Full Title: A Phase 2 Study of Multi Oral Immunotherapy in Multi Food Allergic Patients to Test Immune Markers after Minimum Maintenance Dose

Short Title: Multi **I**mmunotherapy to test **Mi**nimum dose using **X**olair (**MIMiX)**

NCT03181009
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Amendment 26

Key Roles

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PROTOCOL APPROVAL

Declaration of Sponsor or Responsible Medical Officer

Full Title: A Phase 2 Study of Multi Oral Immunotherapy in Multi Food Allergic Patients to Test Immune Markers after Minimum Maintenance Dose

I have read this study protocol and approve it. I agree to meet all obligations of the responsible medical officer and sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigators and all other Investigators of all relevant information that becomes available during the conduct of the study.

_____ _____

Kari Nadeau, MD PhD Date
Protocol Director

PROTOCOL ACKNOWLEDGEMENT

Full Title: A Phase 2 Study of Multi Oral Immunotherapy in Multi Food Allergic Patients to Test Immune Markers after Minimum Maintenance Dose

I have read this Clinical Study Protocol. As Principal Investigator, I agree to conduct this protocol according to Good Clinical Practice, as delineated in the United States Code of Federal Regulations (CFR)-21 CFR Parts 50, 54, and 312 (Subpart D), the international Council of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice, and according to the criteria specified in this protocol. Furthermore, I will conduct this protocol in keeping with local, state and federal requirements.

_____
Principal Investigator (Print)

_____ _____
Principal Investigator (Signature) Date

Table of Contents

1. Synopsis

Full Title	A Phase 2 Study Multi Oral Immunotherapy in Multi Food Allergic Patients to test immune markers after minimum maintenance dose
Short Title	Multi Immunotherapy to test dose
Clinical Trial Phase	Phase 2
IND Sponsor (if applicable)	Kari C. Nadeau, MD, PhD
Conducted By	n/a
Protocol Director	Kari C. Nadeau, MD, PhD
Sample Size	60
Study Population	We will enroll food allergic subjects (2-25 years of age) with proven food allergies. We anticipate enrolling 60 subjects with multi food allergies at two sites. Subjects must have food specific IgE>4kU/L for each allergen or a skin test reactivity to each food allergen greater than or equal to 6mm wheal diameter for at least two allergens.
Accrual Period	We estimate it will take 15 months to enroll 60 subjects into the study.
Study Design	This is a phase 2 multisite study that will be conducted at two centers in the U.S. All subjects will receive oral immunotherapy for their specific food allergies (limited to those food allergens in the CMC section of IND 14831). All participants will receive three doses of Omalizumab 4 weeks apart over 8 weeks (Week-8 to 0). The subject's allergens will be introduced on desensitization Day 1 of week 0, after receiving the third omalizumab dose. Subjects will return to clinic to escalate the dose of their allergens until 300 mg (group A) vs. 1200 mg (group B) total protein daily dose is reached. There will be equivalent allergen protein portions depending on test allergen per each subject's history. Subjects will be randomized 1:1 to either group A or group B after meeting eligibility criteria. All subjects and study personnel will be blinded to group A vs B.

	Safety is a paramount concern in the study design and will be monitored carefully throughout the study. Study subjects and their parents/guardians will receive extensive education on food allergy reactions and medication use.
Study Duration	Each subject is planned to be enrolled in the treatment phase of the study for 26 weeks.
Study Agents/Intervention Description	Food protein and powder will be obtained and prepared as per IND 14831 and will be in compliance with all applicable regulations. Omalizumab is approved by the European Medicines Agency (European FDA) and by the US FDA for patients with severe asthma >6 years of age.
Primary Objective	To determine if the combination of omalizumab and multi OIT will increase the IgG4 /IgE ratio of at least 2 allergens by ≥25% at week 18 from baseline in multi food allergic patients.
Major Secondary Objectives	To determine if the combination of omalizumab and multi OIT will increase IgG4/IgE ratio of at least of 3 allergens by ≥25% at week 18 from baseline in multi food allergic patients. To determine if the combination of omalizumab and multi OIT will increase IgG4/IgE of at least of 4 allergens by ≥25% at week 18 from baseline. To determine if the use of combination of omalizumab and multi OIT will increase IgG4/IgE of at least of 5 allergens by ≥25% at week 18 from baseline in multi food allergic patients.

Exploratory Objectives	We will perform high dimensional and innovative immune monitoring during the study. The long term objective of this study is to develop a potentially curative therapy for patients with multi food allergies. We hypothesize that young and older subjects with multi food allergies who receive a combination of Omalizumab and multi oral immunotherapy (OIT) can be rapidly desensitized and tolerate higher doses of food protein. We also hypothesize that 300 mg total protein dose daily, when compared to 1200mg total protein dose daily, is enough to achieve the primary endpoint in the majority of participants. However, we will explore if age, sex, body mass index, years with disease, and degree of polysensitization affect study outcomes, as well as characterize the treatment related adverse events throughout the study.
Endpoints	**Primary Endpoint:** The proportion of subjects on a combination of omalizumab and multi oral immunotherapy who have an increase the IgG4 /IgE ratio of at least of 2 allergens by ≥25% from baseline, at week 18. **Major Secondary Endpoints:** The proportion of subjects on a combination of omalizumab and multi oral immunotherapy who have an an increase the IgG4 /IgE ratio of at least of 3 allergens by ≥25% from baseline, at week 18. The proportion of subjects on a combination of omalizumab and multi oral immunotherapy who have an increase the IgG4 /IgE ratio of at least of 4 allergens by ≥25% from baseline, at week. The proportion of subjects on a combination of omalizumab and multi oral immunotherapy who have an increase the IgG4 /IgE ratio of at least of 5 allergens by ≥25% from baseline, at week 18.

2. Background Information and Scientific Rationale

2.1 Background Information

The long-term goal of our studies is to develop a better and safer treatment for, and to potentially cure patients with multiple food allergies. Many food allergic patients suffer from more than one food allergy. One report has published that up to 70% of food allergic patients suffer from another food allergy. We recently surveyed the children and adults in our clinics at Stanford Hospital and Clinics and many of the children and adults treated at our Allergy Clinics have had a near fatal anaphylaxis and have concomitant food allergies to peanut and/or milk and/or egg and/or seed and/or tree nut and/or shrimp and/or cod and/or salmon. Currently, subcutaneous immunotherapy to environmental allergens employs multiple allergens. Although studies have been performed to evaluate the efficacy of oral immunotherapy (OIT) for single food allergens, sufficient studies evaluating OIT to multiple food allergens have not yet been performed to address this substantial unmet need.

A pilot study by our group under a separate IND (103080) was the first of its kind to show that milk desensitization can occur relatively rapidly when combined with Omalizumab (Xolair) treatment in severely milk allergic patients. In this separate IND application, we are applying to conduct a Phase 2 study of OIT in patients with multiple food allergies.

Thus far, few studies have been conducted to optimize safety of OIT in conjunction with Omalizumab as well as to identify the immunological mechanism(s) underlying any long-lasting effects of OIT. To address these issues in the field of food allergy research, we have designed a study to test whether: 1) Omalizumab improves the safety of OIT, 2) Omalizumab treatment with multiple food allergen OIT is associated with the ability to tolerate a lower maintenance dose of each food allergens used in the OIT regimen, particularly in younger subjects with food allergies.

Omalizumab is a recombinant DNA-derived humanized IgG1 monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody of an approximate molecular weight of approximately 149 kilodaltons is produced by a Chinese hamster ovary cell suspension culture. Omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response. Treatment with omalizumab also reduces the number of FcεRI receptors on basophils in atopic patients.

In previous studies in children with severe asthma (as per product insert and Therapeutic Biologic Application (BLA) submitted by Genentech and approved by the FDA in June 2003 with a recent approval for use in 6 years and above-2016), anti-IgE treatment was found to be effective in preventing and reversing IgE-mediated allergic asthma symptoms . This novel protocol, aims to test whether Omalizumab can improve the safety of OIT in subjects with multi food allergies. The hypothesis is that the treatment protocol will allow study subjects with multi food allergies to be safely and rapidly desensitized to multiple food allergens. The design of this protocol is unique in that: 1) Omalizumab is included to improve OIT tolerability, 2) study subjects are desensitized more rapidly than in other studies (which do not use Omalizumab), and 3) the use of minimum maintenance dose of OIT (300mg versus 1200mg total protein daily).

We chose 2 years old as the minimum age due to a previous published study and a study under investigation. (J Investig Allergol Clin Immunol. 2015;25(4):303-4 and 'Controlling and Preventing Asthma Progression and Severity in Kids (CASK)', sponsored by Dr. Wanda Phipatanakul at Boston Children's, with an age range of 24 to 47 months. NCT02570984. The dosing used was the standard 0.016 mg/kg/(IU/mL).

Our reasons for not requiring a food challenge to diagnose food allergies at screening or to prognosticate for clinical outcomes:

1) Based on our data using IgE and skin test levels with these cutoffs, we will have a very high likelihood of enrolling children with clinically relevant food allergies (submitted manuscript by Andorf, et al.). Our criteria are: food specific IgE>4kU/L for each allergen or a skin test reactivity to each food allergen greater than or equal to 6mm wheal diameter.
2) Food challenges are associated with a higher level of anxiety and stress in clinical trials and have served as deterrents for many patients/families with food allergies who would likely be eligible for clinical trials to test food immunotherapy.
3) There are other markers of clinical outcomes that one can use, namely, IgG4/IgE ratios [there is a large body of evidence (1-8) supporting the use of these immune markers] and the tolerability of maintenance doses at minimal levels. We feel that this is a pilot study and it could be that these minimal dosing scenarios (only up to 300 mg total protein, compared to the 1200mg total protein dose, and only 8 weeks of omalizumab) could result in a food challenge with an allergic reaction; therefore, we prefer only to examine biomarkers at this time to see if there are trends that would substantiate future randomized controlled studies that incorporate food challenges. Therefore, we have proposed this study as a pilot study to test concepts that could be basis for moving forward in larger, phase 2 studies.

We aim to determine whether a minimum maintenance dose for food allergen oral immunotherapy (300 mg total protein daily vs. 1200 mg total protein daily) will be sufficient at 18 weeks to increase IgG4/IgE ratios by 25% (for each separate food allergen). This dose volumes were chosen because 300 mg is approximately the dose of one nut's worth of protein if an accidental ingestion were to occur. There is evidence (Byrd, et al 2016, EAACI, Vienna, Austria) that a maintenance of 300 mg food allergen protein a day will protect approximately 70% of participants up to 1000 mg or more of food allergen protein at 40 weeks into therapy. At Stanford, our phase 1 and long term studies have confirmed these findings (Monahar, et al, submitted); however, with the combination of omalizumab, our data demonstrate that it could be possible to have a total protein dose of 300 mg (for example, if a subject had been enrolled for 5 food allergies, then their mixture would contain 60 mg of food allergen protein each). A total of 300 mg of food allergen protein can be achieved much more rapidly with omalizumab, leading to decreased dropout rates and potentially longer lasting effects of immunotherapy. Finally, instead of accomplishing a degree of immune protection for some (70%) and instead of waiting for 40 weeks (which is associated with a dropout rate of 20% or more), we are proposing in this protocol to test outcomes at 18 weeks, and expect higher rates of immune protection due to combination dosing of omalizumab and multi food allergen immunotherapy, the latter customized based on the food allergies documented for the subject). We will compare with a group receiving 1200 mg of total protein since 1200 mg is approximately the amount involved in an accidental ingestion (for example, if one bites into a nut bar or nut-containing cookie). It is possible that 1200 mg total vs 300 mg total will have an enhanced effect on IgG4 and

IgE. This is a pilot phase 2a study and our sample size is likely not large enough to detect a difference between 1200 mg vs 300 mg for the primary endpoint; therefore, we will only examine trends.

This protocol is designed to try to maximize safety (with Xolair dosing used concomitantly with OIT therapy), to try to maximize customization of therapy (i.e. multiple food allergic patients will receive the food allergens they are allergic to), and to try to test practical applications of OIT in clinical management scenarios (i.e. use minimal amount of maintenance dose and minimal amount of Omalizumab and minimal time periods).

Lastly, we will examine biomarkers that could predict a patient's eventual outcome for desensitization. High dimensional and innovative immune monitoring will occur on the same participants in the clinical trial. We believe it will be important to test for trends of differences between age groups, specifically, to examine the immune repertoire of the very young (prethymic involution) vs older (postthymic involution). It may be possible that intervening with omalizumab and multifood oral immunotherapy in the very young (i.e. around 2 yr of age) has a more permanent beneficial effect to desensitize the child to their food allergies.

Outside of the conductance of this particular study, we will ask the PIs and staff at each site to consider a long term follow up study to ensure the longitudinal follow up of the participants after they finish the active phase of the study. In this long term follow up study, food challenges will be offered to participants once skin tests become negative for a particular food under a separate IRB-approved study.

2.1.1 Description of the Study Agent(s)/Intervention(s)

Study Agents: Omalizumab is approved by the European Commission and US FDA for patients with severe asthma $\geq$6 years of age. Therefore the risk of Omalizumab is relatively low. In an expanded access protocol at Stanford (PI, Nadeau) under this IND (14831) and in a study run by Dr. Wanda Phipatanakul at Children's Boston, young children are receiving Omalizumab with no adverse effects.

Food flours will be obtained from commercial manufacturers. CMC documents are available and written according to GCP/CFR guidelines and are cross referenced for their INDs (milk, egg, almond, cashew, hazelnut, walnut, peanut, sesame seed, soy, wheat, shrimp, cod and salmon).

2.1.2 Summary of Relevant Clinical Studies and Rationale

We have incorporated procedures of peanut OIT as conducted and published by others- Section 16 (1-3). In addition, we have conducted studies with Omalizumab for food allergy subjects over the past 8 years at Stanford (4-6).

We recently published phase 2 studies using Omalizumab and food allergen immunotherapy (Wood, et al. 2016, and MacGinnitie, et al. 2016). In addition, we have submitted two manuscripts which further justify our dosing, eligibility criteria, and our immune markers chosen for this study (Andorf et al. accepted in JACI In Practice and Monahar, et al.).

Preliminary results of some patients in the phase 1 study results have been published (8).

We have recently used Omalizumab pretreatment to rapidly and successfully desensitize children with severe milk allergy, suggesting that such an approach might be useful for inducing tolerance in patients with multiple food allergies. Oral desensitization for food allergy is currently being studied by many investigators (without Omalizumab), but because of significant side effects, it cannot be recommended for routine use.

2.2 Potential Risks and Benefits

2.2.1 Potential Risks

Omalizumab is approved by the European Commission and US FDA for patients with severe asthma ≥6 years of age. Therefore the risk of Omalizumab is relatively low (please refer to investigator's brochure and cross-reference of IND 103080).

The overall risks of participation range from mild to moderate to severe due to the OIT (oral immunotherapy). These could be as mild as transient pruritus to as severe as anaphylaxis. We are employing procedures that have been used with many children and adults in other studies and have been found to be acceptable around the world. Relative to the information to be gained, these risks are acceptable.

Protection Against Risk: Each research center keeps injectable epinephrine in case of an anaphylactic reaction, and all staff are trained in their use and how to obtain emergency help, if needed. After skin testing, subjects may be given topical low to mid potency steroid cream such as triamcinolone or hydrocortisone for application to affected areas if the patient complains of itching.

All patients will sign a current IRB approved consent and assent if applicable, and will be given written instructions about home dosing and epinephrine use.

2.2.2 Potential Benefits

The only direct and major benefit to the subjects is for those subjects are able to tolerate the OIT and improve their immune protection to the offending food allergens. There is a theoretical benefit of multiple allergen therapy to enable the immune system to develop long-term tolerance with multiple allergen therapy. We will make any of the medically relevant data [skin test results, blood tests (IgE levels)] available to the medical provider upon written request of the parent/guardian.

Importance of the knowledge to be gained: There is considerable discrepancy on which subjects benefit from immunotherapy for their food allergy health outcome and there is a need to determine the success of immunotherapy used in conjunction with Omalizumab; this study will contribute to developing criteria for optimizing this therapy.

3.0 Study Objectives

3.1 Primary Objective

To determine if the use of combination of omalizumab and multi OIT will increase the IgG4 /IgE ratio of at least 2 allergens by ≥25% at week 18 from baseline in multi food allergic patients. .

3.2 Secondary Objectives

To determine if the use of combination of omalizumab and multi OIT will increase IgG4/IgE ratio of at least of 3 allergens by ≥25% at week 18 from baseline in multi food allergic patients.

To determine if the use of combination of omalizumab and multi OIT will increase IgG4/IgE of at least of 4 allergens by ≥25% at week 18 from baseline.

To determine if the use of combination of omalizumab and multi OIT will increase IgG4/IgE of at least of 5 allergens by ≥25% at week 18 from baseline in multi food allergic patients.

Other objectives include monitoring treatment related adverse events according to CTCAE v4.03 criteria. Allergic reactions will be monitored separately as allergic adverse events.

We will also explore immune monitoring studies and we will perform high dimensional and innovative immune monitoring during the study. The long term objective of this study is to develop a potentially curative therapy for patients with multi food allergies. We hypothesize that young and older subjects with multi food allergies who receive a combination of Omalizumab and multi oral immunotherapy (OIT) can be rapidly desensitized and tolerate higher doses of food protein. We also hypothesize that 300 mg daily total protein dose will be adequate and similar to 1200 mg daily total protein dose to achieve the primary endpoint in the majority of participants. However, we will explore if age, sex, body mass index, years with disease, and degree if polysensitization affect outcomes, as well as characterize the treatment related adverse events throughout the study.

4.0 Study Design

4.1 Description of Study Design

This is a phase 2 multisite study which will be conducted at two centers in the U.S. All subjects will receive oral immunotherapy for their specific food allergies (limited to those food allergens in the CMC section of IND 14831). All participants will receive three doses of omalizumab over 8 weeks. The subject's allergens will be introduced on desensitization day 1 at week 0, after receiving the third omalizumab dose. Subjects will return to clinic to escalate the dose of their allergens until 300 mg or 1200 mg daily total protein, depending on randomization assignment, is reached. Clinical and laboratory based assessments will be performed at certain visits throughout the study as per the schedule of events (Appendix D) and as needed per the investigator's discretion.

4.2 Study Endpoints

4.2.1 Primary Endpoint

The proportion of subjects on a combination of omalizumab and multi oral immunotherapy who have increase in the IgG4 /IgE ratio of at least of 2 allergens by ≥25% from baseline at wk18.

4.2.2 Secondary Endpoints

The proportion of subjects on a combination of omalizumab and multi oral immunotherapy who have an increase the IgG4 /IgE ratio of at least of 3 allergens by ≥25% from baseline, at week 18.

The proportion of subjects on a combination of omalizumab and multi oral immunotherapy who have an increase the IgG4 /IgE ratio of at least of 4 allergens by ≥25% from baseline, at week.

The proportion of subjects on a combination of omalizumab and multi oral immunotherapy who have an increase the IgG4 /IgE ratio of at least of 5 allergens by ≥25% from baseline, at week 18.

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5.0 Study Population

5.1 Description of Study Population

We will enroll food allergic subjects (2-25 years of age) with proven food allergies. We anticipate enrolling 60 subjects with multi food allergies at two sites.

5.1.1 Subject Inclusion Criteria

Subjects who meet all of the following criteria are eligible:

1. Subjects aged 2 to 25 years, inclusive, with clinical history of allergy to at least two of the following:
    - milk
    - egg
    - peanut
    - almond
    - wheat
    - cashew
    - sesame seed
    - soy
    - walnut
    - hazelnut
    - shrimp
    - cod
    - salmon
2. Sensitivity to food allergens documented by a positive skin prick test result ≥6mm wheal diameter to each allergen at screening or ImmunoCAP IgE level >4kU/L for each allergen at screening.
3. If female of child bearing potential, a negative urine pregnancy test at screening, and week 0 visit if visit is more than 7 days from screening.
4. Female subjects who are of child-bearing potential must agree to comply with using medically-approved method of contraception (please see Section 7.4.5 Pregnancy Test) for the duration of the study.
5. Agrees to comply with study protocol visits, procedure requirements, and to remain in the area of the research center during the trial.

6. Able to follow anaphylaxis action plan including administration of epinephrine and is trained on the proper use of the Epinephrine autoinjector as indicated by signing the epinephrine autoinjector training form. (see appendix A).
7. Able to eliminate other known food allergens from subject's diet so as not to confound the safety and efficacy data from the study
8. Willing to avoid open or blinded food challenges to food allergens, other than study designated allergens, for the duration of the study.

5.1.2 Subject Exclusion Criteria

Subjects who meet any of the following criteria are not eligible:

1. Previous anaphylactic reaction to Omalizumab.
2. Allergy to oat.
3. A history of severe anaphylaxis to food allergens that will be desensitized in this study requiring intubation or admission to an ICU, frequent allergic or non-allergic urticaria, or history consistent with poorly controlled persistent asthma.
4. Unstable angina, significant arrhythmia, uncontrolled hypertension, chronic sinusitis, or other chronic or immunological diseases that, in the judgment of the investigator, might interfere with the evaluation or administration of the test drug or pose additional risk to the subject (e.g., gastrointestinal or gastroesophageal disease, chronic infections, scleroderma, hepatic and gallbladder disease, chronic non-allergic pulmonary disease).
5. An average FEV1 or PEF less than 80% predicted (moderate persistent asthma) with or without controller medication (if able to perform the maneuver) at screening, or at up dosing visits.
6. Current users of oral, intramuscular, or intravenous corticosteroids, tricyclic antidepressants, or are taking a beta-blocker (oral or topical).
7. Routinely using medication that, in the investigator's judgement, could induce adverse gastrointestinal reactions during the study.
8. Pregnant or breast feeding women.
9. Use of omalizumab or any other monoclonal antibody therapy, or use of immunomodulatory therapy, besides aeroallergen or venom immunotherapy, within 6 months of screening.
10. Diagnosis of eosinophilic esophagitis, eosinophilic colitis, or eosinophilic gastritis.

5.2 Study Protocol Stopping Criteria

During the course of the study, if the investigator or DSMB discover conditions that indicate that the study should be discontinued, an appropriate procedure for terminating the study will be instituted, including notification of the FDA and IRB or EC (ethics committee).

Stopping rules for the study:

- Any death related to dosing
- More than one participant has systemic allergic symptoms associated with hypotension in response to oral immunotherapy
- More than 3 participants require more than 2 injections of epinephrine during dosing of the food products
- More than 3 of the following events:
    - Severe adverse event, other than anaphylaxis, related to investigational product
    - Eosinophil Esophagitis

5.3 Individual Subject Stopping/Termination Criteria

A subject may be prematurely terminated from the study for the following reasons:

- The investigator feels that it is not safe for the subject to continue receiving treatment.
  - Examples include significant side effects from the study drug (any Bock's criteria grade 3 reaction that is associated with hypoxia (less than 92% oxygen saturation) or blood pressure changes (greater than 20 mm Hg drop in systolic or diastolic blood pressure)
- Any serious or unexpected adverse event
- Serious intercurrent illness
- Progression of disease that requires alternative treatment
- The subject desires to discontinue participation in this study.
- The subject is unwilling or unable to comply with the protocol.
- The subject becomes pregnant.
- The subject misses more than 5 consecutive study visits.
- The subject does not tolerate 5mg total dose at desensitization (week 0).
- The subject misses 7 consecutive days or more days of OIT dosing due to non compliance.

5.4 Documentation of Termination from Study

The reasons for termination of a subject from the study must be documented clearly on the termination page of the subject's CRF, and must be completed for any subject who has received any amount of test drug. If the reason for termination is an adverse event, the specific event or test result must also be recorded on the subject's AE CRF page.

5.5 Follow Up of Subject who Discontinue Treatment

A subject can voluntarily withdraw from the study at any point in the study. If the subject withdraws consent to participate in the study, and/or subjects who prematurely discontinue treatment at any other time during the study, will return for an Early Discontinuation visit that consists of the same procedures as the end of study visit. Early discontinuation visit must occur within 14 days after the last dose of subject's allergen.

5.6 Replacement of Subject who Discontinues Study Treatment

Terminations due to safety or issues that are not treatment-related, such as relocation, will be included in the analyses up and through the last valid visit prior to withdrawal. Subjects who withdraw/are terminated may not be replaced.

6.0 Study Agent/Interventions

6.1 Omalizumab

6.1.1 Formulation, Packaging and Labeling

Omalizumab is a sterile, white, preservative-free, lyophilized powder contained in a single-use vial that is reconstituted with Sterile Water for Injection (SWFI), USP, and administered as a subcutaneous (SC) injection.

6.1.1.2 Preparation, Administration, Storage, and Dosage Study Agent(s)/Intervention(s)

Omalizumab will be stored and prepared according to the investigator brochure and the MOP. The omalizumab will should be stored in a secure location and kept refrigerated

between 2-8°C. Sites will maintain temperature logs for all refrigerators storing study drug for the duration of the study.

Dosing for Omalizumab will be 150 mg via subcutaneous injection monthly for three doses for participants ≥4 years of age, and 75 mg via subcutaneous injection monthly for three doses for participants <4 years of age.

6.1.3 Study Agent (Omalizumab) Accountability Procedure

Omalizumab will be ordered and shipped directly to the site according to the site's institutional policies. Documentation of omalizumab receipt will include date of receipt, lot number and expiration date. Dispensation of omalizumab will include date of dispensation, participant ID and lot number.

The site investigator will agree to administer study drug only to subjects in the research clinic who have signed the informed consent. The investigator will not supply study drug to any person not authorized to receive it.

Following study drug administration, the research staff will retain all empty or partially used vials and return to investigational pharmacist until appropriately accounted for during a monitoring visit. All vials may be then be disposed of per hospital destruction policies.

6.2 Food Protein

6.2.1 Formulation, Packaging and Labeling

Food flours will be obtained from commercial manufacturers. CMC documents are available and written according to GCP/CFR guidelines and are cross referenced for their INDs (milk, egg, almond, cashew, hazelnut, walnut, peanut, sesame seed, soy, wheat, shrimp, cod and salmon) (see **Error! Reference source not found.**).

6.2.2 Preparation, Administration, Storage, and Dosage Study Agent(s)/Intervention(s)

All food flours will be obtained from the same manufacturer (Stanford) per the CMC; a certificate of analysis **will be prepared by Stanford** according to FDA requirements and the CMC. All food flour doses will be packaged, inventoried, and labeled at Stanford GMP facility. The doses will be shipped to the site pharmacy for distribution to subject/subject's parents by site study personnel. The food flours will be stored at the sites per the CMC and SOPs to maximize stability. Research staff will administer food flour to the subject orally in an age-appropriate food vehicle. Each food flour dose containing equivalent portions of test allergen protein will be prepared into a separate container by the Stanford GMP staff and labelled with the subject identifier. Dosage for OIT will be prepared in accordance by Stanford GMP with each subject's allergen history and will be sent to the site in advance of subjects clinic visit. Food flour doses may also contain oat flour so that the volume of group A and group B doses are the same size in order to maintain the blind.

Table 2: Up Dosing Schedule Group A.

Dosing Interval	Total Protein Dose (mg)
Week 0	5
Week 4	60
Week 8	300

Week 12	300
Week 16	300

Table 3: Up Dosing Schedule Group B.

Dosing Interval	Total protein Dose (mg)
Week 0	5
Week 4	240
Week 8	1200
Week 12	1200
Week 16	1200

6.2.3 Study Protein Accountability Procedures

The Investigational Pharmacist will maintain adequate records of the receipt of all food flours shipped to the site. Records will include dates, quantities received, quantities dispensed, and the identification code number of the subject who received the study drug.
The investigator will agree to administer test drug only to subjects under his or her personal supervision. The investigator will not supply test drug to any person not authorized to receive it.

Following administration of food flours, the site personnel will destroy used containers and document on the product accountability log.

6.2 Concomitant Medications and Procedures

During the study, subjects will be allowed to use medications for allergic rhinitis, asthma, and atopic dermatitis, including intranasal glucocorticoids, inhaled corticosteroids, inhaled beta 2 antagonist, antihistamines, and leukotriene inhibitors. Daily concomitant medication use will be documented in the subject's chart. Subjects may use an antihistamine such as diphenhydramine or cetirizine for pruritis and other allergy symptoms. More specifically the following are permitted medications:

- Oral antihistamines (must abstain before skin prick testing)
- Oral and inhaled corticosteroids (duration should be limited and ideally stopped upon AE resolution).
- Topical steroids to treat any local cutaneous AE
- Intramuscular injectable epinephrine
- Treatment prescribed in case of any AE
- Treatment with Cromolyn sodium, and leukotriene inhibitors

6.3 Prohibited and Rescue Medications

Refer to the most recent package insert or investigator's brochure to access additional current information on prohibited and precautionary medications for Omalizumab (cross-reference IND 103080).

6.3.1 Prohibited Medications and Procedures

At any time during study participation, subjects may not receive any of the following treatments:

- Another investigational drug or approved therapy for investigational use
- Systemic steroids (intravenous, intramuscular or oral dosing) for more than 5 consecutive days or 15 days total in the study period

Prior to skin prick-testing subjects will be asked to restrict the use of antihistamines (short-acting, 72 hours: long-acting, 7 days).

6.3.2 Rescue Medications

Rescue medications for any clinically significant reaction will include Epinephrine, including autoinjectors (dosed according to product insert), antihistamine class of medications (dosed according to weight of subject and according to package guidelines), and inhaler medications (short-acting beta agonist class of medications). The investigators will use their clinical judgment to apply these medications in an event of a reaction. In addition, all rescue medications are available within immediate reach in each room of the research clinic while dosing occurs. Rescue medications can be given IV, IO, IM, by inhalation, and/or by oral route as dictated by the research clinician.
For home dosing, the same class of medications will be available and all the subjects/parents/guardians will receive detailed instructions and education on the use of these reaction medications. Subjects must have their own epinephrine auto injector supply for use per the food allergy action plan. A prescription for epinephrine auto injector may be provided to subjects, as appropriate.

6.4 Description of Facility

The study visits will be conducted in a research center at each study site location. Beds or chairs are dedicated to clinical research and will be used for the conduct of food allergy OIT studies. A code team will be available to the food allergy research center and clinical staff should have immediate access to a code cart and emergency personnel. Each site should have a documented code plan for emergency use. In addition, the research center will have vital sign monitors, oxygen tanks, and reaction medications.
Emergency trained health care professionals are located within 25 feet of the rooms in which oral immunotherapy is being performed.

7.0 Study Procedures/Evaluations

7.1 Clinical Evaluations

Subjects will keep electronic diaries during the study to document daily dosing and any symptoms during the oral immunotherapy perios. Please refer to the **Study Schedule of Events (appendix D)**, for full details.

Missed OIT Doses

- If the subject misses up to three consecutive days of the daily dose for any reason then he/she may resume with same dose at home or in to the research center.

- If the subject misses >3 but <6 consecutive days of the daily dose for any reason then he/she may be asked to return to the research center for the next daily dose for observe dosing, if deemed appropriate by the investigator.
- If the subject misses more than six days of the daily dose for any reason he or she will return to the research center for the next daily dose possibly for dose reduction or discontinue OIT updosing (may be deemed a desensitization failure based on PI discretion), as deemed appropriate by the investigator.
- If the subject misses 14 or more days of the daily dose for any reason, subject will be terminated from the study.

7.2 General safety precautions for entire study

1. If the subject develops a mild objective reaction, the next dose may be kept the same until no reaction for at least 2 weeks occurs before continuing dose escalation.
2. If a significant acute viral infection (i.e. gastroenterological, upper airway) is diagnosed, the dosing will be decreased or stopped up to 4 days at any time during OIT dosing per Investigator's discretion.
3. If any subject has a serious adverse reaction (serious as defined by CFR/GCP [Code of Federal Regulation/ Good Clinical Practice] Guidelines, http://www.fda.gov/Safety/Med Watch/ HowTo Report/ucm053087.htm), the principal investigator will report to the FDA and DSMB and ask the subject to discontinue OIT.
4. The subject will be told to eat the OIT dose within an hour of eating a meal and to drink at least 4 ounces of cold water or suck on ice cubes after the ingestion to try to prevent local reactions in the mouth and throat.
5. If, at any point in the study, the subject complains of new onset vomiting, dysphagia, chronic abdominal pain, and difficulty swallowing for more than 6 weeks, the patient will be referred to a gastroenterologist for assessment of possible gastroenterological disorders associated with food allergy (i.e., eosinophilic esophagitis).
6. If there is abdominal pain or vomiting within or outside of a 2 hr window from eating the food allergen mixture for more than 4 days in a row - without the presence of a gastroenterological virus, we suggest a decrease in the dose by 25%, encourage participant to start an antacid or protein pump inhibitor, take 5-10 mg of cetirizine one hour ahead of food allergen mixture dosing, and drinking water or sucking on ice cubes after ingestion of the food allergens. If within about 5 days, symptoms have not subsided, decrease dose again by 25% and continue other above procedures. When there is two weeks with no abdominal pain or vomiting symptoms then consider dose escalation.
7. If there is a medical necessity to take oral prednisone (i.e., any oral steroid class of agents), the daily dose of prednisone must be limited to 5 consecutive days or 15 total days during the study. If additional daily doses are needed, the patient will be terminated from the study.
8. All precautions as suggested by Varshey, P. et al. (2009)(1) and by Hofmann, et al. (2009)(2) will be implemented.
9. Daily doses of 5-10 mg of cetirizine (as per product label) are strongly encouraged throughout the study unless otherwise specified.
10. If there are other concomitant allergic medical issues (i.e. allergic rhinitis, allergic conjunctivitis, eczema) that the PI is concerned about, the subject may be asked to decrease their dose per investigator discretion.

7.3 Laboratory Assessments

7.3.1 Clinical and Research Laboratory Evaluations and Specimen Collection

The laboratory assessments for each subject includes ImmunoCap (Phadia, Sweden) to food allergen IgEs and IgG4s, total IgE, and other translational and mechanistic laboratory tests. Baseline labs will include ImmunoCap to food allergens and will be documented to confirm inclusion criteria.

Plasma and cells will be banked for future translational research if patient agrees per the informed consent.

Blood sample collection and shipment to the Nadeau laboratory are required procedures in the protocol (please see Study Schedule of Events-Appendix D).

7.3.2 Specimen Preparation, Handling and Shipping

Quality Assurance: All samples will be coded, processed, and stored. Whole blood will be collected. Each laboratory that stores specimens has a 24-hour, 7-days a week monitoring of the storage units, and has a back-up generator in case of power outage. Sites sending specimens to Stanford should send specimens the same day per the MOP.

Standard Operating Procedures (SOPs) are in place for: 1) sample handling (aliquoting, transfer of samples); 2) record keeping (chain of custody forms, shipping inventory, data entry to laboratory databases); 3) storage and shipping conditions (temperature requirements, back- up power systems, overnight delivery); and 4) problem resolution (discrepancy reports, etc).

Every aliquot is labeled that uniquely identifies it according to participant ID, visit, sample type, and aliquot number. Samples will be sent to the Nadeau lab per the MOP. Samples received at the Nadeau lab will be barcoded to enter the sample ID into the database to a location unique to that aliquot. The Nadeau laboratory biorepository has developed a customized database to track and locate all bar-coded samples. The database information does not contain any personal identifiers and is backed up nightly on a secured Stanford server with up-to-date network protection.

7.4 Other Safety Assessments

7.4.1 Physical Examination and Vital Signs

Physical examination will be conducted at visits indicated in the Schedule of Event (AppendixD). Height and weight will also be recorded. Vitals signs will also be assessed to include resting blood pressure, heart rate, respiratory rate, body temperature, and oxygen saturations.

7.4.2 Spirometry

Spirometry to determine FEV_1 (3 attempts are to be performed). For subject <6 or who are unable to do spirometry may complete Peak expiratory flow rate (PEFR) assessment. Subjects who are unable to complete either should be assessed by an investigator by physical examination. If possible, airflow assessment should be measured at each visit.

7.4.3 Skin Prick Test

Skin testing will be performed per standard techniques. Subject have to be off antihistamine for an appropriate length of time (5 half lives of the antihistamine that is being used) prior to testing.

7.4.5 Pregnancy Test

All females of child-bearing potential will undergo a urine Human Chorionic Gonadotropin (HCG) test at screening, prior to initial administration of Omalizumab at week 0 visit, if more than 7 days from screening, and when deemed necessary by the investigator.

All women of child-bearing potential must agree to practice preventive measures regarding pregnancy with the prevention measures of their choosing. If they choose oral contraceptives, a

prescription will be provided to them or they will be referred to an OB/GYN physician. They will be required to disclose their method of pregnancy prevention at the initial screening visit and at the initiation of Omalizumab dosing.
If a participant becomes pregnant during the course of the study, she will be required to cease all study-related treatments immediately. She will continue to be followed until study completion and monitored until the conclusion of the pregnancy.

7.5 Data management

All research data that is required at each study time point will be documented using Stanford Allergy Center templates. If there are outside records from healthcare providers or clinics, these will be kept as source documents. These may include lab results, progress notes, etc. during screening or any visits that do not occur at the study site following randomization. Electronic Data Capture will be via Redcap.

8.0 Study Schedule of Events

See 17.0.4 Appendix D:

8.1 Screening – Week -36 thru Day-1

Written informed consent will be obtained prior to any study related procedures by the principal investigator or their designee according to ICH/GCP guidelines.

Screening Procedures will be completed within 36 weeks prior to Week -8 visit and will include the following:

- Obtain informed consent, and assent if applicable
- Review of inclusion/exclusion criteria
- Medical, allergy, and dietary history
- Concomitant medication review
- Physical exam
- Vital signs including resting blood pressure, heart rate, respiratory rate, body temperature, height, and weight
- Spirometry
- Skin prick testing, if applicable per investigator discretion
- Urine pregnancy test for women of child bearing potential
- Blood draw to collect sample for:
    - Allergen specific IgE, total IgE
    - Allergen specific IgG4
    - Mechanistic labs
    - The amount of blood to be taken for the above assays will not exceed a total volume of 50mL or 3ml/kg, whichever is lesser, within an 8 week period in children, and lesser of 300mL or 5ml/kg within a 12 week period in adults.
- Training on Epinephrine autoinjector use and food allergy action plan.

If the subject meets initial eligibility based on skin testing, allergen-specific IgE, spirometry, total IgE, they may undergo further screening to determine eligibility (e.g assess commitment to compliance).

Subjects will be monitored for adverse events (categorized as allergic vs. non allergic adverse events) and any changes in concomitant medications at every study visit after Screening.

Eligible subjects will be enrolled and randomized in the study, then initiate Omalizumab therapy .

8.3 Treatment Period

8.3.1 Week -8 and -4 - Omalizumab Treatment (Dose 1 and 2) ±5 days

Once deemed eligible, subjects will be randomized 1:1 to either group A (300mg) or Group B (1200mg). All subjects will be treated with three doses of Omalizumab over 8 weeks (Week -8, Week-4 and Week 0 prior to starting oral allergen immunotherapy) to allow food-specific IgE on mast cells and basophils to equilibrate with anti-IgE mAb. Omalizumab will be dosed as 0.016 mg omalizumab/kg/total IgE U/mL per product brochure guidelines.(see **Error! Reference source not found.**)

The following procedures will be completed at Week -8 and -4 visits:

- Symptom directed physical exam
- Review of adverse events and concomitant medication
- Administration of omalizumab. Subjects will stay for post dose observation at the research center for at least 90 minutes after injection or longer as deemed necessary by the investigator.

8.3.2. Week 0 – Last Omalizumab dose (Dose 3) and First dose of food allergen and desensitization

After the last dose of omalizumab administration, subjects will undergo an oral desensitization to up to five offending food allergens. The allergen mix will be prepared by the Stanford GMP Facility and include the total number of allergens (1:1 in mg protein) for an initial dose of 5 mg total protein dose. Food vehicles may include applesauce, chocolate pudding or vanilla pudding or other age appropriate food vehicles. Heating or cooking of food flour will not be allowed.

The following procedures will be completed at Week 0 visit

- Complete physical examination
- Predose vital sign measurement (heart rate, respiratory rate, blood pressure and pulse oximetry)
- Spirometry
  - If spirometry FEV1 and/or peak flow is less than 80% of predictive values, clinician must document clear breath sounds before dose escalation.
- Administration of Omalizumab subcutaneous injection.
- Oral administration of food flour 5mg total protein dose at least 60 minutes after last Omalizumab injection.
- Post dose vital signs measurements (heart rate, respiratory rate, blood pressure and pulse oximetry) within15 minutes post dose then every 15 minutes for the duration of the minimum 2 hour post dose observation period or longer as per investigator discretion.
- Treatment for objective symptoms should occur via treatment recommendations as per institutional and NIAID published guidelines for anaphylaxis. (https://www.niaid.nih.gov/topics/foodAllergy/clinical/Documents/FAguidelinesPatient.pdf)
- AEs will be monitored, including allergic symptoms
- When dosing with the allergen/s elicits an acute reaction, the investigator will assess if the

dose was tolerated or not.

- Subjects who tolerates 5 mg of total protein with no grade >1 objective allergic reaction (as per Bock's criteria in Section **Error! Reference source not found.**) during dosing a nd until 2 hour post dose observation period will be dispensed 4 week supply of 5 mg total protein allergen doses. They will be instructed to continue daily oral dosing at home, starting the following day (day 2), and to continue daily home dosing at that dose level for 4 weeks until the next escalation.
- Subjects who do not tolerate 5mg total protein, deemed to have dose limiting symptoms such as grade 3 reaction by Bock's criteria or who receive intensive therapy for allergic reaction, will be classified as **desensitization failures**. There will be no further dosing of study product and subject will return to the research unit about 14 days after last allergen dose for an early discontinuation visit.
- Subjects will be given home dosing instructions, which will include a 24-hour emergency contact information, and contact information for the research team for questions or concerns with home dosing.
- Subjects will be instructed to keep an electronic diary of food allergy symptoms.
- Subjects will be reminded to continue allergen avoidant diet for the duration of the study.

A starting dose of 5mg total dose of the food allergens was chosen since this is the starting dose given in most single food allergen oral immunotherapy regimens. Since all participants are receiving 3 doses of Omalizumab prior to initiation of oral immunotherapy (OIT), we expect participants to tolerate at least 625 mg or more of total food allergen protein (Nadeau et al. JACI 2011).

The oral immunotherapy treatment period will last approximately 18 weeks and comprise of up dosing visits every 4 weeks until reaching a the assigned maintenance dose, with the potential for unscheduled visits for assessments of dose tolerability, dose reduction, dose re escalation, or assessment and management of AEs.

8.3.2.1 Discharge criteria for any subjects upon completion of procedures:

Subjects will only be discharged from the research center all allergic symptoms have resolved or significantly improved for at least 60 consecutive minutes.

8.3.2.2 Criteria that would require further observation and/or hospital admission.

1. Any allergic symptom that are mild or moderate (Bock's criteria 1 or 2, reference 7) will be observed for at least 60 minutes per the NIAID food allergy guidelines or per PI or their designee discretion.

2. Any allergic symptom that is severe (Bock's criteria 3, reference 7) or that is deemed medically worrisome by the medical staff and principal investigator, will be considered for a possible hospital admission or observation.

8.3.3. Weeks 4 through 16 ±5days

Subjects will return to clinic every 4 weeks for dose escalation to a maximum daily total protein dose of 300 for group A and 1200mg for group B participants.

The first dose of each new dose level will be administered in the research unit under direct observation and medical supervision. Subjects should withhold their daily home dose on in clinic dosing days.

At week 4 visit, total protein daily dose will be increased to 30 mg (group A) or 240 mg (group B) of their food allergens. (see Table 2: Up Dosing Schedule Group A. and Table 3: Up Dosing Schedule Group B.)

The following procedures will be completed at each up dosing visit:

- Adverse event and concomitant medication review
- Diet (food allergen exposure) history review
- Return unused allergen doses to clinic, and assess compliance
- Diary review with subject
- Symptom directed physical exam
- Predose vital signs measurement (BP, HR, RR, body temperature, oxygen saturation)
- Spirometry
- Oral allergen dose administration under observation in clinic
- Post dose vital signs measurements (heart rate, respiratory rate, blood pressure and pulse oximetry) within 15 minutes post dose then every 15 minutes for a minimum of 2 hours post dose observation period or longer as per investigator discretion.
- Remind subject to keep an electronic diary of food allergy symptoms.
- Remind subject to continue allergen avoidant diet for the duration of the study.
- Review of food allergy action plan and epinephrine autoinjector use

Subjects must be free from active wheezing, a flare of atopic dermatitis, or suspected inter-current illness prior to any dose escalation.

If increased dose was tolerated with no dose limiting symptoms detected during the post dose observation period, the subject may be sent home with increased tolerated dose for daily home dosing.

- If subject has mild reactions to the increased dose in the research center, subject will continue with the previous dose at home. No increase in the dose will occur for that visit. A dose escalation will be attempted in 2-4 weeks until the maximum daily total protein dose is reached per subject treatment assignment. Dose must be tolerated for at least 2 weeks prior to any dose escalation.
- If subject has moderate reactions to the increased dose in the research center, dose escalation will not occur. Subject will continue with the previous dose at home. A dose escalation will be attempted in 2 weeks to approximately half of the dose eliciting the moderate allergic reaction. Another dose escalation may be scheduled every 2-4weeks until the maximum daily total protein dose is reached per subject treatment assignment. Subject requiring partial dosing will have to maintain and tolerate the new dose level for a 2 week period prior to attempting to re-escalate.
- If subject has severe reactions to the increased dose in the research center that included hypoxia, hypotension, or change in mental status, or who receives intensive therapy such as IV epinephrine or intubation or admission as assessed by an investigator, subject will be terminated from the study. There will be no further dosing of study product and subject will return to the research unit about 14 days after last allergen dose for an early discontinuation visit.

It is possible that allergic cell (i.e. mast cell, basophil, eosinophil) activity will be present. Therefore, subjects will be observed closely (every 15 min vital signs in a facility with trained personnel

and access to reaction medications) for the development of symptoms, including hives, worsening of eczema or wheezing during this time period, and will be reminded to keep a diary of food allergy symptoms. It is expected that patients will remain tolerant to this dose of cumulative offending food allergen(s) even when Omalizumab is discontinued at week 0 since the half life is approximately 26 days, and should remain effective at 3 months. Omalizumab is deemed to continue to have some effects up to week 12 of the study, as was observed in the milk desensitization study (5) and phase 1 study results of this IND (8). (Section 16.0).

8.3.4 Early Discontinuation/ End of Study (week 18 ±5 days)

Subjects who tolerate their oral allergen doses to the maximum total protein dose per treatment assignment will have an End of Study visit at week 18.
Subjects who fail dose escalation, or who prematurely discontinue treatment at any other time during the study, will return for an Early Discontinuation visit that consists of the same procedures as the end of study visit. Early discontinuation visit must occur within 14 days after the last dose of subject's allergen.

The following procedures will be performed at the End of Study/Early Discontinuation Visit:

- Adverse event and concomitant medication review
- Diet (food allergen exposure) history review
- Return unused allergen doses to clinic, and assess compliance
- Diary review with subject
- Complete physical exam
- Vital signs measurement (BP, HR, RR, body temperature, oxygen saturation)
- Spirometry
- Skin Prick Testing
- Blood draw to collect sample for:
    - Allergen specific IgE, total IgE
    - Allergen specific IgG4
    - Mechanistic labs
- The amount of blood to be taken for the above assays will not exceed a total volume of 50mL or 3ml/kg, whichever is lesser, within an 8 week period in children, and lesser of 450mL or 5ml/kg within a 12 week period in adults.
- Training on Epinephrine autoinjector use and food allergy action plan.

8.3.5Unscheduled Visits

The procedures performed at unscheduled visits may include any or all of those performed at Visit 1. Unscheduled visits will take place for an unexpected pregnancy or any complication or AE/SAE that requires an extra visit. These visits will be documented in the source document and the unscheduled visit electronic case report form.

9.0 Assessment of Safety

9.1 Adverse Event (AE)

An adverse event is defined as any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's

participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07) http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2).
For this study, an adverse event will include any untoward or unfavorable medical occurrence associated with:

- **Study therapy regimen**:

  Home OIT Dosing
  - Food allergy episodes in response to home dosing that are Grade 1 or 2 by Modified Bock's Criteria (**Appendix B**) will be recorded on the AE CRFs.
  - Food allergy episodes in response to home dosing that are Grade 3 by Modified Bock's Criteria (**Appendix B**) or that are classified as SAEs defined in Section 12.2.3 below will be recorded on the AE/SAE CRF, as appropriate.

- **Study mandated procedures**:

  For the procedures below, clinical situations are listed that are considered to be outside the normal range of outcomes and will be recorded as Adverse Events. These situations do not limit an investigator from recording and reporting any other events, associated or not with these procedures as AEs.
  Allergen Skin Testing
  - Prolonged (>24 hours) itching at test site
  - Swelling (> 10 cm) at site of test lasting more than 24 hours
  - Nasal allergic symptoms within 30 minutes from the procedure
  - Fainting /Vasovagal event within 30 minutes from the procedure

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

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

9.2 Unexpected Adverse Event

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

investigational plan or elsewhere in the IND or protocol.
The Principal Investigator will review all adverse events related to skin prick testing, spirometry, food challenge, or other study procedures to determine if they are unexpected.

9.3 Serious Adverse Event (SAE)

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

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

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

9.4 Grading and Attribution of Adverse Events

Grading Criteria

The study investigator will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v4.0. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the Principal Investigator and has been deemed appropriate for the subject population to be studied in this protocol.
Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

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

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

Anaphylaxis will be defined when there is: 1) Symptomatic bronchospasm, with or

without urticaria, with parenteral intervention indicated for edema and hypotension; or
2) Life-threatening consequences with urgent intervention indicated.

Attribution Definitions
The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator/study physician and recorded on the appropriate AE/SAE paper case report form and according to SUSAR guidelines (http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf). Final determination of attribution of SAE for safety reporting will be determined by PD.
For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: http://ctep.cancer.gov/reporting/ctc.html.

9.5 Collection and Recording of Adverse Events

9.5.1 Collection Period

Adverse events will be collected from the time of consent until a subject completes study participation or until 30 days after last OIT dose.

AEs related to allergic reactions will be collected separately. Allergy reactions are expected during this study. Reactions due to allergy are within the first 2 hours after dosing with the food allergen mix.

9.5.2 Collecting Adverse Events

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

- Observing the subject.
- Interviewing the subject [e.g., using a checklist, structured questioning, diary, etc].
- Receiving an unsolicited complaint from the subject.
- Review of medical records/
- Review of home dosing symptom log in subject diary (symptoms between visits)

9.5.3 Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously in this section on the appropriate AE/SAE source document regardless of the relationship to study therapy regimen or study procedure. Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until 30 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.
Allergic reactions will be recorded separately as allergic adverse events.

9.6 Reporting of Serious Adverse Events and Adverse Events

9.6.1 Reporting of Serious Adverse Events to Sponsor

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

E6 guidelines.
The site investigator will report to the Protocol Director/Sponsor all serious adverse events within 24 hours of becoming aware of the event, regardless of relationship or expectedness.

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

9.6.2 Reporting of Unexpected Non-Serious Adverse Events

An unexpected, non-serious adverse event that is of Grade 2 severity or higher **and** study related will be recorded and reported to the Protocol Director/Sponsor under the serious adverse event reporting procedure above (i.e. within 24 hours).

9.6.3 Reporting to Health Authority

Dr. Nadeau will be the sponsor of the IND and has the responsibility of reporting all AEs and SAEs to the FDA within the reporting time limits set forth by the FDA.

Standard Reporting (IND Annual Report)
This option applies if the AE is classified as one of the following:

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

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

Expedited Safety Reporting

- Expedited reporting is required.

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

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

- The IND sponsor, Dr. Nadeau, must report any suspected adverse reaction that is both serious and unexpected. The IND sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:
  - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure.
  - One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug
- Aggregate analysis of specific serious adverse events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment

group than in a concurrent or historical control group.

- Any findings from clinical or epidemiological studies, analysis of data pooled across multiple studies, published or unpublished scientific papers, or from animal or in vitro testing that would result in a safety-related change in the protocol, informed consent, General Investigational Plan section of the IND or other aspects of the overall conduct of the trial.

SUSARs must be reported to the FDA within 15 calendar days; fatal or life threatening events must be reported to the FDA as soon as possible, but no later than 7 calendar days.

To report a SUSAR, a finalized, initial SAE case report form and a MedWatch 3500A form will be generated by the site Principal Investigator

Any findings from studies that suggests a significant human risk

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

Reporting of Adverse Events to IRBs/IECs

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

9.7 Pregnancy Reporting

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

The investigator and sites shall report to the sponsor all pregnancies within 1 business day of becoming aware of the event. All pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported.

Information requested about the delivery shall include:

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

Any complication to pregnancy such as a congenital abnormality or birth defect shall be submitted as an SAE to the sponsor using the SAE reporting procedures described above

and to the FDA.

9.8 Reporting of Other Safety Information

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

Specification of Safety Parameters

Research staff will report any clinical adverse event (AE), whether it is observed by the investigator or the subject (see Adverse Events, below, for further details regarding the definition, management, and reporting of AEs).

9.9 Monitoring and Treatment of Toxicity

The investigator, sub-investigator, or designated health professional must be present during initial test drug administration and for increases in dose for the evaluation and treatment of any AEs.

10 Clinical Monitoring Structure

10.1 Site Monitoring Plan

Every effort will be made to maintain the anonymity and confidentiality of subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow representatives of the DSMB, and authorized employees of the appropriate regulatory agencies and the sponsor (i.e. Stanford University) to inspect the facilities used in this study and to inspect, for purposes of verification, the hospital or clinic records of all subjects enrolled into this study.

10.2 Study Monitoring Plan

The investigators will work with the independent Data and Safety Monitoring Board (DSMB).

11.0 Statistical Considerations

The design of this study is a multi-site, trial assessing desensitization following treatment with Omalizumab+food OIT. Ability to tolerate offending food for subjects will be evaluated by immune biomarkers (IgG4/IgE ratio) and monitoring of adverse events.

11.1 Description of the Analysis

Primary efficacy analyses will be conducted using an Intention to Treat (ITT) population and will include all subjects. Subjects who withdraw/are terminated will be considered treatment failures for subsequent efficacy outcomes. There will be no adjustment made for multiple testing done within this study.

11.2 Measures to Minimize Bias

Participants will be seen by trained personnel. Subjects and assessing study personnel will also blinded to the maintenance dose assignment.

11.3 Appropriate Methods and Timing for Analyzing Outcome Measures

11.3.1 Primary Endpoint

To proportion of subjects on a combination of omalizumab and multi oral immunotherapy who have increase in the IgG4 /IgE ratio of at least of 2 allergens by ≥25% from baseline at wk18.

4.2.2 Secondary Endpoints

The proportion of subjects on a combination of omalizumab and multi oral immunotherapy who have an an increase the IgG4 /IgE ratio of at least of 3 allergens by ≥25% from baseline, at week 18.

The proportion of subjects on a combination of omalizumab and multi oral immunotherapy who have an increase the IgG4 /IgE ratio of at least of 4 allergens by ≥25% from baseline, at week.

The proportion of subjects on a combination of omalizumab and multi oral immunotherapy who have an increase the IgG4 /IgE ratio of at least of 5 allergens by ≥25% from baseline, at week 18

Other endpoints include monitoring safety outcomes according to CTCAE v4.03 criteria. Allergic reactions will be monitored separately as allergic adverse events.

We will also explore immune monitoring studies and we will perform high dimensional and innovative immune monitoring during the study. The long term objective of this study is to develop a potentially curative therapy for patients with multi food allergies. We hypothesize that young and older subjects with multi food allergies who receive a combination of Omalizumab and multi oral immunotherapy (OIT) can be rapidly desensitized and tolerate higher doses of food protein. We also hypothesize that 300 mg total protein dose vs 1200 mg total protein dose will be adequate to achieve the primary endpoint in the majority of participants. However, we will explore if age, sex, body mass index, years with disease, and degree of polysensitization affect outcomes; as well as characterize the treatment related adverse events throughout the study. .

11.4 Study Hypothesis

To address the primary objective of this trial of assessing the ability of a combination of omalizumab and multi food allergen oral immunotherapy to increase IgG4/IgE to at least 2 food allergens by equal or greater to 25% at week 18 in patients who have multi food allergy, we will test the following null hypotheses:

1. There is less than a 25% increase in IgG4/IgE among multi

11.5 Sample Size Considerations

To address the primary objective of this trial and test the primary study hypotheses as stated in section 11.5, we are planning to enroll total of 60 subjects. Assuming 15% drop out from the trial, we expect to have primary endpoint observation on 50 subjects in each treatment group. Based on our phase 1 study of Omalizumab and multiple OIT (Begin, et al. AACI 2014) and the paper by Andorf, et al (accepted, attached), we expect that 70% of subjects will reach the primary endpoint.

11.6 Maintenance of Trial Treatment Randomization Codes

Subjects will be randomized 1:1 into one of two study groups:

Group A- 300 mg total food allergen protein,
Group B- 1200 mg total food allergen protein,
A randomized block design will be used. A Master Randomization Assignment List will be kept by the designated unblinded personnel in a secure limited access location in order to ensure that the list is available only to unblinded study personnel.

Once a patient is eligible for enrollment to the treatment phase of the study, blinded site personnel will complete and submit a request for randomization form to the unblinded sponsor personnel in order to randomize the participant. This request will include date of request, subject initials and screening number, allergens to be included in their OIT, and an acknowledgement that the participant has met all eligibility criteria for randomization. Treatment will be assigned by the unblinded sponsor personnel based on a Randomization Master List. The designated unblinded personnel will ensure that the assigned randomization number is in fact the next unused treatment assignment on the master list. He/she will then complete the Randomization Allocation form with the treatment assignment and randomization information including, randomization number/participant ID, randomization date, and treatment assignment. A copy of the completed randomization allocation form will be provided to GMP and site unblinded personnel in a manner that maintains the blind. GMP will prepare and distribute the appropriate daily dose kits to the unblinded personnel at each site. Dosing kits will be labelled in a blinded manner, but will include an unblinded tear-off label that includes unbinded treatment identity and expiration date. This unblinded label will be removed by the unblinded site personnel prior to dispensing and placed on the appropriate subject accountability log. Strict compliance with documentation of randomization procedures is essential to ensure there is a reliable, verifiable link between the study subject's study ID and the treatment assignment. At the end of the study, the Master Randomization List with all randomization numbers and corresponding treatment assignments will be provided as an Excel file to the biostatistician as a further check on the randomization process.

11.7 Subject Enrollment and Follow-Up

We will maximize study subject compliance with the maintenance protocol with frequent contact with subjects and by reviewing the home diary. Our sites have extensive experience in clinical trials, and in enrolling and retaining subjects.

11.8 Planned Interim Analyses (if applicable)

Formal interim analyses of efficacy endpoints are not planned. Interim analyses will be descriptive analyses of safety data.

11.9 Safety Review

Please refer to individual and study stopping rules.

11.10 Immunogenicity Review or Efficacy Review

Information on immunogenicity of Omalizumab can be provided in the investigator's brochure. The primary investigator is aware of possible human anti human antibodies that could be generated against Omalizumab. We will be monitoring for any side effects related to immunogenicity of Omalizumab by monitoring clinical reactions associated with the administration of the

Omalizumab.

12.0 Quality Control and Quality Assurance

Following written standard operating procedures, the monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

Stanford will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

13.0 Ethics/Protection of Human Subjects

13.1 Institutional Review Board/Ethics Committee

The investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki, or with the International Conference for Harmonization Good Clinical Practice (ICH-GCP) regulations and guidelines, whichever affords the greater protection to the subject.

13.2 Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study procedures, Omalizumab dosing, and allergen protein dosing procedures and risks are given to the subject and written documentation of informed consent is required prior to starting study agent/intervention. Consent forms will be IRB approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The subject may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subject for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.2.1 Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or study staff will review the consent and answer questions with the potential participant and must

sign the consent form with the participant and document the informed consent process. For minors participating in this study, informed consent will be obtained from their parent(s) or legal guardian(s). Minors participating in this study will provide assent if they are capable. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

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

13.3 Assent of Informed Consent Process (in Case of Minor)

A separate IRB-approved assent form, describing (in simplified terms) the details of the study, Omalizumab dosing, and food protein dosing procedures and risks will be used. Assent forms will not substitute for the consent form signed by the subject's legally authorized representative.

13.4 Subject Confidentiality

By conducting this study, the investigator affirms that all study results and information furnished will be maintained in strict confidence. Such information will be communicated to the investigator's review committee under an appropriate understanding of confidentiality.

A published summary of the results of this study is not inconsistent with the preceding affirmation of confidentiality. Any formal publication of data collected as a result of this study will be considered a joint publication by the investigator and the appropriate personnel.

13.5 Study Discontinuation

In the event that the study is discontinued, we will not continue therapy.

13.6 Other

Subjects may withdraw with or without medical advice, or if it is determined that the subject is non-compliant. Withdrawal of the subject will not impact upon future care of any subjects at the Stanford University Hospital or clinics.

14 Data Handling Documentation

Study center personnel will complete individual source documents in black or blue ink. All corrections to entered data will be made by drawing a single line through the information to correct. All corrections must be initialed and dated. Personnel will not use "white-out" or obscuring correction fluid/tape. Electronic case report forms are required for every subject who signs consent for participation in the study.

The investigator will retain a copy of all files pertaining to this study for 2 years following the date of marketing approval in an International Conference on Harmonization (ICH) region and until there are no contemplated marketing applications in an ICH region. If an application is not filed or not approved for the indication under study, all study-related files will be retained for at least 2 years following the date of discontinuance of the clinical development program.

14.1 Data Capture Methods

All data will be captured using source document and then entered into the electronic case report forms. The study personnel will enter the data into the electronic case report forms, the study investigator will review data for accuracy, completeness and accurate documentation.

14.2 Types of Data

The data collected include demographics, physical exam information, vital signs, food challenge results, total and specific IgE and IgG4, adverse events, concomitant medications, dose escalations home diary reviews and adverse events. The EDC should be completed within 10 days of each visit.

14.3 Source Documents and Access to Source Data/Documents

Each site will maintain medical and research records for this trial including source documents and CRFs, in compliance with ICH-GCP, local and national regulatory requirements for the protection of confidentiality of subjects. Source data will include information including original records of clinical finds, observations or other activities relevant to the clinical trial. These can include, but not limited to hospital records, clinical and office charts, laboratory notes, subjects' diaries, recorded data from automated instruments, x-rays, pharmacy records, laboratory records.

Approved study staff will have access to subject records. Further, as required by law or other regulations, the IRB, and FDA will have access to the study records.

14.4 Timing/Reports

Annual reports will be generated for the FDA and IRB. The DSMB will meet every 6-12 months or earlier if needed.

14.5 Study Records Retention

The investigator will hold research records for a minimum of two years. Permission is required from Dr. Nadeau prior to destruction of records. All Omalizumab dispensing logs will be kept and destroyed only with permission by Dr. Nadeau.

14.6 Protocol Deviations

Dr. Kari Nadeau will consider any deviations from the protocol on a case-by-case basis. The investigator or other health professional in attendance must contact Dr. Nadeau as soon as possible to discuss the associated circumstances. The principal investigator (with the DSMB panel if needed) will then decide whether the subject should continue to participate in the study. All protocol deviations and the reasons for such deviations must be noted on the appropriate page of the subject's CRF and recorded on a protocol deviation logs.

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedures requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with Good Clinical Practice (GCP ICH E6) Sections:
Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
Quality Assurance and Quality Control, section 5.1.1

Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations according to the guidelines of the IND sponsor. Protocol deviations will be sent to each local IRB/IEC per their guidelines and policies. The site PI/study staff is responsible for understanding and adhering to their central IRB reporting requirements.

15.0 Publication Policy

Following completion of the study, the investigator may publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine.

16.0 Scientific References

1. VARSHNEY P, STEELE PH, VICKERY BP, et al. Adverse reactions during peanut oral immunotherapy home dosing. *J Allergy Clin Immunol* 2009: **124**: 1351-1352.

2. HOFMANN AM, SCURLOCK AM, JONES SM, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. *J Allergy Clin Immunol* 2009: **124**: 286-291, 291 e281-286.

3. VARSHNEY P, JONES SM, SCURLOCK AM, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol*: **127**: 654-660.

4. GERNEZ Y, TIROUVANZIAM R, YU G, et al. Basophil CD203c levels are increased at baseline and can be used to monitor omalizumab treatment in subjects with nut allergy. *Int Arch Allergy Immunol*: **154**: 318-327.

5. NADEAU KC, SCHNEIDER LC, HOYTE L, BORRAS I, UMETSU DT. Rapid oral desensitization in combination with omalizumab therapy in Participants with cow's milk allergy. *J Allergy Clin Immunol*: **127**: 1622-1624.

6. YU GP TK, HAMILTON RG, NADEAU KC. Omalizumab in Peanut-allergic Participants Reduces Free IgE to Peanut and Skin Prick Tests to Peanut. *Journal of Allergy and Clinical Immunology* 2010: **125**: AB22.

7. BOCK SA, SAMPSON HA, ATKINS FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988: **82**: 986-997.

8. BEGIN P, DOMINGUEZ T, MEHROTRA A, O'RIORDAN G, and NADEAU KC. *Phase 1 study results of Rush multi oral immunotherapy with omalizumab in a single center.* Allergy, Asthma, and Clinical Immunology. (February 2014).

17.0 Appendices

17.1 Appendix A: Epinephrine autoinjector Training Form

Training Form

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

_____ _____

Signature of Adult Participant Date

_____ _____

Signature of LAR (Parent, Guardian or Conservator) Date

_____

Authority to act for participant

Current wt: _____kg

Dose: ☐ **EpiPen 0.3mg or equivalent** ☐ **EpiPen Junior 0.15mg or equivalent**

ANAPHYLAXIS INFORMATION (All boxes must be checked)

☐ Subject and/or family given verbal and written instructions on anaphylaxis.

☐ Subject and/or family given Food Allergy Action Plan with a verbal review to ensure understanding

☐ Subject and/or family given information on how to purchase medical identification jewelry tag (e.g. MedicAlert bracelet.

_____ _____

Signature of trainer Date

_____

Printed Name of Trainer

17.2 Appendix B: Scoring of Clinical Food Related Reactions that Occur During study

Note: Grade 1=mild, Grade 2=moderate, Grade 3=severe reaction

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

Appendix B (cont'd)

Symptoms and/or Signs of an Allergic Reaction (Bock Scoring Challenge)
Grade 1-mild, Grade 2-moderate, Grade 3-severe

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

Appendix B (cont'd)

Symptoms and/or Signs of an Allergic Reaction (Bock Scoring Challenge)
Grade 1-mild, Grade 2-moderate, Grade 3-severe

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

Bock SA, Sampson HA, Atkins FM, Zieger RS, Lehrer S, Sachs M, et al. J. Allergy Clin Immunol 1988;82:986–97.

17.3 Appendix C: GMP and Manufacturing Facility

We follow all phase 2 guidelines for CMC and for drug preparation as per FDA (http://www.fda.gov/ohrms/dockets/98fr/990674gd.pdf). In addition, we have a Manufacturing facility approved by the Stanford IRB that we have used for the phase 1 study for the same flours and powders listed in the IND 14831 (please see separate CMC and Investigational Brochures for each food/powder The facility is located in the same hospital in a double locked area to meet specifications for a GMP facility as per the FDA guidelines. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070273.pdf.)

Stanford Food Allergy Center Manufacturing Facility
2500 Grant Rd, 1st Floor, El Camino Hospital
Mountain View, CA 94043
Tel. 650-724-0293
Email:knadeau@stanford.edu

Monitoring: Our facility will be independently monitored per the Data Safety Monitoring Plan approved by the Stanford IRB for Stanford food allergy clinical trials. The same monitor as University of North Carolina Chapel Hill GMP facility will monitor the Stanford University Manufacturing facility. The monitor will use the same procedures to monitor as used at University of North Carolina.

Shipment of Study Drug to participating Sites: After preparation of doses per the CMC and SOPs, each lot will have a Certificate of Analysis (see below) which will list the release criteria. Batch records will document preparation of all doses for all subjects. The study drug will be put into individual soufflé cups, wrapped with paraffin, labelled and shipped to the designated pharmacy at the site. A chain of custody form will be completed at Stanford and upon receipt at the site pharmacy, the form will be faxed back to Stanford. Shipment will be with a courier that will have tracking systems in place to ensure quality shipment and compliance of study drug.

Certificate of Analysis Example:

Protocol #	IND 14831

Lot Number	(to be filled in for each lot)
Product	(to be filled in for each product)
Date Processed	(to be filled in)

Microbiological	- Test done at Deibel Laboratories, S. San Francisco, CA
E. Coli	Negative or positive
Salmonella	Negative or positive
Total Mold Count	---- cfu/g
Total Yeast Count	---- cfu/g
Acceptable Results for E. Coli and Salmonella	negative
Acceptable Results for TAMC and TYMC	< 140 cfu/g

Analysis of Flour	- testing done at the laboratory of Dr. Kari Nadeau, S303, Grant Building, 300 Pasteur Drive, Stanford, CA. 94305.
Was the completion of Gel and Densitometry run? Date of ~~Gel~~ was run?	Yes or No, Date
% variation from Reference Standard	(to be filled in)
% variation from previous lot #	(to be filled in)
Previous Lot #:	(to be filled in)
Acceptable answer to: Was Gel and Densitometry Results completed ?	Yes
Acceptable Results for % variance	<30%

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Appearance	- testing done at GMP facility at Stanford Food Allergy Center
Color	(to be filled in)
Odor	(to be filled in)
Acceptable Result for Color	(to be filled in)
Acceptable Result for Odor	(to be filled in)

Deviations: (to be filled in if appropriate)

In line with the USP proposed criteria, the recorded mold count in this product is within the acceptable limits. Therefore, the product is being released as acceptable for use in this clinical trial.

Reviewer Batch Record

Signature: _____

Date: _____

Name:_____
Title: _____

17.4 Appendix D: Schedule of Events

	Screening/ Baseline	Omalizumab[3] + OIT				End of study/Early Discontinuation
Week (±5 days)	-36	-8	-4	0	4 through 16	18
Omalizumab Administration		X	X	X		
Oral Immunotherapy				X[4]	X	X[5]
Medical History	X					
Physical Exam	X	X	X	X	X	X
Con Meds	X	X	X	X	X	X
Food IgE/IgG4	X					X
Mechanistic labs[1]	X					X
Skin Testing[8]	X					X
Spirometry-full/peak flow[2]	X				X	X
Epinephrine autoinjector Training	X					X
Adverse Events	X	X	X	X	X	X
Diary					X	X
Urine Pregnancy Test	X	X				

[1] Samples for translational research collected at screening and early discontinuation/end of study visit

[2] Full spirometry is preferred, however if subject is unable, peak flow may be performed instead. For those unable to perform peak flow, they will be examined by physical exam.

[3] Dosing for Omalizumab will be 150 mg via subcutaneous injection monthly for three doses for participants ≥4 years of age, and 75 mg via subcutaneous injection monthly for three doses for participants <4 years of age.

[4] If 5mg total is not tolerated at week 0, subject will be a desensitization failure.

[5] If subject has not tolerated 300mg or 1200 mg total of all allergens by week 16, subject may be updosed at week 18 to 300 mg or 1200 mg total.

[6] Baseline/Screening results may be obtained within no more than 9 month prior to week -8

[7] Repeat urine pregnancy test if visit is ≥7 days of Screening visit.

[8] Skin prick test at screening, if applicable per investigator's discretion.