clinical Adverse Event NOT Identified Elsewhere in the Protocol[51]	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or hospitalization indicated

Note: In addition, all deaths related to an AE are to be classified as Grade 5.

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia[51,52] (mEq/L)	130 to <135	125 to <130	121 to <125	≤120 or abnormal sodium AND mental status changes
Sodium – Hypernatremia[51,52] (mEq/L)	146 to <150	150 to <154	154 to <160	≥160 or abnormal sodium AND mental status changes
Potassium – Hyperkalemia[51,53] (mEq/L)	5.6 – 6.0	6.1 – 6.5	6.6 – 7.0	>7.0 or abnormal potassium with life-threatening arrhythmia
Potassium – Hypokalemia[51-53] (mEq/L)	3.0 – 3.4	2.5 – 2.9	2.0 – 2.4	<2.0 mEq/L or abnormal potassium with paresis, ileus or life-threatening arrhythmia
Glucose – Hypoglycemia[50,52] (mg/dL)	65 – 69	55 – 64	45 – 54	<45 or abnormal glucose AND mental status changes
Glucose – Hyperglycemia[50] **Fasting** (mg/dL) **Random** (mg/dL)	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen (BUN)[50] (mg/dL)	23 – 26	27 – 31	>31	Requires dialysis
Creatinine (mg/dL) ≥18 years of age[50] 12 years – 17 years of age[52] 2 years – 12 years of age[52] 3 months to 2 years of age[52]	 1.5 – 1.7 mg/dL 1.0 – 1.7 x ULN*** 0.7 – 1.0 x ULN 0.6 – 0.8 x ULN	 1.8 – 2.0 mg/dL 1.8 – 2.4 x ULN 1.1 – 1.6 x ULN 0.9 – 1.1 x ULN	 2.1 – 2.5 mg/dL 2.5 – 3.5 x ULN 1.7 – 2.0 x ULN 1.2 – 1.5 x ULN	 >2.5 mg/dL or requires dialysis >3.5 x ULN or requires dialysis >2.0 x ULN or requires dialysis 1.5 x ULN or requires dialysis
Calcium – hypocalcemia[50] (mg/dL)	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	<7.0
Calcium – hypercalcemia[50] (mg/dL)	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	>12.0
Magnesium – hypomagnesemia[50] (mg/dL)	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	<0.9
Phosphorous – hypophosphatemia[50] (mg/dL)	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	<1.6
CPK[50] (mg/dL)	1.25 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Albumin – Hypoalbuminemia[50] (g/dL)	2.8 – 3.1	2.5 – 2.7	<2.5	--
Total Protein – Hypoproteinemia[50] (g/dL)	5.5 – 6.0	5.0 – 5.4	<5.0	--
Alkaline phosphate[50] (increase by factor)	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver Function Tests – ALT, AST[50] (increase by factor)	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin[50] (when accompanied by any increase in Liver Function Test, increase by factor)	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin[50] (when Liver Function Test is normal, increase by factor)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN
Cholesterol[50]	201 – 210	211 – 225	>226	--
Pancreatic enzymes – amylase, lipase[50]	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	>5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.[50]

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low calcium that falls in a Grade 2 parameter (7.5 – 7.9 mg/dL) should be recorded as a Grade 4 hypocalcemia event if the participant had a new seizure associated with the low calcium value.[50]

*** ULN is the upper limit of the normal range.[50]

Note: In addition, all deaths related to an AE are to be classified as Grade 5.

Hematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female)[50,52] (gm/dL)	**≥18 years of age**: 11.0 – 12.0; **2 – 17 years of age**: 10 to <LLN; **>3 months to <2 years of age:** 9 to <LLN	**≥18 years of age:** 9.5 – 10.9; **2 – 17 years of age:** 7.0 – 9.9; **>3 months to <2 years of age:** 7.0 – 8.9	**≥18 years of age:** 8.0 – 9.4; **>3 months – 17 years of age:** <7.00;	**≥18 years of age:** <8.0; **>3 months – 17 years of age:** Cardiac failure secondary to anemia
Hemoglobin (Female) change from baseline value[50] (gm/dL)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
Hemoglobin (Male)[50,52] (gm/dL)	**≥18 years of age:** 12.5 – 13.5; **2 – 17 years of age:** 10 to <LLN; **>3 months to <2 years of age:** 9 to <LLN	**≥18 years of age:** 10.5 – 12.4; **2 – 17 years of age:** 7.0 – 9.9; **>3 months to <2 years of age**: 7.0 – 8.9	**≥18 years of age:** 8.5 – 10.4; **>3 months – 17 years of age:** <7.00;	**≥18 years of age:** <8.5; **>3 – 17 years of age:** Cardiac failure secondary to anemia
Hemoglobin (Male) change from baseline value[50] (gm/dL)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
WBC Increase[50] (cell/mm^3)	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC Decrease[50] (cell/mm^3)	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes Decrease[50] (cell/mm^3)	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils Decrease[50] (cell/mm^3)	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils[50] (cell/mm^3)	650 – 1500	1501 – 5000	>5000	Hypereosinophilic
Platelets Decreased[50] (cell/mm^3)	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
PT[50] (increase by factor (prothrombin time))	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	>1.25 x ULN
PTT[50] (increase by factor (partial thromboplastin time))	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	>1.5 x ULN
Fibrinogen increase[50] (mg/dL)	400 – 500	501 – 600	>600	--

Hematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fibrinogen decrease[50] (mg/dL)	150 – 200	125 – 149	100 – 124	<100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.[50]

** ULN is the upper limit of the normal range.[50]

Note: In addition, all deaths related to an AE are to be classified as Grade 5.

Urine*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein[50]	Trace	1+	2+	Hospitalization or dialysis
Glucose[50]	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic)[50] – red blood cells per high power field (rbc/hpf)	1 – 10	11 – 50	>50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.[50]

Note: In addition, all deaths related to an AE are to be classified as Grade 5.

Other Laboratory	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Laboratory values not otherwise specified in this table[52]	Abnormal, but requiring no immediate intervention; follow	Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug	Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug	Life-threatening severity; Requires immediate evaluation, treatment, and usually hospitalization; Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism than study drug

Appendix 13: Objective and Endpoint Mapping

Objectives			Endpoints		
Study Level	Within Stage Level[1]	Objective	Study Level	Within Stage Level[1]	Endpoint
Stage 1					
Primary	Primary	To compare the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab or placebo for omalizumab.	Primary[2]	Primary	Consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.
			Key Secondary Endpoint Family 1-3[2]	Secondary	Consumption of a single dose of ≥1000 mg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 for cashew, milk, and egg.
			Other Secondary Endpoint 5	Secondary	Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 (except those endpoints already defined by the primary and key secondary endpoints for Stage 1).
			Other Secondary Endpoint 6	Secondary	Number of foods consumed at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 1.
Secondary Objective 1	Secondary	To evaluate safety during treatment with either omalizumab or placebo for omalizumab.	Secondary Endpoint 11 (Safety)	Secondary	An AE related to study therapy regimen received during Stage 1.
Exploratory Objective 1	Exploratory	To compare quality of life after treatment with either omalizumab or placebo for omalizumab.	Exploratory Endpoint 4	Exploratory	Change in quality of life between Week 0 in Stage 1 and the first DBPCFC Visit at the end of Stage 1.
Exploratory Objective 12 (PK)	Exploratory	To evaluate serum omalizumab concentrations during treatment with omalizumab.	Exploratory Endpoint 5 (PK)	Exploratory	Omalizumab trough concentration at the first Screening DBPCFC Visit and the first DBPCFC Visit at the end of Stage 1.
Exploratory Objective 15 (Biomarker)	Exploratory	To compare immunological responses after treatment with either omalizumab or placebo for omalizumab.	Exploratory Endpoints 6-13 (Biomarker)	Exploratory	Change in all immune biomarkers[3] between the first Screening DBPCFC Visit and the first DBPCFC Visit at the end of Stage 1.
Exploratory Objective 16 (Biomarker)	Exploratory	To determine whether immunological responses can be used to predict the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab or placebo for omalizumab.	Exploratory Endpoints 6-13 (Biomarker)	Exploratory	Change in all immune biomarkers[3] between the first Screening DBPCFC Visit and the first DBPCFC Visit at the end of Stage 1.
Stage 1 OLE					
Exploratory Objective 2	Primary	To assess the safety and efficacy of either 24 or 40 weeks of treatment with omalizumab.	Exploratory Endpoint 2	Primary	Consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.
			Exploratory Endpoint 2	Secondary	Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE (except the endpoint already defined by the primary endpoint for Stage 1 OLE).
			Exploratory Endpoint 3	Secondary	Number of foods consumed at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE.
			Secondary Endpoint 12 (Safety)	Secondary	An AE related to study therapy regimen received during Stage 1 OLE.
Exploratory Objective 3	Secondary	To assess quality of life at the end of either 24 or 40 weeks of treatment with omalizumab.	Exploratory Endpoint 4	Exploratory	Change in quality of life between Week 0 in Stage 1 and the first DBPCFC Visit at the end of Stage 1, the first omalizumab injection visit in Stage 1 OLE, the first DBPCFC Visit at the end of Stage 1 OLE,

Objectives			Endpoints		
Study Level	Within Stage Level[1]	Objective	Study Level	Within Stage Level[1]	Endpoint
					and the last DBPCFC Visit at the end of Stage 1 OLE.
Exploratory Objective 13	Exploratory	To assess serum omalizumab concentrations at the end of either 24 or 40 weeks of treatment with omalizumab.	Exploratory Endpoint 5	Exploratory	Omalizumab trough concentration at the first Screening DBPCFC Visit, the first DBPCFC Visit at the end of Stage 1, and at the first DBPCFC Visit at the end of Stage 1 OLE.
Exploratory Objective 17 (Biomarker)	Exploratory	To assess immunological responses at the end of either 24 or 40 weeks of treatment with omalizumab.	Exploratory Endpoints 6-13 (Biomarker)	Exploratory	Change in all immune biomarkers[3] between the first Screening DBPCFC Visit, the first DBPCFC Visit at the end of Stage 1, and the first DBPCFC Visit at the end of Stage 1 OLE.
Stage 2					
Secondary Objective 2	Primary	To compare the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.	Key Secondary Endpoint 4	Primary	Consumption of≥1 dose of 2000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2.
			Other Secondary Endpoint 7	Secondary	Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2 (except the endpoint already defined by the primary endpoint for Stage 2).
			Other Secondary Endpoint 8	Secondary	Number of foods consumed at a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of Stage 2.
Secondary Objective 3	Secondary	To evaluate safety during treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.	Secondary Endpoint 13 (Safety)	Secondary	An AE related to study therapy regimen received during Stage 2.
Exploratory Objective 4	Exploratory	Among participants who do not respond to treatment with omalizumab alone, compare the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.	Key Secondary Endpoint 4	Primary	Consumption of≥1 dose of 2000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2.
			Other Secondary Endpoint 7	Secondary	Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2 (except the endpoint already defined by the primary endpoint for Stage 2).
Exploratory Objective 5	Exploratory	Among participants who respond to treatment with omalizumab alone, compare the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.	Key Secondary Endpoint 4	Primary	Consumption of≥1 dose of 2000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2.
			Other Secondary Endpoint 7	Secondary	Consumption of a single dose of ≥600 mg, ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2 (except the endpoint already defined by the primary endpoint for Stage 2).
Exploratory Objective 6	Exploratory	To compare the change in the dose of each food that is consumed without dose-limiting symptoms during a DBPCFC at the end of Stage 1 and during a DBPCFC at the end of Stage 2 between treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.	Exploratory Endpoint 1	Exploratory	Percent change in the maximum dose of food protein consumed without dose-limiting symptoms during the DBPCFC at the end of Stage 1 and during the DBPCFC at the end of Stage 2.
Exploratory Objective 7	Exploratory	To compare quality of life after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.	Exploratory Endpoint 4	Exploratory	Change in quality of life between Week 0 in Stage 1 and the first DBPCFC Visit at the end of Stage 1, the first omalizumab injection visit in Stage 2, the first DBPCFC

Objectives			Endpoints		
Study Level	Within Stage Level[1]	Objective	Study Level	Within Stage Level[1]	Endpoint
					Visit at the end of Stage 2, and the last DBPCFC Visit at the end of Stage 2.
Exploratory Objective 14 (PK)	Exploratory	To evaluate serum omalizumab concentrations during treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.	Exploratory Endpoint 5 (PK)	Exploratory	Omalizumab trough concentration at the first Screening DPBCFC visit, the first DBPCFC Visit at the end of Stage 1, the IDE Visit during Stage 2, and the first DBPCFC Visit at the end of Stage 2.
Exploratory Objective 18 (Biomarker)	Exploratory	To compare immunological responses during and after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.	Exploratory Endpoints 6-13 (Biomarker)	Exploratory	Change in all immune biomarkers[3] between the first Screening DBPCFC Visit and the first DBPCFC Visit at the end of Stage 1, the IDE Visit during Stage 2[4], the Initial Maintenance Dose Visit during Stage 2[4], and the first DBPCFC Visit at the end of Stage 2.
Exploratory Objective 19 (Biomarker)	Exploratory	To determine whether immunological responses can be used to predict the ability to consume foods without dose-limiting symptoms during a DBPCFC after treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT.	Key Secondary Endpoint 4	Primary	Consumption of ≥1 dose of 2000 mg protein of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 2.
Stage 3					
Secondary Objective 4	Primary	To compare dietary consumption of foods after the conclusion of treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.	Other Secondary Endpoint 9	Primary	Number of weeks in each eight-week period during Stage 3 where ≥300 mg of peanut protein is consumed at least twice per week.
			Other Secondary Endpoint 9	Secondary	Number of weeks in each eight-week period during Stage 3 where ≥300 mg protein of each food is consumed at least twice per week (except the endpoint already defined by the primary endpoint for Stage 3).
			Other Secondary Endpoint 10	Secondary	Number of weeks in each eight-week period during Stage 3 where each food protein is not consumed.
Secondary Objective 5	Secondary	To evaluate safety after the conclusion of treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.	Secondary Endpoint 14 (Safety)	Secondary	An AE related to oral food intake received during Stage 3.
Exploratory Objective 8	Exploratory	To compare quality of life after the conclusion of treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT during a follow-up period in which participants either receive guided dietary instructions and/or rescue OIT for up to three foods.	Exploratory Endpoint 4	Exploratory	Change in quality of life between Week 0 in Stage 1 and the first DBPCFC Visit at the end of Stage 1, the first omalizumab injection visit in Stage 2, the first DBPCFC Visit at the end of Stage 2, the last DBPCFC Visit at the end of Stage 2, and six months after beginning Stage 3.
Exploratory Objective 9	Exploratory	To describe dietary consumption of foods after the conclusion of either 24 or 40 weeks of treatment with omalizumab during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.	Other Secondary Endpoint 9	Primary	Number of weeks in each eight-week period during Stage 3 where ≥300 mg protein of each food is consumed at least twice per week
			Other Secondary Endpoint 10	Secondary	Number of weeks in each eight-week period during Stage 3 where each food protein is not consumed.
Exploratory Objective 10	Exploratory	To assess safety after the conclusion of either 24 or 40 weeks of treatment with omalizumab during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.	Secondary Endpoint 14 (Safety)	Secondary	An AE related to oral food intake received during Stage 3.
Exploratory Objective 11	Exploratory	To measure quality of life after the conclusion of either 24 or 40 weeks of treatment with omalizumab during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.	Exploratory Endpoint 4	Exploratory	Change in quality of life between Week 0 in Stage 1 and the first DBPCFC Visit at the end of Stage 1, the first omalizumab injection visit in Stage 1 OLE, the first DBPCFC Visit at the end of Stage 1 OLE, the last DBPCFC Visit at the end of Stage 1 OLE, and six months after beginning Stage 3.

Objectives			Endpoints		
Study Level	Within Stage Level[1]	Objective	Study Level	Within Stage Level[1]	Endpoint
Exploratory Objective 20 (Biomarker)	Exploratory	To compare immunological responses after the conclusion of treatment with either omalizumab-facilitated OIT or omalizumab + placebo OIT during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.	Exploratory Endpoints 6-13 (Biomarker)	Exploratory	Change in all immune biomarkers[3] between the first Screening DBPCFC Visit and the first DBPCFC Visit at the end of Stage 1, the IDE Visit during Stage 2[4], the Initial Maintenance Dose Visit during Stage 2[4], the first DBPCFC Visit at the end of Stage 2, and six months after beginning Stage 3.
Exploratory Objective 21 (Biomarker)	Exploratory	To assess immunological responses after the conclusion of either 24 or 40 weeks of treatment with omalizumab during a follow-up period in which participants either received guided dietary instructions and/or rescue OIT for up to three foods.	Exploratory Endpoints 6-13 (Biomarker)	Exploratory	Change in all immune biomarkers[3] between the first Screening DBPCFC Visit and the first DBPCFC Visit at the end of Stage 1, the first DBPCFC Visit at the end of Stage 1 OLE, and six months after beginning Stage 3.

1. Objectives and endpoints within each stage are listed as primary, secondary, or exploratory for that specific stage.
2. Under Type I error control (described in Section 13.5.5.2).
3. Immune biomarkers include total IgE, total free IgE, allergen-specific IgE, allergen-specific IgG4, allergen-specific IgA, IgG4/IgE ratio, basophil activation, and SPTs.
4. SPTs, total IgE, and allergen-specific IgE will not be measured at the IDE Visit during Stage 2 or at the Initial Maintenance Dose Visit during Stage 2.