Full Title: A Phase 2 Study Multi Oral Immunotherapy in Multi Food Allergic Patients to test Tolerance –'MTAX' study

Short Title: Multi Immunotherapy to test Tolerance

Stanford University

Protocol Director: Kari Nadeau, MD, PhD

IND **14831**

Amendment 24

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Protocol: IND 14831	**Version/Date Amendment 24/20APR2016**
Site Principal Investigator:	
Protocol Title: A Phase 2 Study Multi Oral Immunotherapy in Multi Food Allergic Patients to test Tolerance –'MTAX' study	
Study Sponsor: Kari Nadeau, MD, PhD, Sponsor-Investigator, Stanford University.	
INSTRUCTIONS: *The site Principal Investigator should print, sign, and date at the indicated location below. A copy should be kept for your records and the original signature page sent. After signature, please return the original of this form by surface mail to the Lead Site Stanford University.:*	

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the International Conference on Harmonization (ICH) document *Guidance for Industry: E6 Good clinical Practice: Consolidated Guidance* dated April 1996. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.

_____

Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

Protocol Synopsis

Full Title	A Phase 2 Study Multi Oral Immunotherapy in Multi Food Allergic Patients to test Tolerance –'MTAX' study
Short Title	Multi Immunotherapy to test Tolerance
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	70
Study Population	We will enroll multi food allergic subjects (4-55 years of age) with proven multi food allergies. We anticipate enrolling 70 subjects with multi food allergies at more than one site. 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. In addition, subjects must have a total IgE <2,000kU/L, a clinical reaction during a double blind placebo controlled food challenge (DBPCFC) with food protein/powder to establish sensitivity to given food protein/powder (pecan, milk, egg, peanut, almond, wheat, cashew, sesame seed, soy, walnut, hazelnut, shrimp, cod, salmon) and no clinical reaction during placebo (oat) as per CMC section of IND.
Accrual Period	We estimate it will take 15 months to enroll 70 subjects into the study.
Study Design	This is a phase 2 randomized withdrawal, double-blind study which will be conducted at multiple centers in the U.S. All subjects will receive oral immunotherapy for their specific food allergies (limited to 5 of those food allergens in IND 14831). All participants will receive Omalizumab for 16 weeks. The subject's allergens will be introduced in a rush desensitization day at week 8. Subjects will return to clinic to escalate the dose of their allergens until ≥1,000-protein of each allergen is reached. Subjects will return to clinic for a DBPCFC to each allergen at week 30. If subjects are nonreactive to 2 or more allergens at 2,000 mg during their DBPCFC at week 30, they will be randomized to one of three double blinded arms: Group A- 1,000 mg each food allergen protein; Group B-300 mg of each

	food allergen protein; Group C-placebo (300mg oat flour equivalent for each food allergen). All subjects will return to clinic for a DBPCFC to each allergen at week 36. The final challenge of week 36 will be the final end of study visit. 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 active phase of the study for 36 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) for patients with severe asthma >6 years of age, and by the US FDA for patients >12 years of age. Omalizumab will be dosed according to Genentech Dosing Omalizumab will be provided by the site.
Primary Objective	To determine the ability to tolerate an oral food challenge to 2,000mg at least of 2 allergens at week 36 (i.e. the end of the randomized withdrawal/tolerance phase).
Major Secondary Objectives	To determine the ability to tolerate an oral food challenge to 4,000mg of 2 allergens at week 36. To determine the ability to tolerate an oral dose of 2,000mg each of 3 allergens separately (when applicable) at week 36. To determine the ability to tolerate an oral dose of 2,000mg each of 4 allergens separately (when applicable) at week 36. To determine the ability to tolerate an oral dose of 2,000mg each of 5 allergens separately (when applicable) at week 36.
Exploratory Objectives	The long term objective of this study is to develop a potentially curative therapy for patients with multi food allergies. We hypothesize that 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 and that this tolerance can be maintained.
Endpoints	**Primary Endpoint:** The proportion of subjects who tolerate an oral food challenge (i.e. no reaction of grade 1 or more according to Bock's criteria) to 2,000mg at least of 2 allergens at week 36 (i.e. the end of the randomized withdrawal/tolerance phase). **Major Secondary Endpoints:** • The proportion of subjects who tolerate an oral food challenge (i.e. no reaction of grade 1 or more according to Bock's criteria) to 4,000mg each of 2 food allergens at week 36. • The proportion of subjects who tolerate an oral food challenge (i.e. no reaction of grade 1 or more according to Bock's criteria) to 2,000mg each of 3 food allergens (when applicable) at week 36. • The proportion of subjects who tolerate an oral food challenge (i.e. no reaction of grade 1 or more according to Bock's criteria) to 2,000mg each of 4 food allergens (when applicable) at week 36. • The proportion of subjects who tolerate an oral food challenge (i.e. no reaction of grade 1 or more according to Bock's criteria) to 2,000mg each of 5 food allergens (when applicable) at week 36.

1. Key Roles
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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 suffer from having 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 each food allergens used in the OIT regimen, particularly in subjects with severe 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 (FceRI) on the surface of mast cells and basophils. Reduction in surface bound IgE on FceRI-bearing cells

limits the degree of release of mediators of the allergic response. Treatment with Omalizumab also reduces the number of FceRI 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), anti-IgE treatment was found to be effective in preventing and reversing allergic asthma symptoms induced by IgE formation. 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 multi food allergies. The design of this protocol is unique in that: 1) Omalizumab is included to improve OIT tolerability and 2) study subjects are desensitized more rapidly than in other studies (which do not use Omalizumab).

Since the ultimate goal of this study is to develop a therapy that can be used safely in clinical settings, the results of this study and other studies may ultimately lead to FDA approval for the use of Omalizumab in the setting of food allergy desensitization.

'Tolerance' testing is important to be able to test whether a period of avoidance will decrease the level of desensitization. 'Immune Tolerance' will be helpful to examine whether to allow patients to go 'ad lib' after a period of immunotherapy. In addition, there are clinically practical issues of decreasing dose amounts after a period of time on therapy; therefore, we are testing the ability of patients to continue to stay desensitized after decreasing their daily dose to 300 mg.

Overall, this protocol is written 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. Lastly, we will examine biomarkers that could predict a patient's eventual outcome for desensitization vs tolerance vs failure.

Outside of this study, we will ask sites to consider a long term follow up study to ensure the longitudinal follow up of the participants after they finish the study.

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

Study Agents: Omalizumab is approved by the European Commission for patients with severe asthma ≥6 years of age, and by the FDA for patients ≥12 years of age. Therefore the risk of Omalizumab is relatively low.

Food flours and powders 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, pecan, peanut, sesame seed, soy, wheat, shrimp, cod and salmon).

2.1.2 Summary of Relevant Clinical Studies

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).

Preliminary results of some patients in the phase 1 study results of IND 14831 have been published (8).

2.2 Rationale

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. Our phase 1 study results show that multiple oral immunotherapy given in the same method with Omalizumab can be safe and show trends towards efficacy (Begin, et al. AAI, 2014). Therefore, a phase 2 randomized, controlled, blinded study has been proposed to further test safety, efficacy and 'tolerance' in a larger group of subjects.

All DBPCFCs or OFCs should be performed on participants who have ingested food (non allergic) prior to the start of the food challenge and the participants are allowed to eat food (non allergic) during the food challenge. Also, between each dose of a food allergen during the food challenge, the participant should be encouraged to drink at least 4 oz of water and suck on ice if appropriate and safe.

Procedure

Screening DBPCFC: In the proposed study with multiple food allergies, we will pretreat these allergic patients with anti-IgE monoclonal antibody (Omalizumab). We anticipate enrolling 70 subjects (4-55 yrs. old) with multiple food allergies. Patients must also undergo a double-blind, placebo- controlled challenge (DBPCFC) with each food item to establish allergy to these foods; placebo challenge and allergenic food challenges will be carried out in all patients, the order of which will be randomized. The challenge will consist of at least 3 separate days during which patients are given placebo, or food flours orally (order randomized). A minimum of two and a maximum of five positive food challenges will be documented per participant. The food flours used in each of the DBPCFCs will depend on the subject's history of clinical reactivity, skin testing, and specific IgE testing for that food allergen. For Cashew allergic individuals, we would suggest also performing skin testing for pistachio and a DBPCFC for pistachio; for Walnut allergic individuals, we would suggest also performing skin testing for pecan and a DBPCFC for pecan (these additional challenges will not be included in the maximum of five positive food challenges to be documented for each participant). For this DBPCFC, patients will first perform spirometry and have pulse oximetry monitoring and vital signs checked, every 15 minutes before being given increasing doses of placebo or allergenic food protein until an objective reaction occurs. The doses are as follows:

Table 1: 500mg Cumulative DBPCFC

Dose Administered (mg protein)	Time Until Next Dose (minutes)
5	15
20	15
50	15

100	15
100	15
100	15
125	

- The dosing interval is the minimum number of minutes before the next dose may be given. This time may be extended up to 60 minutes if the study staff determines that a reaction may have started in order to continue to monitor the patient for objective signs/symptoms.
- Objective reaction according to Bock grading scale (see appendix C) during the DBPCFC is required for admission of that allergen into the study.
- Lack of a reaction does not prove the absence of an allergy. All negative DBPCFCs will be referred to the outpatient allergy clinic for further evaluation and food challenges.

1. Omalizumab Pretreatment (weeks 1-8)
After enrollment, all subjects will be pretreated with Omalizumab for 8 weeks to allow food-specific IgE on mast cells and basophils to equilibrate with anti-IgE mAb. Subjects will perform spirometry before each injection and will be observed for at least 60 minutes after the first injection and at least 30 minutes for all subsequent injections.

2. Rush Desensitization (week 8)
On the 8th week of receiving Omalizumab, subjects will undergo an oral rush 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 per the DBPCFC unblinding form for a total protein dose per Table 2 below. Example food vehicles that may be used are applesauce, chocolate pudding or vanilla pudding.

Table 2: Food Allergen Dosage Escalation Schedule on the Rush Desensitization Day (i.e., 1st Day of Desensitization at week 8)

Dose (total mg of all allergens)	Time Until Next Dose (minutes)
5	30
50	30
150	30
300	30
625*	30
1250	

- Vital signs (heart rate, respiratory rate, blood pressure and pulse oximetry) will be monitored every 15 minutes.
- After the final dose, subjects will be observed for a minimum of 2 hours or longer at discretion of the Principal Investigator or their designee.
- If objective symptoms (grade 1 or more of Bock's criteria) develop, the dosing will be stopped unless the symptoms involve only mild itching of the mouth or throat and the supervising investigator determines that advancing the dose is safe. All symptoms and signs will be evaluated and rated based on a standardized oral food challenge scoring

system (please see Appendix and IND 103080). 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)

- All subjects are provided with a 24-hour emergency contact information and contact information for the research team.
- Clinicians will dispense to the subject the 2 week home doses which will be the highest tolerated dose (i.e. that dose with no reaction associated with it) during rush desensitization day.
- If subject does not tolerate 5mg total protein, subject will be a treatment failure.
- Subjects will be instructed on home dosing instructions which will include a phone number for any questions.

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 Omalizumab, we expect participants to achieve a total dose of at least 625 mg or more of total food allergen protein (Nadeau et al. JACI 2011).*

3. Updosing Period: Every other week, the subjects will return for the first of an increase in the daily oral dose to a total maximum dose of up to 2,000mg of each allergen protein (up to 1:1:1:1:1 offending food allergen mixture). The dose will be mixed by the Stanford GMP facility as a total dose as follows (note that the dose chosen to begin with 5 or 50 or 150 or 300 or 625 mg of protein will depend on the last dose the subject was able to safely tolerate on the rush desensitization day):

Total Dose (mg)-split evenly between 2, 3, 4, or 5 food allergens	Increase of (mg)
*	
*	
150	100
300	150
625	325
1,250	625
3,000	1,750
5,000	2,000
7,000	2,000
8,000	1,000
9,000	1,000
10,000	1,000

Subjects who have moderate to severe reactions on the increased dose in the research center will continue with the previous dose at home (no increase in the dose will occur for that week). In addition, the clinician may use clinical judgment to decide that the subject should not increase their

dose and the subject will remain on the current dose for an additional 2 weeks (± 5 days).

Even after tolerating the maintenance dose of 2,000mg of each allergen, it is possible that allergic cell (i.e. mast cell, basophil, eosinophil) activity will increase as the level of Omalizumab decreases. Therefore, subjects will be observed closely for the development of symptoms, including hives, worsening of eczema or wheezing during this time period, and will be instructed to keep a diary of food allergy symptoms. However, we expect that patients will remain tolerant to this dose of cumulative offending food allergen(s) even when Omalizumab is discontinued, which is what we observed in our milk desensitization study (5) and phase 1 study results of this IND (8). (Section 16.0).

4. Discontinuation of Omalizumab

After 16 weeks of Omalizumab subjects will continue updosing, however no more Omalizumab will be administered. If a subject has not tolerated 300mg total of each allergen by the end of visit at week 16, the subject will be considered a treatment failure. This will be calculated per the total dose and number of allergens. Please refer to section 8.3 for more information on treatment failures.

5. DBPCFC of OFC (oral food challenge) for each food allergen during active phase of study

Subjects who continue to tolerate oral daily OIT doses following the discontinuation of Omalizumab treatment will undergo separate DBPCFCs for each offending food allergen used in the OIT protocol at week 30 and at week 36 if they enter randomized withdrawal phase of the study. Each allergen will be ingested on separate days or, if no reaction occurs, with a minimum of 2 hours between challenges. Challenges may be blinded where subjects are given placebo and allergens in a random order and then unblinded 2 hours after final dose of final challenge or as per PI discretion. Open OFC could be done without placebo to each allergen on separate days or, if no reaction occurs, with a minimum of 2 hours between challenges. Subjects will be given up to 6 doses at a minimum of 15-minutes apart as stated below:

Dose (mg)—one allergen or placebo	Minimum Time Until Next Dose (minutes)
750	15
1,250	15
2,000	15
2,000	15
2,000	15
4,000	

Note:

- **Bold** indicates primary endpoint achieved if participant ingests a cumulative dose of 2 g of each of two food allergens at week 36 (750 mg + 1250 mg = 2,000 mg).
- *Italics* indicates secondary endpoint achieved if participant ingests a cumulative dose of 4 g of each of two food allergens at week 36 (750 mg + 1250 mg + 2000 mg = 4000 mg).

We encourage staff to continue dosing so as to determine the cumulative dose safely tolerated for each participant. (i.e. up to 12 g is possible for each food allergen).

- Vital signs (heart rate, respiratory rate, blood pressure and pulse oximetry) will be monitored every 15 minutes.
- After the final dose, subjects will be observed for 2 hours or longer at discretion of the Principal Investigator or their designee.
- Subjects will skip daily home dosing on DBPCFC/OFC days.
- DBPCFCs/OFCs must be performed with a minimum of 2 hours between each challenge if there have been no reactions, otherwise, the challenges should be 24 hours apart.
- If objective symptoms (grade 1 or more of Bock's criteria) develop, the protocol will be stopped. All symptoms and signs will be evaluated and rated based on a standardized oral food challenge scoring system (please see Appendix and IND 103080). 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).
- All subjects are provided with 24-hour emergency contact information and contact information for the research team.

Note: For cashew allergic individuals, we would suggest also performing skin testing for pistachio and a DBPCFC for pistachio (the open OFC will not be supplied by Stanford GMP facility to sites). For walnut allergic individuals, we would suggest also performing skin testing for pecan and a DBPCFC for pecan.

6. End of Omalizumab+OIT Phase of Study

Although subjects will undergo DBPCFC up to 4000mg at week 30, the ability to tolerate 2000 mg of at least 2 of their allergens will qualify them for randomization into the randomized withdrawal / tolerance phase of the study.

7. Randomized Withdrawal / Tolerance Phase of study

Subjects will be randomized in 1:1:1 ratio to one of the three groups of daily dosing:
Group A- 1,000 mg each food allergen protein,
Group B-300 mg of each food allergen protein,
Group C-placebo (300mg oat flour equivalent for each food allergen).

8. End of Randomized Withdrawal / Tolerance Phase and end of Active Phase of Study

Subjects reach the end of the active phase of study at their final week 36 food challenge.

9. Follow-Up Phase/End of Study/Early Termination

All subjects will complete an end of study or early termination visit at week 36 or earlier if deemed necessary by the PI.

Discharge criteria for any subjects upon completion of procedures:

Subjects will only be discharged from the research center if all allergic symptoms have resolved or significantly improved for at least 30 consecutive minutes.

Criteria that would require further observation and/or hospital admission.
1. Any allergic symptom that is 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.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Omalizumab is approved by the European Commission for patients with severe asthma ≥6 years of age, and by the FDA for patients ≥12 years of age. Therefore the risk of Omalizumab is relatively low (please refer to investigator's brochure in Appendix and cross-reference of IND 103080).

The screening visit includes skin prick testing, blood draws, and double-blind, placebo-control food challenges (DBPCFCs). Skin prick tests carry three risks: 1) anaphylaxis, which is extremely rare; 2) large local reaction that is itchy and/or painful; and 3) in theory, precipitation of an asthma attack. Blood draws carry the risk of transient bleeding and/or bruising at the site of the blood draw. A DBPCFC carries the risk of anaphylaxis. All screening tests will occur in the research center with trained staff under the management of the site investigator. All reaction medications for the possibility of anaphylaxis are located in the research center. Subjects will be given all information for the conduct and risks of these procedures.

The overall risks of participation range from mild to moderate to severe due to the OFC (oral food challenge) and OIT (oral immunotherapy). These could be as mild as transient pruritis 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.

2.3.2 Potential Benefits

The only direct and major benefit to the subjects is for those subjects are able to tolerate the OIT and decrease their reactions to the offending food allergens. There is a theoretical benefit of multiple allergen therapy to enable the immune system to develop long-term tolerance and of multiple allergen therapy to provide a bystander response to other food allergens that are related. 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 the ability to tolerate an oral food challenge to 2,000mg at least of 2 allergens at week 36 (i.e. the end of the randomized withdrawal/tolerance phase).

3.2 Main Secondary Objectives

- To determine the ability to tolerate an oral food challenge to 4,000mg each of 2 allergens at week 36.

- To determine the ability to tolerate an oral dose of 2,000mg each of 3 allergens separately (when applicable) at week 36.

- To determine the ability to tolerate an oral dose of 2,000mg each of 4 allergens separately (when applicable) at week 36.

- To determine the ability to tolerate an oral dose of 2,000mg each of 5 allergens separately (when applicable) at week 36.

Other Objectives

- To determine safety outcomes for all subjects
- To evaluate cross reactivity of specific nuts

4.0 Study Design

This is a phase 2 randomized withdrawal multi-center study of tolerance of OIT using Omalizumab in subjects ages 4 to 55 years with severe food allergy. Omalizumab will be administered for 16 weeks total. At week 8, OIT will be introduced. Subjects will updose every 2 weeks to reach $\geq$1,000 mg protein of each allergen. At the discretion of the Principal Investigator, updosing may occur by completing additional visits at 1 week intervals, if necessary, to allow a participant the opportunity to achieve the minimum dose required to qualify for the DBPCFC for each allergen at Week 30. The procedures outlined in the Schedule of Events must occur at the specified time points.

A DBPCFC will be performed at week 30. Subjects who are nonreactive to 2 or more of their DBPCFCs at 2,000 mg at week 30 will be randomized to one of 3 arms: Group A-1,000mg each

allergen), Group B- reduce OIT dosing (300 mg each allergen), Group C-placebo (300mg oat flour equivalent for each food allergen). OIT will be given for another 6 weeks. Final open OFC will occur at week 36. The final challenge at week 36 will be the end of study. Clinical and laboratory based assessments will be performed at certain visits throughout the study as per the investigator's discretion.

Subjects will be screened for reactivity (onset of clinical symptoms) to food by undergoing a DBPCFC with food protein. To maximize safety and prevent severe reactions, the highest tolerated dose (i.e. with no allergic reaction) for the DBPCFC will be the threshold dose for stopping the DBPCFC. Subjects will be enrolled only if a clinical reaction occurs during a DBPCFC to small doses of food defined as $\leq$125 mg dose of food protein or a cumulative dose of 500mg food protein and no clinical reaction is observed during the placebo (oat) challenge as per CMC section of IND. In addition to be eligible for the study, subjects must have food-specific IgE >4kU/L for each allergen or a skin test reactivity (reagents from Greer) to each food allergen greater than or equal to 6mm wheal diameter and a total serum IgE <2,000kU/L.

A group of subjects at Stanford University were enrolled before the addition of the 'tolerance' testing endpoint and did not undergo 'tolerance' testing; therefore, they will be considered a separate group in the statistical analysis.

4.2 Study Endpoints

4.2.1 Primary Endpoint

Primary Endpoint: The proportion of subjects who tolerate an oral food challenge (i.e. no reaction of grade 1 or more according to Bock's criteria) to 2,000 mg at least of 2 allergens at week 36 (i.e. the end of the randomized withdrawal/tolerance phase).

4.2.2 Main Secondary Endpoints

- The proportion of subjects who tolerate an oral food challenge (i.e. no reaction of grade 1 or more according to Bock's criteria) to 4,000mg each of 2 food allergens at week 36.
- The proportion of subjects who tolerate an oral food challenge (i.e. no reaction of grade 1 or more according to Bock's criteria) to 2,000mg each of 3 food allergens (when applicable) at week 36.
- The proportion of subjects who tolerate an oral food challenge (i.e. no reaction of grade 1 or more according to Bock's criteria) to 2,000mg each of 4 food allergens (when applicable) at week 36.
- The proportion of subjects who tolerate an oral food challenge (i.e. no reaction of grade 1 or more according to Bock's criteria) to 2,000mg each of 5 food allergens (when applicable) at week 36.

5.0 Study Population

5.1 Description of Study Population

We will enroll multi food allergic subjects (4-55 years of age) with proven multi food allergies. We anticipate enrolling 70 subjects with multi food allergies at more than one site. 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. In addition, subjects must have a total IgE <2000/L, a clinical reaction during a double blind placebo controlled food challenge (DBPCFC) with food protein/powder to establish reactivity to a given food protein/powder (milk, egg, peanut, almond, wheat, cashew, sesame seed, soy, walnut, pecan, hazelnut, shrimp, cod and salmon) and no clinical reaction during placebo (oat) as per CMC section of IND.

5.1.1 Subject Inclusion Criteria

- Aged 4 to 55 years with moderate to severe allergy to at least two of the following: milk and/or egg and/or peanut and/or almond and/or wheat and/or cashew and/or sesame seed and/or soy and/or pecan and/or walnut and/or hazelnut and/or shrimp and/or cod and/or salmon and
- Sensitivity to food allergens documented by a positive skin prick test result greater than or equal to 6mm wheal diameter to each allergen or
- ImmunoCAP IgE level >4kU/L for each allergen and
- A clinical reaction during a DBPCFC to small doses of food defined as ≤125 mg dose of food protein or a cumulative dose of 500mg food protein (see **Appendix C** for details) and
- No clinical reaction observed during the placebo (oat) challenge and
- If female, willing to provide a human chorionic gonadotropin urine sample for pregnancy testing and
- If female of child bearing potential, a negative urine pregnancy test 60 hours before being allowed to participate in the study (week 0) and
- A plan to remain in the study area of the research center during the trial and
- Be trained on the proper use of the Epinephrine autoinjector and agree to follow epi training (see **Appendix B)** to be allowed to enroll in the study and
- If female of child-bearing potential, willing to be compliant with a medically-approved method of contraception (please see **Pregnancy section** under Patient Disposition in this IND document) and
- Agree to eliminate other known food allergens from subject's diet so as not to confound the safety and efficacy data from the study and
- Avoid open or blinded food challenges to other allergens outside of this study

5.1.2 Subject Exclusion Criteria

- A total serum IgE at screening of >2000 kU/L
- A total serum IgE and weight combination that is not in the Omalizumab dosing parameters per the U.S. product insert dosing schedule.
- Previous anaphylactic reaction to Omalizumab
- 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
- 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)
- 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, an oral desensitization visit, or a food challenge visit

- Current users of oral, intramuscular, or intravenous corticosteroids, tricyclic antidepressants, or are taking a beta-blocker (oral or topical)
- Routinely using medication that could induce adverse gastrointestinal reactions during the study
- Refusing to sign or follow the Epinephrine autoinjector Training Form (see **Appendix B**)
- Pregnant or breast feeding women
- A history of oat allergy (since oat is the placebo agent in the DBPCFC, as per IND 14477)
- An objective reaction to the screening DBPCFC to oat
- Unwilling to avoid other allergens outside this study
- Concurrent/prior use of immunomodulatory therapy (within 6 months)
- A diagnosis of eosinophilic esophagitis, eosinophilic colitis, or eosinophilic gastritis.

5.2 Strategies for Recruitment and Retention

Patients will be recruited from current Allergy Clinics at Stanford and/or specific research sites that are participating in this trial. Additional recruitment will be done by posting on clinical trials.gov, and local media (if necessary).

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.

Dosing Interval	Screening IgE (IU/mL)	Body weight (kg)/ Study drug dose (mg)								
Every 4 weeks		**15-20 kg**	**21-25 kg**	**26-30 kg**	**31-40 kg**	**41-50 kg**	**51-60 kg**	**61-70 kg**	**71-80 kg**	**81-90 kg**
	30-100	75 mg	75mg	75mg	75mg	150mg	150mg	150mg	150mg	150mg
	101-200	150 mg	150 mg	150 mg	150 mg	300 mg	300 mg	300 mg	300 mg	300 mg
	201-300	150 mg	150 mg	150 mg	225 mg	300 mg	300 mg			
	301-400	225 mg	225 mg	225 mg	300 mg					
	401-500	225 mg	225 mg	300 mg						
	501-600	300 mg	300 mg	300 mg						
	601-700	300 mg	300 mg							

Dosing Interval	Screening IgE (IU/mL)	Body weight (kg)/ Study drug dose								
Every 2 weeks		**15-20 kg**	**21-25 kg**	**26-30 kg**	**31-40 kg**	**41-50 kg**	**51-60 kg**	**61-70 kg**	**71-80 kg**	**81-90 kg**
	201-300							225mg	225mg	225mg
	301-400					225mg	225	225	300	300
	401-500				225mg	225	300	300	375	375
	501-600				225mg	300	300	375	450	525

	601-700			225mg	225	300	375	450	525	600
	701-800	225mg	225mg	225	300	375	450	450	600	*
	801-900	225mg	225	225	300	375	450	525	*	*
	901-1000	225mg	225	300	375	450	525	600	*	*
	1001-1100	225mg	225	300	375	450	600	*	*	*
	1101-1200	300mg	300	300	450	525	600	*	*	*
	1201-3000	300mg	300	375	450	525	*	*	*	*
	1301-1500	300mg	300	375	525	600	*	*	*	*
	1501-2000	375mg	450	600	600	600	*	*	*	*

Asterisk * denotes parameters in which no subject will be dosed with drug.

6.1.1.2 Preparation, Administration, Storage, and Dosage Study Agent(s)/Intervention(s)
Omalizumab will be prepared according to the investigator brochure and the MOP. The study drug should be stored in a refrigerator in a pharmacy and dispensed by a pharmacist who is on the Delegation of Authority log.

6.1.1.3 Study Agent (Omalizumab) Accountability Procedure
Omalizumab will be ordered and received by the pharmacist. Documentation of omalizumab 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.

6.1.2 Food Protein
6.1.2.1 Formulation, Packaging and Labeling
A CMC (Chemistry, Manufacturing and Controls) section is available for each food allergen (see Appendix).

6.1.2.2 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, and 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 appropriate age-appropriate food vehicle. Each food flour/powder 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.

6.1.2.3 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

Once eligible for the study, subjects will be allowed to use intranasal medications for rhinitis, including glucocorticoids, antihistamines, and leukotriene inhibitors, per their primary allergist. Daily concomitant medication use will be documented in the subject's chart. Subjects can 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 SPTs)
- Orally and nasally 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

6.3 Precautionary and Prohibited Medications and Procedures

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 the food challenges, subjects will be asked to restrict the use of beta-agonists (12 hours), theophylline (12 hours), and cromolyn (12 hours).

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

6.4 Rescue Medications

Rescue medications for any clinically significant reaction will include Epinephrine 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.

6.5 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 all clinical staff should be in close proximity 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 OIT is being performed.

7.0 Study Procedures/Evaluations

7.1 Clinical Evalutions

Subjects will keep e-diaries during the study to document daily dosing and any symptoms. Blood sampling will be performed at scheduled intervals. If the subject experiences signs of a systemic allergic reaction during the study, an additional sample may be drawn for comparison. Serum and cells will be banked and stored at Stanford for future translational research if subjects agree per the informed consent. Please refer to the **Study Schedule of Events**, for full details.

Missed OIT Doses

- If the subject misses one to three days of the daily dose for any reason then he or she will continue on the same dose at home or in to the research center.
- If the subject misses four to six days of the daily dose for any reason then based on clinician discretion he or she will return to the research center for the next daily dose, a 1-2 step dose reduction or discontinue OIT updosing (and be deemed a desensitization failure based on PI discretion).
- If the subject misses 7 or more days of the daily dose for any reason, subject will be terminated from the study.

7.2 Laboratory Evaluations

7.2.1 Clinical and Research Laboratory Evaluations and Specimen Collection

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

standard techniques. Serum 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 (refer to Schedule of Events).

7.2.2 Specimen Preparation, Handling and Shipping

Quality Assurance: All samples will be de-identified, 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.

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

See Schedule of Events

8.1 Screening

Subjects will need copies of/ or original source documents of the following procedures or labs prior to week 0 (first Omalizumab injection):

Within no more than 36 weeks prior to week 0:
Physical Exam (including vital signs, height and weight)
Spirometry
Listing of concomitant medications
Review of Epinephrine autoinjector or other self-injectable epinephrine device use
Urine pregnancy test if applicable (must be repeated 24 hours prior to week 0)
Skin prick testing

Total IgE
Specific IgE if necessary

Within no more than 12 months prior to week 0:
DBPCFC for each allergen (up to 5) and placebo

A verbal description of the study will be provided to parents/guardians and subjects with an opportunity for them to ask questions prior to enrollment. Written informed consent will be obtained prior to any study related procedures by the principal investigator, a sub-investigator or their designee. An investigator or designee will be a clinical practitioner (MD, NP, PA) who is listed on the 1572 and directly involved with the care of the patient for this study.

8.2 Baseline/screening

Study subjects will have a baseline/screening visit that can occur up to 9 months prior to week 0 to include a physical exam, height and weight, a review of past medical history and concomitant medications, spirometry, skin prick testing, and total IgE.

If the subject meets initial eligibility based on skin testing, allergen-specific IgE, spirometry, total IgE, they will undergo a DBPCFC to determine eligibility (unless it was performed within the previous 12 months prior to week 0).

Subjects will be eligible after the DBPCFCs if there is no reaction to the placebo (oat) and there is an objective reaction at less than a cumulative total of 500mg of food protein of a minimum of two allergens to a maximum of five allergens.

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 visit 0.

Week 0
Physical Exam, review of medications, weight (+ or - 2 weeks), spirometry and vital signs will be documented. At least one baseline blood sample will be collected prior to, or at Week 0 (refer to Schedule of Events).

Eligible subjects will be enrolled and receive Omalizumab.

8.3 Active Study Phase and Follow-Up

Omalizumab After eligibility is determined, the study participant will receive Omalizumab from week 0 to week 16.

Omalizumab and rush desensitization (week 8)

At week 8 visit, subject will receive Omalizumab injection as well as a rapid oral desensitization. If

5mg total is not tolerated at this visit, subject will be a treatment failure. We expect subjects should be able to tolerate at least 625 mg total of food allergen proteins (Nadeau, et al. JACI 2011).

Omalizumab and updosing (weeks 10-30)

At each biweekly visit on weeks 10-16 increasing doses of food allergens will be given as well as Omalizumab/ (dependent on weight and total IgE). During each of these visits subjects will be seen in person by the study staff to assess for adverse events, changes in medications, and study participation. The time between visits should be 2 weeks +/- 5 days.

At the discretion of the Principal Investigator however, updosing may occur by completing additional visits at 1 week intervals, if necessary, to allow a participant the opportunity to achieve the minimum dose required to qualify for the DBPCFC for each allergen at Week 30. The procedures outlined in the Schedule of Events must occur at the specified time points.

The subjects will be encouraged to call any other time they have questions or to report adverse events or potential changes in medications. If subject has not tolerated 300mg total of all allergens by end of the week 16 visit, subject will be considered a treatment failure.

Discontinuation of study drug (Omalizumab) and continuation of updosing

Subjects will continue to updose every two weeks (+/- 5 days) to reach a dose of ≥ 1,000mg , of each allergen, however subjects will not receive any Omalizumab after week 16. At the discretion of the PI, the subject may updose at 1 week intervals as described above.

2 weeks after discontinuing Omalizumab (week 18)

Subjects will be required to come in for a visit 2 weeks after discontinuation of study drug (week 18) for review of diaries, concomitant medication, interval medical history, any adverse events experienced and collection of lab samples.

8 weeks after discontinuing Omalizumab (week 24)

Subjects will be required to come in for a visit 8 weeks after discontinuation of study drug (week 24) for review of diaries, concomitant medication, interval medical history, any adverse events experienced and collection of lab samples.

Maximum OIT Dose

Once subject updoses to ≥1,000mg of each allergen, subject will maintain ≥1,000mg of each allergen until week 30). The maximum OIT dose will not go above 2,000 mg for each allergen. Subjects will be followed closely for the development of symptoms, including hives, worsening

of eczema or wheezing during this time period and will be instructed to keep a home diary of food allergy symptoms. We expect that subjects will remain tolerant to this dose of food even when Omalizumab is discontinued based on what we observed in our milk desensitization protocol, multi OIT Omalizumab phase I study (IND 14831).

14 weeks after discontinuing Omalzumab (week 30)

Subjects will be required to come in for a visit 14 weeks after discontinuation of Xolair (week 30). If subject updosed to ≥1,000 mg of each allergen (total protein dose per the dosing table) by Week 30, subject will undergo a DBPCFC to each allergen. Although DBPCFC during active phase of the study will go up to 4000mg as previously described, if a subject is nonreactive (no objective allergic symptom) to 2 or more allergens during the week 30 DBPCFCs at 2,000mg, the subject will be randomized on the final DBPCFC day to one of 3 arms: Group A- 1,000 mg each allergen), Group B, 300mg each allergen, Group C, placebo (300mg oat flour protein equivalent for each food allergen). The visit will also include review of concomitant medication, interval medical history, any adverse events experienced, collection of lab samples and skin testing.

If subject has not updosed to ≥1000 mg each allergen by 1 week prior to week 30 (i.e. week 29), subject will be considered a desensitization failure (See section 8.3). Subjects will continue their daily dose between the DBPCFC visits and hold the dose on the DBPCFC clinic visit.

DBPCFCs during active phase of study

Week 30 DBPCFCs can be conducted as OFCs at PI discretion.

Randomized Withdrawal / Tolerance Phase

There will be a 6 week tolerance phase. At week 36, subjects will undergo final open OFC. The final open OFC will be the end of study. The study endpoints are between 2,000-4,000 mg for two or more allergens. Challenges may go up to 12,000 mg for each food allergen. Determine the dose that can be safely tolerated by each participant.

General Information

For the duration of the study, all subjects will be asked to continue to follow a food elimination diet of their food allergens and will be continually monitored for compliance by questioning and review of the diaries at every study visit.

If subjects are having difficulty updosing, at the discretion of the PI, subjects may updose by a minimum of 12.5% every one to two weeks up to a dose of ≥1,000 mg *of each allergen as tolerated by the subject. Subjects will not continue to updose past week 29. Week 36 is the end of the study.*

Treatment Failure

Subjects may be deemed treatment failures at any time during weeks 0 and 30 if deemed necessary by the overall PD and site PI (Nadeau).

Treatment Failures include:

Subjects who do not reach at least 5mg on week 8 (Rush desensitization).

Subjects who do not reach 300 mg of food allergens (total protein as calculated by the dosing table) by week 16.

Desensitization Failure

Subject will be a desensitization failure if subject has not updosed to ≥ 1,000mg of each allergen by week 29 or if subject has been deemed a desensitization failure by PD/PI or their designee at week 30 DBPCFC due to an objective reaction (grade 1 or more Bock's criteria). Desensitization failures will continue to be followed in the study at visits and will have an end of study visit at week 36 to include review of diaries, concomitant medication, interval medical history, any adverse events experienced, collection of lab samples and skin testing.

Treatment failures and desensitization failures will be followed until the end of the study at the specified study visits and complete procedures including skin prick testing and collection of lab samples according to the Schedule of Events but will not undergo further DBPCFCs. Subjects will remain at the highest dose of allergens achieved by week 30 (for desensitization failures) until they complete week 36 or the highest dose achieved by the end of week 16 (for treatment failures) until they complete week 36. They will be considered in statistical analyses of the intent-to-treat population.

Tolerance Failure:
Tolerance Failure is defined when a participant has a clinical reaction (1 or more on Bock's criteria) when undergoing the oral food challenge at week 36 for at least 2 food allergens.

Reaching ≥ 1,000mg earlier than week 29

Even after reaching ≥1000mg each allergen, follow-up visits will be done every two weeks +/- 5 days until the DBPCFCs at week 30. At the discretion of the Principal Investigator however, updosing may occur by completing additional visits at 1 week intervals, if necessary, to allow a participant the opportunity to achieve the minimum dose required to qualify for the DBPCFC for each allergen at Week 30. The procedures outlined in the Schedule of Events must occur at the specified time points.

Allergic events and adverse events (that are not allergic in nature) will be monitored at each visit. Also immunological parameters will be measured at each visit. Repeat skin testing will be done approximately every 6 weeks during the study and at the end of study visit.

Unblinding

Unblinding of the food allergen therapy during randomized withdrawal / tolerance phase or during DBPCFC will take place in the event of a complication or if the PI and/or DSMB determine(s) that unblinding is necessary. Unblinding will only take place with permission from the Stanford Protocol Director. If verbal instruction is given in an emergency, it must be provided in writing as soon as possible. Otherwise, unblinding for each participant will occur after the participant completes the final week 36 oral food challenge and all data has been entered for the participant through week 30 and up to the week 36 challenges. The study pharmacist(s) at each site will document the participant's treatment assignment on the MTAX study Unblinding Form and provide a copy to the Site Investigator and Stanford site pharmacist. Copies of the completed Unblinding Form will be maintained in the pharmacy binder and the subject's study binder.

8.4 After last study visit

Subjects will be contacted by phone 30 days after the last visit for follow-up or until the adverse events have resolved. Study staff will assess medications and changes in symptoms during the follow-up contact with the subject.

8.5 Early Termination Visit

If the subject withdraws voluntarily from the study, he/she will be offered a visit to assess disease status, skin testing, specific IgE and immunological markers. Subjects may withdraw voluntarily from participation at any time. Withdrawal from this study will not affect their clinical care at the institution. Subjects may withdraw voluntarily from receiving study intervention for any reason.

If voluntary withdrawal due to adverse events occurs, the study subject should complete the end-of-study evaluation until adverse events resolve. Follow-up will be maintained by telephone or in person examination as necessary.

8.6 Pregnancy Visit

All females of child-bearing potential will undergo a urine Human Chorionic Gonadotropin (HCG) test within 24 hours prior to initial administration of Omalizumab (week 0). In addition, we will administer a repeat urine HCG any time that a patient has missed Omalizumab, OIT, or both, enough doses to require administration of the next dose at the research center. 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 OIT 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 with laboratory studies every 6 months until study completion.

8.7 Unscheduled Visits

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 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 (**AppendixC**) will be recorded on the paper AE CRFs.
  - Food allergy episodes in response to home dosing that are Grade 3 by Modified Bock's Criteria (**Appendix C**) 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

  Double-Blind Placebo Controlled Food Challenges
  - During screening DBPCFCs, reactions will not be recorded as AEs and will be documented as dosing reactions. SAEs will be reported as per standard reporting guidelines.

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)).

Unexpected Adverse Event
An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or package insert or is not listed at the specificity, severity or rate of occurrence that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the IND or protocol.
The Principal Investigator will review all adverse events related to skin prick testing, spirometry, DBPCFC, or other study procedures to determine if they are unexpected.

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.

Grading and Attribution of Adverse Events

Grading Criteria
The study physician will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v4.0. 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 paper AE case report form for this study.

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

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.

Collection and Recording of Adverse Events

Collection Period

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

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.

Recording Adverse Events
Throughout the study, the investigator will record adverse events and serious adverse events as described previously on the appropriate AE/SAE paper CRF regardless of the relationship to study therapy regimen or study procedure.
Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until 30 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

Reporting of Serious Adverse Events and Adverse Events

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

Please note that use of injectable epinephrine can be for either life threatening (i.e. SAE) or non-life threatening (i.e. AE) reactions.

Life threatening reactions in which injectable epinephrine and other appropriate medications are used will be defined as those events that led to severe hypoxemia or severe hypotension (as per CTCAE v4.03 guidelines). Non-life threatening reactions in which injectable epinephrine is used could include, for example, wheezing, shortness of breath, and vomiting. The use of injectable epinephrine occurs immediately to prevent any possibility of severe or serious adverse event. We conduct our clinical studies using the same validated and standard procedures as per the NIH and previous clinical studies, with the same definitions of AE reporting for epinephrine use (1,3,8).

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).

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

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

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 *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. All of these must also be reported to the sponsor within 24 hours so that s/he can report to the FDA within the same 15 or 7 day timeframe. The site principal investigator must report SAEs to their respective IRBs as mandated by them. The site principal investigator must report SAEs to their respective IRBs as mandated by them.

  To report a SUSAR, a finalized, initial SAE case report form and a MedWatch

3500A form will be generated by the site Principal Investigator. Forms are available from the sponsor/PD.

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. Rael and Dr. Nadeau.

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.

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
Comprehensive assessments of any apparent toxicity experienced by the subject will be performed throughout the course of the study. 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).

9.2 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.

9.3 Modification of Study Agent(s)/Intervention(s) for a Subject
9.4 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 occurs before continuing updosing visits.
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.
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/MedWatch/ HowTo Report/ucm053087.htm), the principal investigator will report to the FDA and DSMB and ask the subject to discontinue OIT.
4. 5. 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.
6. 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).
7. 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 the site decrease the dose by 25%, encourage participant to start an antacid or protein pump inhibitor, take 5-10 mg of cetirizine one hr 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 updosing.
8. 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. If additional daily doses are needed, the patient will be terminated from the study.
9. All precautions as suggested by Varshey, P. et al. (2009)(1) and by Hofmann, et al. (2009)(2) will be implemented.
10. Daily doses of 5-10 mg of cetirizine (as per product label) are strongly encouraged throughout the study unless otherwise specified.
11. If there are other concomitant allergic medical issues (i.e. allergic rhinitis, allergic conjunctivitis, eczema) that the PI is concerned about, the subject could be asked to decrease their dose.

9.5 Halting Rules for the Protocol
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 or oral food challenge
- 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

9.6 Reasons for Termination for an Individual Subject/Cohort

A subject may be 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 at least 5mg total dose at rush desensitization (week 8).
- The subject misses 7 or more days of OIT dosing.

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 or an abnormal laboratory value, the specific event or test result must also be recorded on the subject's AE CRF page.

Follow Up for Terminated Subjects

If the subject is terminated from the study, tests and evaluations required at the early termination (ET) visit should occur 14 days. Laboratory assessments at this ET visit will include immunological parameters, translational studies and skin testing.

9.7 Premature Withdrawal of a Subject

A subject can voluntarily withdraw from the study at any point in the study. If the subject withdraws from the study, tests and evaluations required at the early termination (ET) visit should occur 14

days after the last dose of the study drug. Laboratory assessments at this ET visit will include immunological parameters, translational studies, and skin testing.

9.8 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.

10.0 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 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 Data and Safety Monitoring Board (DSMB).

11.0 Statistical Considerations

The design of this study is a multi-site, double-blind randomized withdrawal trial assessing desensitization and tolerance following treatment with Omalizumab+food OIT. Ability to tolerate offending food for subjects with proven food allergy will be measured by standard double blind placebo controlled food challenges (DBPCFC) and monitoring of adverse events.

11.1 Study Population

The study population of interest is individuals 4-55 years of age with proven multiple food allergies as evidenced by a clinical reaction to DBPCFCs at less than 125 mg and a cumulative total of 500mg of food protein.

Each site will plan to enroll approximately 5-10 subjects in the study. We expect a 15% drop out rate; therefore, we will enroll 70 subjects to have at least 60 subjects (approx. 16 per group) reach the end of the study evaluation at week 36.

11.2 Description of the Analysis

Although this phase II study will present data for multiple endpoints and will not be the definitive evaluation of the proposed treatment and withdrawal schedule, the statistical tests performed will be under the null hypothesis that there is no difference between randomized withdrawal groups at the end of study at week 36. The comparisons will be carried out in pairwise fashion, pooling of the two active groups and against the two-sided alternative. Primary efficacy analyses will be conducted using an Intention to Treat (ITT) population and will include all subjects who are randomized into the withdrawal/tolerance part of this trial. Subjects who withdraw/are terminated during the randomized withdrawal/tolerance part of the trial will be considered treatment failures for subsequent efficacy

outcomes. Subjects who withdraw/are terminated during the Omalizumab+food OIT part of the trial will be included in the exploratory efficacy analyses for that part of the trial and will be included in all safety analyses. There will be no adjustment made for multiple testing done within this study.

11.3 Measures to Minimize Bias

Blinding, placebo control and randomization will be the main methods to minimize bias in this trial.
DBPCFCs will be performed during screening, at week 30 and at week 36. During DBPCFC, the order of food allergen protein flours and placebo flour will be randomly permuted and both the patient and study staff will be blinded to the randomized order and the allergen involved in the specific challenge.
, At the end of week 30 DBPCFC and upon qualification for withdrawal/tolerance part of the study, subjects will be randomized into 3 blinded groups:
Group A- 1,000 mg each food allergen protein,
Group B-300 mg of each food allergen protein,
Group C-placebo ((300mg oat flour equivalent for each food allergen)
The randomization will be centrally implemented through Stanford.

11.4 Analyzing Outcome Measures

11.4.1 Primary Objective

To determine the ability to tolerate an oral food challenge to 2,000mg each of 2 allergens at week 36.

11.4.2 Main Secondary Objectives

- To determine the ability to tolerate an oral food challenge to 4,000mg each of 2 allergens at week 36.
- To determine the ability to tolerate an oral dose of 2,000mg each of 3 allergens separately (when applicable) at week 36.
- To determine the ability to tolerate an oral dose of 2,000mg each of 4 allergens separately (when applicable) at week 36.
- To determine the ability to tolerate an oral dose of 2,000mg each of 5 allergens separately (when applicable) at week 36.

Other Secondary Objectives:

- To determine bystander effects of cashew with pistachio and walnut with pecan allergies by skin testing and DBPCFCs.(baseline vs week 36)
- To determine ‘loss of protection’ by calculating the level of mg of food allergen cumulative dose during a food challenge, if a patient were to be defined as non tolerant after the 6 week withdrawal phase.

11.5 Study Hypothesis

To address the primary objective of this trial of assessing the ability of subjects in 3 randomized withdrawal groups to tolerate an oral food challenge to 2,000mg each of at least 2 food allergens

at week 36, we will test the following two null hypotheses:

1. There is no difference in the proportion of subjects who can tolerate 2000mg during week 36 DBPCFC of at least 2 food allergens in treatment groups (Group A+B) vs placebo (Group C.)
2. There is no difference in the proportion of subjects who can tolerate 2000mg during week 36 DBPCFC of at least 2 food allergens in each of treatment Groups (A or B) vs Group C.

11.6 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 70 subjects who will be equally randomized into one of the three randomized withdrawal groups at the end of week 30 and who will proceed to the primary endpoint evaluation at week 36. Assuming 15% drop out from the trial and equal randomization, we expect to have primary endpoint observation on 16 subjects in each treatment group. We used nQuery 3.0 and Chi squared Fisher's Exact test of equal proportions as the basis for the following power calculations for a range of assumed true proportions of subjects meeting the primary endpoint in each of groups of interest.

Power calculation for test of no difference in the proportion of subject who can tolerate 2000mg of at least 2 food allergens between Group A+B vs Group C **assuming 16 subjects per group**, two sided two group Chi squared Fisher exact test of equal proportions with unequal n's and significance level alpha=0.05

True proportion		
Group A+B	**Group C**	**Power**
100%	50%	98%
90%	30%	98%
80%	20%	97%

Power calculation for test of no difference in the proportion of subject who can tolerate 2000mg of at least 2 food allergens between Group A or Group B vs Group C **assuming 16 subjects per group**, two sided two group Chi squared Fisher exact test of equal proportions and significance level alpha=0.05

True proportion		
Group A or B	**Group C**	**Power**
100%	50%	96%
90%	30%	92%
80%	20%	91%

Based on our phase 1 study of Omalizumab and multiple OIT (Begin, et al. AACI 2014), we expect that 100% of subjects in Group A will reach the primary endpoint. Although the above tables give us a good sense of the power in this study, the true proportion of subjects in Group C that will tolerate the allergen at the primary endpoint is not known although if the proportion is lower than the assumed proportion, the power will be higher for the assumed proportion in Groups A and/or B. Based on other phase 1 clinical studies of OIT without omalizumab, the immune tolerance rate (after 4 weeks to 3 months withdrawal) was 50% to 33%, respectively

(Vickery et al. JACI 2014, Syed, et al. JACI 2014). Therefore we have calculated our power size according to these data.

11.7 Maintenance of Trial Treatment Randomization Codes

Subjects will be randomized 1:1:1 into one of three study groups:
Group A- 1,000 mg each food allergen protein,
Group B-300 mg of each food allergen protein,
Group C-placebo (300mg oat flour equivalent for each food allergen).

A randomized block design will be used. A Master Randomization Assignment List will be kept by the pharmacist in a locked cabinet. The sponsor's pharmacist will randomize the participant and enter the assignment into the Master List and the respective site's randomization list sequentially only once they are confirmed to be eligible to move to week 30. The pharmacist will verify that the randomization number is in fact the next unused treatment assignment on the master list and the respective site randomization list. On the Randomization Allocation CRF, the sponsor's pharmacist will record the randomization number, randomization date, group assignment, study subject's initials, study ID, and study site. The sponsor's pharmacist will notify GMP of the treatment assignment. GMP will prepare the appropriate week 30 DBPCFC kit and document Kit Number and Lot Numbers on the Randomization Allocation CRF and return the CRF to the sponsor's pharmacist. The sponsor's pharmacist will provide a copy of the CRF to the off-site pharmacist. GMP will ship the 6-week randomized treatment to the site. 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.

A similar procedure will be followed for the screening DBPCFC, except it may be the nutritionist rather than the pharmacist who implements the randomization (between food followed by placebo or placebo followed by food) and prepares the material for the blinded study staff to administer.

11.8 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 site has extensive experience in clinical trials, and in enrolling and retaining subjects.

11.9 Planned Interim Analyses (if applicable)

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

11.10 Safety Review

Please refer to individual and study stopping rules.

11.11 Immunogenicity 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.

11.12 Final Analysis Plan

Study subject baseline, demographic and clinical information including medical history by the randomized withdrawal / tolerance groups and overall will be summarized with means and standard deviations, medians and ranges, or counts and percentages as appropriate. The distributions of these variables across treatment groups may be compared using t-tests, Wilcoxon rank sum tests, and Fisher's exact tests, as appropriate.

To address the primary objective of this trial of assessing the ability of subjects in 3 randomized withdrawal groups to tolerate an oral food challenge to 2,000mg each of at least 2 food allergens at week 36 and to test the associated defined hypotheses, we will summarize the proportion of subjects who can tolerate 2000mg during week 36 DBPCFC of at least 2 food allergens in treatment groups (Group A+B), Group A, Group B and Group C. We will report the associated 95% exact binomial confidence intervals and the p values for the Fisher's exact test for the comparison of Group A+B vs Group C, Group A vs Group C and Group B vs Group C.

In each randomized withdrawal/tolerance group and overall, the percentage of subjects who are able to tolerate the DBPCFC for each food protein at each dose of interest (2000mg, 4000mg, cumulative doses etc.) at study week 30 and week 36 will be reported along with the 95% binomial exact confidence interval. Comparisons of Group A+B vs Group C as well as all the pairwise comparisons among the three groups will be performed using Fisher's exact test. Additional summaries will be provided for the number of allergen food protein tolerated and various doses at two time points of interest, week 30 and 36 as part of exploratory efficacy analysis.

The planned efficacy analyses will be performed on an "intention to treat" basis. For primary efficacy analyses, this means that only subjects that qualified and were randomized into tolerance phase of the trial will be included in the analysis and that all subjects who are terminated/withdraw after week 30 randomization and before week 36 will be considered treatment failures. Secondary efficacy outcomes observed at week 36 will be reported and compared similarly. For the secondary and exploratory efficacy analyses at week 30, all subjects treated in the study will be included in the analyses and those who are terminated / withdrawn early, will be considered Omalizumab+OIT treatment failures.

Safety information including reported adverse events by seriousness and severity as well as relationship to study treatment will be summarized by randomized withdrawal group and overall and also separately for Omalizumab+OIT and tolerance phase of the study.

In order to assess potential bias due to loss to follow-up, demographic and clinical variables will be

summarized and compared (if sample size permits) for subjects who do and do not complete the study and each phase of the study.

In addition, a group of subjects enrolled at the Stanford University site will be considered as a separate group since they were part of an original cohort which did not undergo the tolerance endpoint.

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 Process

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, 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 Informed Consent Process

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.

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

Not applicable.

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 or CRFS in black or blue ink. All corrections to entered data will be made by drawing a single line through the information to be corrected. All corrections will be initialed and dated. Personnel will not use "white-out" or obscuring correction fluid/tape. A final CRF will be prepared for each subject within 14 days from the study termination. A CRF is required for every subject who received any amount of test drug.

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 templates and then entered into the EDC, Redcap. The study personnel will enter the data into the EDC, 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, laboratory values, food challenge results, total and specific IgE, adverse events, concomitant medications,

dose escalations home diary reviews and adverse events. The EDC should be completed within 3 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

The site PI will consider any deviations from the protocol on a case-by-case basis. The investigator or other health professional in attendance must contact the sponsor/PD (Dr. Nadeau) as soon as possible to discuss the associated circumstances. The principal investigator and sponsor (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. BEGINP, 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 (see attached)

17.0.1 Appendix A: Values of Potential Clinical Concern

APPENDIX A: Values of Potential Clinical Concern[1]

Systemic	
Fever	≥ 38.5°C, unresponsive to antipyretics for > 2 hr
Chills	moderate shaking for > 30 min
Allergic	edema/urticaria or any respiratory problem
Hematologic	
Hemoglobin	males < 12.0 and females < 10.5 g/dL
Granulocytes	< 1000
Platelets	< 100,000
Hemorrhage	petechiae/mild blood loss
GI/Hepatic	
Nausea/Vomiting	nausea > 2 consecutive hr, not alleviated with medication; vomiting 4x over 24 hr
Diarrhea	> 24 hr of loose stools not controlled by medication
Bilirubin, total	> 1.5x upper limit of reference range
AST, ALT, GGT, Alkaline Phosphatase, Amylase	> 2x upper limit of reference range
Renal	
Serum creatinine	> 2.0 mg/dL
Proteinuria	> 1.0 g/day
Hematuria	> 15 rbc/hpf
Neurologic	
Central	difficulty in concentration > 24 hr Peripheral paresthesia and weakness lasting > 24 hr
Headache	headache requiring narcotics more than once
Constipation	requires non-OTC enema
Pulmonary	
Breathing	dyspnea at rest > 6 hr
Cardiac	
Heart rate	supine: < 35 or > 120 bpm; erect: < 40 or > 140 bpm
Blood pressure	systolic: > 30 mm Hg change from baseline in same posture; diastolic: > 20 mm Hg change from baseline in same posture
Rhythm	atrial arrythmia, unifocal PVC < 24 hr not requiring therapy
Function	transient asymptomatic dysfunction not requiring therapy
Other	
Glucose, fasting	< 60 or > 140 mg/dL
Albumin	> 0.5 g/dL above or below the limits of the reference range
Total protein	> 1.0 g/dL above or below the limits of the reference range
Electrolytes	> 10% above or below the limits of the reference range

[1] These values apply to adults

17.0.2 Appendix B: Epinephrine autoinjector Training Form

EpiPen Training Form

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

_____ _____
Signature of Adult Participant Date

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

_____
Authority to act for participant

_____ _____
Signature of Trainer Date

_____
Printed Name of Trainer

Current Wt:_____kg ❑ **EpiPen** ❑ **EpiPen Junior**

ANAPHYLAXIS INFORMATION (All boxes must be checked)

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

❑ Subject and/or family given an Anaphylaxis Emergency 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

17.0.3 Appendix C: 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 C (cont'd)

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

Category		Grade and Symptom(s)
Nasal itching	Grade 0:	Sign or symptom not observed
	Grade 1:	Mild itching
	Grade 2:	Intermittent rubbing of nose or eyes
	Grade 3:	Continuous rubbing of nose and/or eyes; periocular swelling and/or long bursts of sneezing
Nasal congestion	Grade 0:	Sign or symptom not observed
	Grade 1:	Some hindrance to breathing
	Grade 2:	Nostrils feel blocked, breathes through mouth most of the time
	Grade 3:	Nostrils occluded
Rhinorrhea	Grade 0:	Sign or symptom not observed
	Grade 1:	Occasional sniffing
	Grade 2:	Frequent sniffing, requires tissues
	Grade 3:	Nose runs freely despite sniffing and tissues
Airway obstruction	Grade 0:	Sign or symptom not observed
	Grade 1:	Voice change mild
	Grade 2:	Voice change moderate
	Grade 3:	Voice change severe 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 C (cont'd)

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

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

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

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

17.0.05 Appendix D: 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
erael@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 Randomized, Controlled, Blinded, Phase 2 Study Using Omalizumab in Rush Multi Oral Immunotherapy in Multi Food Allergic Patients

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 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%

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

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: _____

17.0.06 Appendix E: Schedule of Events

	Screening DBPCFCs[7]	Screening/Baseline	Omalizumab				Omalizumab OIT					OIT						DBPCFC[8], Randomization	Follow-Up/End of study
Week (±5 days)**		-36	0	2[4]	4	6[4]	8	10	12	14	16	18	20	22	24	26	28	30	36
Omalizumab/ Placebo Administration			X	X	X	X	X[5]	X	X	X	X								
Oral Immunotherapy							X	X	X	X	X[6]	X	X	X	X	X	X	X	X
Medical History	X	X																	X
Weight*		X							X						X				X
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total IgE[9]		X																	
Food IgE[9]		X																X	X
Mechanistic labs[1]		X	X				X					X			X			X	X
Skin Testing[9]		X	X									X			X			X	X
Spirometry-full/peak flow[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Epi Pen Training		X							X			X			X			X	X
DBPCFC[7,8]/OFC[3]	X																	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[10]		X									X							X	

1 Samples for translational research to include at termination visit
2 Full spirometry is preferred, however if subject is unable, peak flow may be performed instead.
3 Screening visits must have DBPCFCs. The DBPCFC during the active phase of study may occur within a period of 4 weeks to allow scheduling flexibility.
4 Dosing for Omalizumab will be either every 2 or 4 weeks depending on study subject's weight and total IgE.
5 If at least 5mg total is not tolerated at this visit, subject will be a treatment failure.
6 If subject has not tolerated 300mg total of all allergens by the end of visit at week 16, subject will be considered a treatment failure.

7 Baseline/Screening DBPCFC results may be obtained within 12 months prior to Week 0.
8 If subject has not updosed to ≥1,000 mg of each allergen at week 30 or before, subject will be considered desensitization failure and not complete week 36 DBPCFCs. Desensitization failures will be followed until week 36/End of Study visit.
9. Subjects who complete labs and SPT during screening (-36 weeks) do not need to repeat again at week 0.
10. Must be within 24 hours before day 0
* Week 0 weight can be + or – 2 weeks

** At the discretion of the Principal Investigator however, updosing may occur by completing additional visits at 1 week intervals, if necessary, to allow a participant the opportunity to achieve the minimum dose required to qualify for the DBPCFC for each allergen at Week 30. However, the procedures outlined in the Schedule of Events must occur at the specified time points.