AADCRC-STAN-004

LONG TITLE Phase 2 Randomized Controlled Trial using Biologics to Improve Multi OIT Outcomes

SHORT TITLE COMBINE Study

VERSION 10.0 / 03FEB2025

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Study Drug Manufacturer/Provider: Stanford Investigational Pharmacy (for Omalizumab and Dupilumab), Sean N. Parker (SNP) Food Allergy Manufacturing Facility at Sean N Parker Center for Allergy and Asthma Research at Stanford University

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INVESTIGATOR SIGNATURE PAGE	
Protocol Number: AADCRC-STAN-004	**Version/Date:** 10.0/ 03FEB2025
Title: **Phase 2 Randomized Controlled Trial using Biologics to Improve Multi OIT Outcomes (COMBINE)**	
IND Sponsor: Sean N Parker Center for Allergy and Asthma Research	
INSTRUCTIONS: *The site Principal Investigator should print, sign, and date at the indicated location below. Retain the original signed signature page for your records. Return an electronic PDF copy to the DAIT Regulatory Management Center (DRMC) via email to* [redacted]	

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(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* dated March 2018. 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, STANFORD and DAIT/NIAID.

_____

Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

Protocol Synopsis

Title	Phase 2 Randomized Controlled Trial using Biologics to Improve Multi OIT Outcomes
Short Title	COMBINE Study
Clinical Phase	Phase II
Number of Sites	Three (3)
IND Sponsor/Number	[redacted] (with cross reference to IND [redacted]/Andrew Long, PharmD for food powder/powders)
Study Objectives	**Primary Objective:** To determine whether suppression of allergic responses by anti-IgE followed by the combination of oral immunotherapy with IL4R blockade will increase the ability to sustain clinical tolerance in the absence of continued therapy. **Secondary Objectives:** **Clinical** • To compare the ability of the different treatment regimens (Cohort A: omalizumab/placebo + mOIT; Cohort B: omalizumab/Dupilumab + mOIT; and Cohort C: placebo/Dupilumab + mOIT) to desensitize participants to different thresholds and different numbers of foods. • To compare the ability of the different treatment regimens to enable sustained unresponsiveness (SU) to one or more foods.To compare treatment success at week 32 between different food allergens **Safety** • To assess safety of the treatment regimens during treatment and after withdrawal. **Exploratory and Mechanistic** • To evaluate the immunological responses that underlie success and failure with respect to treatment and sustained unresponsiveness outcomes.
Study Design	This is a prospective Phase 2, multi-allergen OIT study in participants with proven allergies to 2 or 3 different foods in which one must be peanut. Our intent to treat population

	will be 110 participants, ages 4 to 55 years that present with history of multiple food allergies of 2 or 3 different foods including peanut, food-allergen (FA)-specific IgE levels, and positive skin prick test (SPT). Enrolled participants must react positively during DBPCFCs at or before the 300 mg (444 mg cumulative) dosing level of FA proteins of 2 or 3 allergens in which one must be peanut. There will be three study cohorts, all will be double blinded: Cohort A (50 participants) will be treated with omalizumab for 8 weeks followed by 24 weeks of treatment with placebo. Cohort B (50 participants) will be treated with omalizumab for 8 weeks, followed by 24 weeks of treatment with dupilumab. Cohort C (10 participants) will be treated with placebo for 8 weeks followed by 24 weeks treatment with dupilumab. All cohorts will receive multi-food allergen oral immunotherapy. At week 8, all participants will undergo an Initial Dose Escalation Day (IDED) for all foods chosen (2 or 3 foods, one which is peanut), starting at a dose of 1 mg of protein of each food allergen (FA) and escalating to 10 mg, 50 mg, 100 mg, 210 mg, 420 mg, and 1,000 mg (per FA). Participants that tolerate the 1,000 mg dose per food will continue on 1,000 mg of each food protein until week 32. Participants that fail to reach the 1,000 mg dose of each food allergen will receive the highest tolerated dose on IDED as their home dose and then return to the clinic every two weeks for up dosing to the next step. These attempts will continue until week 30 or until they reach 1,000 mg of each FA. At week 32, participants will discontinue dupilumab or placebo treatment and will undergo DBPCFCs. Participants who tolerate food challenges to any foods with a cumulative dose of ≥1,043 mg with no or mild objective reactions of the FAs at week 32 will stop active OIT dosing and undergo DBPCFCs at week 44. Those with no or mild objective reactions to a cumulative dose of $\underline{\geq}$1,043mg of the FAs at week 44 will be considered as achieving sustained unresponsiveness and will have successfully met the primary endpoint.
Primary Endpoint(s) and Analysis	The primary endpoint (via hierarchical design) is: i) the success rates of passing a peanut DBPCFC, and ii) the success rates of passing a DBPCFC to peanut and at least one other FA, and iii) the success rates of passing a DBPCFC to peanut and two other FAs, where for all three endpoints, success is

	defined as passing a cumulative dose of $\geq$ 1,043 mg at the Week 44 DBPCFC if the subject has no or mild objective reactions. The primary endpoints would be compared between cohort A and cohort B.
Secondary Endpoint(s)	**Clinical Endpoints:** • Proportion of participants who successfully pass DBPCFCs to a cumulative dose of ≥1,043 mg protein to 1, 2, or 3 FAs when applicable at week 44 (SU). • Proportion of participants who successfully pass DBPCFCs to a cumulative dose of ≥2,043 mg to 1, 2, or 3 FAs when applicable at week 32. • Proportion of participants who pass DBPCFCs for each FA at a cumulative dose of ≥1,043 mg, ≥2,043 mg, or ≥4,043 mg at week 32 **and/or** week 44. • Proportion of participants who have a 10-fold change in the cumulative tolerance dose for each FA at weeks 32 and/or week 44, compared to baseline. **Safety Endpoints:** • Frequency of AEs, SAEs, and safety events in each cohort during the first 32 weeks of treatment • Frequency of AEs, SAEs, and safety events among treatment cohorts after completing their mOIT withdrawal to week 44 or end of study participation. **Exploratory and Mechanistic** • Differences in immunological responses, as measured by allergen-specific and non-specific markers, such as free allergen-specific IgE, specific IgG4, total IgE, specific IgG4/IgE ratios, basophil activation tests (BAT), basophil phenotyping, BCR (B cell receptor) repertoire features, B cell phenotyping, TCR (T cell receptor) levels, T cell phenotyping, and other immune-related cells measured at: o Baseline o IDED at week 8 o End of maintenance phase at week 32 o End of withdrawal (sustained unresponsiveness) phase at week 44

	• Quality of life questionnaires at baseline, week 32, and week 44. • Time to maintenance by arm and by number of FAs
Accrual Objective	110
Study Duration	Participants will be in an active phase of the protocol for about 44 weeks (see Figure 2 for individual subject timeline).
Treatment Description	Participants will be randomized 5:5:1 to one of three study cohorts: Cohort A will be treated with omalizumab for 8 weeks followed by 24 weeks of treatment with placebo. Cohort B will be treated with omalizumab for 8 weeks and followed by 24 weeks treatment with dupilumab. Cohort C will be treated with placebo for 8 weeks, followed by 24 weeks treatment with dupilumab. At week 8, all participants will undergo an Initial Dose Escalation Day (IDED) for 2 or 3 foods chosen starting at a dose of 1 mg protein of each food allergen (FA) and escalating to 10 mg, 50 mg, 100 mg, 210 mg, 420 mg, and 1,000 mg (per FA). Participants that tolerate the 1,000 mg dose of each food allergen will continue on that dose until week 32. Participants that fail to reach the 1,000 mg dose for each FA will receive the highest tolerated dose on IDED as their home dose and then return to the clinic every two weeks for up dosing to the next step. These attempts will continue until week 30 or until they reach 1,000 mg of each FA, whichever occurs first, while receiving dupilumab or placebo every 2 to 4 weeks. At week 32, participants will discontinue dupilumab or placebo treatment and will undergo DBPCFCs. Participants who tolerate food challenges to any foods with a cumulative dose of ≥1,043 mg with no or mild objective reactions of the FAs at week 32 will stop active OIT dosing and undergo DBPCFCs at week 44. Those with no or mild objective reactions to a cumulative dose of ≥1,043mg of the FAs at week 44 will be considered as achieving sustained unresponsiveness and will have successfully met the primary endpoint.
Inclusion Criteria	• Age 4 through 55 years (inclusive). • Clinical history of peanut allergy **and** 1 or 2 additional foods from the following foods: almond, shellfish, fish, soy, milk, cashew, hazelnut, egg, walnut, sesame seeds, and wheat. Allergy to milk and egg is defined as unable to tolerate both cooked and uncooked forms.

	• Positive allergy test determined by:
	  ▪ ImmunoCAP serum IgE level >4 kUA/L for each allergen within the past 12 months OR
	  ▪ Skin prick test (SPT) ≥6 mm wheal diameter to each allergen.
	• A clinical reaction during a DBPCFC to small doses of food defined as a cumulative dose of =/<444 mg food protein.
	• No clinical reaction observed during the placebo (oat) challenge.
	• Subject and/or parent guardian must be able to understand and provide informed consent.
	• Written informed consent from adult participants.
	• Written informed consent from parent/guardian for minor participants.
	• Written assent from minor participants as appropriate (e.g., at and above the age of 7 years).
	• For women of childbearing potential, must agree to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods (barrier methods or oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy) during the treatment period and for 60 days after the last dose of study drug.

Exclusion Criteria	• History of cardiovascular disease, including uncontrolled or inadequately controlled hypertension. • Individuals less than 15 kg in weight at start of the study. • History of severe anaphylaxis to participant-specific foods that will be used in this study, defined as neurological compromise or requiring intubation. • History of chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that is, or is at significant risk of becoming, unstable or requiring a change in chronic therapeutic regimen. • History of eosinophilic esophagitis (EoE), other eosinophilic gastrointestinal disease, chronic, recurrent, or severe gastroesophageal reflux disease (GERD), symptoms of dysphagia (e.g., difficulty swallowing, food “getting stuck”), or recurrent gastrointestinal symptoms of undiagnosed etiology.

	• Severe asthma (NAEPP EPR-3 Medication Criteria Steps 5 or 6, appendix 1)[30].
	• Mild or moderate asthma (NAEPP EPR-3 Medication Criteria Steps 1-4, appendix 1), if uncontrolled or difficult to control.
	• Uncontrolled asthma as evidenced by:
	  ○ FEV1 < 80% of predicted, or ratio of FEV1 to forced vital capacity (FEV1/FVC) < 75% of predicted, with or without controller medications (only for age 6 or greater and able to do spirometry reliably. If unable to do spirometry, PEF of >80% is acceptable) or;
	  ○ One overnight admission to a hospital in the past year for asthma or;
	  ○ Emergency room (ER) visit for asthma within six months prior to screening.
	• Inability to tolerate biological (antibody) therapies.
	• Use of immunomodulator therapy (not including corticosteroids).
	• Use of beta-blockers (oral), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB) or calcium channel blockers.
	• Unable to be adequately dosed with omalizumab based on the tables used for this study.
	• Current participation or within the last 4 months in any other interventional study.
	• Pregnancy or lactation.
	• Allergy to oat (placebo in DBPCFC).
	• Use of investigational drugs within 16 weeks of participation.
	• In build-up phase of immunotherapy for aeroallergens or venom.
	• Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements, or that may impact the quality or interpretation of the data obtained from the study.
	• Known hypersensitivity to omalizumab or any of its excipients.
	• Known hypersensitivity to dupilumab or any of its excipients.

Participant Stopping Rules	Participants may be prematurely terminated from the study for the following reasons: 1. The participant elects to withdraw consent from all future study activities, including follow-up. 2. The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed). 3. The participant dies. 4. The Investigator no longer believes participation is in the best interest of the participant. 5. Individual safety stopping rules i. Anaphylaxis resulting in hypotension, neurological compromise or mechanical ventilation secondary to OIT dosing or any food challenge ii. The subject develops biopsy-documented eosinophilic esophagitis (EoE) with synchronous symptoms or other eosinophilic gastrointestinal disease iii. Any subject deemed to have severe allergic reactions and who receives aggressive therapy (e.g., mechanical ventilation, three or more doses of epinephrine for a life-threatening reaction) at any time should be discontinued from further therapy iv. Other circumstances including, but not limited to, the following: • Poor control or persistent activation of secondary atopic disease (e.g., AD, asthma) • Started on beta-blockers, or other prohibited medications, with no alternative medications available per the prescribing physician • Pregnancy
Study Stopping Rules	During the course of the study, if the investigator, Medical Monitor, or the NIAID Medical Officer discovers conditions that indicate that the study should be discontinued, an

	appropriate procedure for stopping the study pending NIAID DSMB review will be instituted, including notification of the FDA and IRB. If any of the stopping rules listed below are met, study enrollment will be suspended, the Initial dose day will be suspended, dose escalation during Build-up will be paused, and all enrolled participants will remain on their current dose pending expedited review of all pertinent data: • Any death related to dosing or study procedure • More than three participants requiring more than two injections of epinephrine during a single OIT dosing • More than 1 case of CoFAR Grade 4 AE (Table 6) related to food allergen dosing • More than 2 cases of CoFAR Grade 4 AE (Table 6) related to oral food challenge • More than 3 serious adverse events related to investigational product or • More than 3 cases of eosinophilic esophagitis with synchronous clinical symptoms and confirmatory biopsy findings If any of the stopping rules listed below are met, injections will be paused and participants will remain on their current OIT dose pending expedited review of all pertinent data: • More than one participant requiring more than two injections of epinephrine during a single omalizumab/placebo or dupilumab/placebo injection

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Glossary of Abbreviations

CFR	Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DBPCFC	Double-Blind Placebo Controlled Food Challenge
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
OIT	Oral Immunotherapy
PI	[Site] Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SNP-CTRU	Sean N Parker-Clinical Translational Research Unit
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Suspected Adverse Reaction

Study Definitions Page

Desensitization	The ability to tolerate a dose of allergen that is greater than was tolerated prior to treatment
Double blind placebo controlled food challenge	A graded challenge of suspect allergenic or placebo food product where neither the participant nor the supervising physician is aware of which product the participant is ingesting.
Lost to Follow-up	Lost to follow-up refers to participants who at one point in time were actively participating in a clinical research trial, but have become *lost* (either by error in a computer tracking system or by being unreachable) at the point of *follow-up* in the trial.
Medical Monitor	A representative of a drug sponsor who has medical authority to evaluate the safety aspects of a clinical trial.
NAEPP EPR-3	The EPR 3 Guidelines on Asthma was developed by an expert panel commissioned by the National Asthma Education and Prevention Program (NAEPP) Coordinating Committee (CC), coordinated by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. Using the 1997 EPR 2 guidelines and the 2004 update of EPR 2 as the framework, the expert panel organized the literature review and final guidelines report around four essential components of asthma care, namely: assessment and monitoring, patient education, control of factors contributing to asthma severity, and pharmacologic treatment. Subtopics were developed for each of these four broad categories. (https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma)
Non-adherence	Excessive missed days of OIT (i.e. > 10 consecutive days missed on 3 or more occasions) without consulting with study staff
Non-related food	Non related-based on non-homologous protein definitions https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3820096/
PRACTALL guidelines	The PRACTALL program is a common initiative of EAACI and the American Academy of Allergy, Asthma and Immunology. It focuses on practical aspects of allergy to deliver updated and evidence-based recommendations for clinicians. DOI: https://doi.org/10.1016/j.jaci.2012.10.017
Project Manager (STANFORD)	A project manager from Stanford.
Principal Investigator	A person responsible and accountable for conducting the clinical trial and for the rights, health and welfare of the subjects in the trial. The principal investigator assumes full responsibility for the evaluation of human subjects, and for the integrity of the research data and results.
Program Officer	A Program Officer is an integral part of a foundation or nonprofit organization. It is up to Program Officers to oversee program development, seek grants and proposals, manage projects and oversee budgets.
Protocol Mandated Procedures	Procedures mandatory per protocol.

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Randomization	The process of assigning clinical study subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Regulatory Affairs Officer	Regulatory affairs officers ensure that products such as cosmetics, pharmaceuticals, and veterinary medicines meet legislative requirements.
Site Principal Investigator	Site Principal Investigator is the Principal Investigator at the lead research site and has responsibility over the conduct of a clinical study at that site.
Site Study Clinical Research Coordinator	A Clinical Research Coordinator (CRC) is a person responsible for conducting clinical trials using good clinical practice (GCP) under the auspices of a Principal Investigator (PI).
Study Termination	Permanent cessation of all research activities.
Study Therapy	Specific intervention according to the research plan or protocol created by the investigator.
Sustained unresponsiveness	Sustained unresponsiveness corresponds to the effects of OIT and will be defined as a participant's passing a Double-blind Placebo-controlled Food challenge (DBPCFC) with no or mild objective reaction to up to a cumulative dose of ≥1,043mg of the FA allergen in their OIT at week 44.
Tolerance (immune)	Long term sustained unresponsiveness: this is a similar definition as sustained unresponsiveness but instead of week **44**, will be determined in long term follow up under a different protocol at 5 years after study start for each participant.
Withdrawal from Therapy	Therapy is stopped as directed per protocol, participant's decision or per study withdrawal criteria.

1. Background and Rationale

1.1. Background and Scientific Rationale

Food allergy (FA) is a serious public health concern that causes potentially-life threatening reactions in affected patients. The prevalence of food allergy in the United States (U.S.) has increased substantially and now affects 15 million patients: 4-8% of children (6 million children, 30% with multiple food allergies) and about 9% of adults. [1,2,3,4,5,35]. It is estimated that approximately 30,000 food-induced anaphylactic events are responsible for U.S. emergency department visits each year and 200 of these events prove fatal. Although many food allergic patients suffer from more than one food allergy, peanut and tree nut allergies are responsible for the majority of morbidity and risk of mortality in affected patients. Foods commonly associated with allergy are pervasive in the U.S. diet making accidental exposure to offending foods difficult to prevent even with arduous diligence and the incidence of anaphylaxis due to accidental ingestion of offending foods in pediatric patients is increasing at an alarming rate.[5] The current standard of care in management of food allergy is strict avoidance of the offending food and ready access to injectable epinephrine in the event of accidental exposure making a significant impact on the affected patient and their families' quality of life.[6,4,7,

In peanut allergy, landmark studies by A. Wesley Burks[8], Stacie Jones[9], and colleagues have shown that children can be desensitized to peanut via an oral immunotherapy (OIT) protocol. We have successfully replicated these results in adults and children (POISED, NCT02103270). We also completed studies showing that FA patients can be desensitized to multiple food allergens simultaneously (i.e., multi-OIT).[10,22,23]

The aim of OIT is to induce desensitization and reduce the risks of allergic reactions after accidental ingestion of food allergen. However, many patients in OIT trials continue to have side effects that can hinder their compliance and the overall efficacy of OIT.[36] Furthermore, current OIT is not universally effective. A significant portion of food allergic patients cannot tolerate OIT or fail to be desensitized, likely due to variability of cellular and molecular endotypes and clinical phenotypes.[11,12]

When patients received omalizumab concomitantly with their multi-OIT, they showed fewer adverse events in their build-up phase.[10] The principle of OIT is to expose the immune system to progressively larger amounts of an allergen in order to induce sustained unresponsiveness (SU)/tolerance. One limit to this approach is that with allergen dose increases, food-allergen-specific IgE on mast cells can trigger allergic reactions and limit the ability to rapidly increase doses with minimal side effects. Omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRIa) on the surface of mast cells and basophils and reduces levels of free IgE in the blood.[13] By pre-treating patients with omalizumab prior to starting OIT, mast cells and basophils start to become depleted of surface IgE. Additionally, the ability of omalizumab:IgE complexes to trap allergen before it reaches IgE bound to mast cells and basophils (similar to IgG4)[14] may play a role in some patients' ability to tolerate higher amounts of allergen at IDED and during build up. However, omalizumab alone has not been demonstrated to improve the ability of OIT to maintain the ability to tolerate a food allergy in the absence of continued OIT.

Recent data suggest that IL-4 and IL-13 may also play a significant role in food allergy pathogenesis.[15,16] These two cytokines are critical to the induction and perpetuation of the Type 2 response and have been implicated in multiple atopic diseases. Dupilumab, a fully human monoclonal antibody directed against interleukin-4

receptor alpha (IL-4Rα), blocks the activity of IL-4 and IL-13. Inhibiting both IL-4 and IL-13 signaling with dupilumab has demonstrated clinical efficacy in moderate-to-severe atopic dermatitis (AD)[17], persistent, uncontrolled asthma[18,19], nasal polyposis[20], and is currently being investigated in eosinophilic esophagitis (EoE) (NCT02379052). It is known that oral allergen up dosing during OIT induces up-regulation of IL-4 and IL-13 as well as other Type 2 inflammatory cytokines and pathway activity, which likely contribute to dose-limiting side effects of OIT such as GI (nausea, vomiting, diarrhea and abdominal pain), respiratory (wheezing and shortness of breath), and skin (generalized rash, pruritus, and angioedema) symptoms. In addition, IL-4 and IL-13 induce isotype class switching to IgE and production of allergen specific IgE. Dupilumab therapy has been shown to reduce IgE levels over time, but slowly and not to the extent of omalizumab.

This study aims to evaluate the effect and tolerability of omalizumab in combination with dupilumab on enhancing the efficacy and safety of OIT in patients with multi-food allergies by lowering the free IgE antibody levels (omalizumab) and by inhibiting IL-4 and IL-13 signaling (dupilumab). In addition to enhancing the safety of OIT by prevention of immediate hypersensitivity reactions as has been previously demonstrated, prevention of release of mediators including eicosanoids, chemokines and cytokines may dampen Th2 inflammation allowing dupilumab to work in a more neutral environment. We theorize that dupilumab may be able to maintain a low IgE by decreasing production of FA specific IgE. We will also explore whether dupilumab has the ability to enhance immunomodulatory effects of OIT by decreasing Type 2 responses and potentially increasing the FA-specific IgG response, which will result in improved safety and tolerability of OIT up dosing as well as improved efficacy as determined by the ability to tolerate a higher cumulative dose of FA protein during a double-blind, placebo-controlled food challenge (DBPCFC) after 32 weeks of therapy compared to placebo. In addition, the study will evaluate whether dupilumab influences known biomarkers important in the allergic response such as a reduction in allergen-specific immunoglobulin sub-class switching to IgE, decrease in basophil activation and decreased Th2 cytokine levels.

1.2. Rationale for Selection of Investigational Product or Intervention

Data collected by the Food Allergy Research and Education organization (FARE) suggest that the incidence and prevalence of food allergy (FA) in adults and children are rising,[21] therefore it is important to rationally design novel therapeutic regimens based on inhibiting the effects of key target molecules such as immunoglobulin E (IgE), or interleukin-4 (IL-4) and interleukin-13 (IL-13) cytokines, molecules that are known to be involved in the pathophysiology of FA and anaphylaxis.

We have published safety and efficacy findings on participants in Phase 1 and 2 OIT studies.[10,22,23,37] The development of more efficacious food allergy treatments is particularly important for patients with multiple food allergies because the co-occurrence of multifood allergies increases risks for accidental ingestions and near-fatal or fatal anaphylaxis.[2] Patients with multiple food (multifood) allergies face additional challenges (as compared to single food allergic patients) related to increased length of oral immunotherapy (OIT) treatment.

Omalizumab is a recombinant DNA-derived humanized IgG1 kappa monoclonal Ab that selectively binds to human IgE and is currently licensed for the indication of moderate to severe persistent allergic asthma in children and adults. Omalizumab inhibits the binding of IgE to the IgE receptor on the surface of mast cells and basophils and results in reductions in levels of free IgE in the blood.[24]

Results from our Phase 2 study to evaluate the safety and tolerability of a “rush” multi-OIT using Xolair (omalizumab) as an adjunctive therapy to multi oral immunotherapy in multi food allergic patients (MAPX Study)[10] demonstrated that subjects pretreated with omalizumab can be rapidly and safely desensitized to

multiple foods simultaneously (the ability to ingest 2g of protein to 2 or more foods to which they were allergic). Subjects who received OIT and omalizumab were 10 times more likely to pass food challenges with at least two offending food allergens after only 36 weeks of therapy compared to those in the placebo arm (p = 0.0022) group. The median per participant percentage of OIT doses associated with any adverse events was 27% in the omalizumab group compared to 68% in the placebo group. These findings suggest that omalizumab improves the efficacy and safety of multi-food allergy OIT, allowing a safe and rapid desensitization.
Recently, phase 2 studies in adults (>18 years) have been reported using subcutaneous dupilumab in asthma and atopic dermatitis.[18, 25] Wenzel, et al. tested dupilumab for its ability to reduce asthma exacerbations in eosinophilic asthma; a total of 52 patients were assigned to receive dupilumab (300 mg q week for 12 weeks), and 52 patients were assigned to placebo[18]. Three patients receiving dupilumab experienced an asthma exacerbation (6%) compared to 23 in the placebo group (44%), corresponding to an 87% reduction with dupilumab (odds ratio, 0.08; 95% confidence interval, 0.02 to 0.28; P<0.001).
By rapidly reducing levels of free IgE antibodies and mast cell/ basophil release reactions, omalizumab may permit the activities of dupilumab to be observed more quickly and/or more substantially than when the agent is used without omalizumab in multi-FA individuals.

1.3. Preclinical Experience
Not Applicable

1.4. Clinical Studies
In a recent study (POISED, NCT02103270) led by our group, participants safely ingested a median dose of 2,000 mg of peanut protein by approximately 40 weeks and reached a median maintenance dose of 4000 mg by approximately 44 weeks. However, there were side effects [3,236 allergic adverse events (AEs) out of 103,755 doses thus far, or 3.12%]. Some of these AEs led to participant dropouts (n=18 withdrawals). Importantly, most allergic AEs occurred in the first 12 weeks of the study (1,608 out of 20,486 doses, or 7.8%) and led to delays in up-dosing in 45% of the participants (41% needing to repeat at least one dose, and 4% needing to down-dose). Few studies have been conducted to optimize safety and to identify the immunological mechanism(s) underlying any long-lasting effects of OIT.

To address these questions in the field of food allergy research, we designed a phase 1 study to test the safety of multi-food OIT[22]. We enrolled children and adults (4-55 years of age) with proven severe multiple food allergies that included peanut, and/or milk, and/or egg, and/or tree nut, and/or sesame seed and/or wheat. The active phase of the study was approximately 12 months, and the follow up phase was approximately 12 months. Overall, at the end of the study, participants were able to escalate to the top dose of each of their allergens (4g of protein). In total, there were 36,606 doses of study drug over approximately 24 months for each participant and 1,227 adverse events related to study drug (about 3.3%). The most frequent reaction involved skin/subcutaneous tissues and was mild (58%). There were no SAEs. Other groups also have published on the importance of minimizing adverse events related to food allergen ingestion to improve efficacy, compliance, and retention in clinical studies. [26,27]

In a pilot, phase 2, placebo-controlled, clinical trial, Xolair in a Rush Multi OIT Pilot in Multi Allergic Patients, MAPX, we studied the safety and efficacy of multi-allergen OIT with concomitant omalizumab in 48 participants. Thirty-six participants were randomized to mOIT with concurrent omalizumab (OmO), while 12

patients were randomized to mOIT with placebo injections[10]. Exactly 50% of participants in the OmO arm were able to reach the maximum dose of 1,250 mg of total allergen protein on the initial dose escalation day (IDED), after 8 weeks of omalizumab treatment, compared to 0% in the placebo group (maximum dose reached within the placebo group was 150 mg by only 8% of participants; 50% reached 50 mg); this suggests that pretreatment targeting of IgE with omalizumab improves the ability to tolerate higher doses of total allergen protein in some individuals. AE rates were similar between groups during the course of the study and there were no grade 3 or higher anaphylactic reactions (Bock's criteria). The OmO group showed improved efficacy compared to that in the placebo group, with 83% able to pass a food challenge to 2 g of at least 2 allergens, versus 33% in the placebo group (p= 0.004). Moreover, we found that there are bystander relationships (i.e. cross-desensitizations between cashew and pistachio, and between walnut and pecan, respectively).

In a separate, multi-center phase 2 study of mOIT with concurrent use of omalizumab (Multi Immunotherapy to test Tolerance [MTAX], NCT02626611), [37] we tested safety, efficacy and tolerance in 60 participants. As in MAPX, participants were treated with omalizumab for 8 weeks before allergenic foods (2-5 allergens) were introduced (IDED). At IDED, 53% of participants were able to tolerate a total dose of 1250 mg allergenic proteins. Following 12 weeks of OIT, participants reached a median dose of 2,000 mg protein of each allergen in their OIT mix. Patients who passed DBPCFCs to at least 2 g of at least 2 allergens at week 30 were randomized into one of 3 arms, differing in the amount of daily protein dose of each allergen in their mix: Arm A at 1000 mg; Arm B at 300 mg; and Arm C, avoidance (placebo). These patients then underwent additional DBPCFCs at week 36. At week 30, 55/55 (100%) participants in Arms A, B, and C were able to pass the DBPCFCs. At week 36, 100%, 89% and 69% in Arms A, B and C, respectively, passed DBPCFCs of at least 2 allergens to 2 g of protein. While 11/16 (69%) participants who avoided allergen dosing for 6 weeks exhibited SU upon rechallenge at 36 weeks, novel therapeutic approaches targeting broader ranges of immune drivers in FA may increase the number of those achieving SU and/or may sustain such responses for longer time periods. AEs were similar between each arm and there was no grade 3 or higher anaphylactic reactions.

2. Study Hypotheses/Objectives

2.1.a. Clinical Hypotheses

We hypothesize that treatment with the IL-4 receptor alpha-chain-targeting antibody, dupilumab, combined with treatment with the anti-IgE antibody omalizumab, will increase the likelihood of sustained unresponsiveness and decrease adverse events associated with multi-food OIT.

2.1.b. Mechanistic Hypotheses

We hypothesize that detailed immune monitoring, which includes assessment of B cell and T cell functional markers and blood basophil function and phenotype, will permit us to predict the grade of clinical reactivity to food allergens in multi-food allergic individuals and will reveal changes in those participants correlated with the efficacy and durability of the clinical benefit of multi-OIT, irrespective of treatment with dupilumab and/or omalizumab.

2.2. Primary Objective(s)

To determine whether suppression of allergic responses by anti-IgE followed by the combination of oral immunotherapy with IL4R blockade will increase the ability to sustain clinical tolerance in the absence of continued therapy.

2.3. Secondary Objective(s)

Clinical

- To compare the ability of the different treatment regimens (Cohort A: omalizumab/placebo + mOIT; Cohort B: omalizumab/Dupilumab + mOIT; and Cohort C: placebo/Dupilumab + mOIT) to desensitize participants to different thresholds and different numbers of foods.
- To compare the ability of the different treatment regimens to enable sustained unresponsiveness to one or more foods.
- To compare treatment success at week 32 between different food allergens

Safety

To assess safety of the treatment regimens during treatment and after withdrawal.

2. 4 Exploratory and Mechanistic Objectives

To evaluate the immunological responses that underlie success and failure with respect to treatment and sustained unresponsiveness outcomes.

3. Study Design

3.1 Description of Study Design

This is a prospective Phase 2, multi-allergen OIT trial, in participants with proven allergies to 2 or 3 unrelated foods of which one must be peanut. Our intent to treat population will be 110 participants, ages 4 through 55 years. Enrolled participants must be positive at or before the 300 mg (444 mg cumulative) dosing level of each food proteins. Blood samples from up to 10 mechanistic controls with multi-FAs, who have not undergone therapy will be included, outside of this protocol.

Screening Phase (week -24 – 0):

We propose to screen 300 individuals ages 4 through 55 years, males and females of any race or ethnicity. To enable a lower number of in clinic screening and lower the rate of screen failures, we will pre-screen participants from our Patient Registry that has about 2,000 participants. Participants will initially be screened for the FA using blood tests for FA-specific IgE and/or SPT. If participants have a positive IgE or SPT to peanut and 1 or 2 other studied FAs (cashew, hazelnut, egg, walnut, sesame seed, wheat, shellfish, fish, almond, soy, or milk), they will undergo multiple DBPCFCs for 2 or 3 FAs that will be performed on different days (Please also see section on bystander food challenges). Participants must be positive at or before the 300 mg (444 mg cumulative) dosing level of FA protein in accordance with PRACTALL (Practical Issues in Allergology) consensus guidelines. Informed consent will be obtained before proceeding with any trial procedures.

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Intervention Phase:

Randomization and Omalizumab/Placebo Treatment (Week 0 – 8): Eligible participants who pass the DBPCFCs at the screening phase will be randomized to one of three cohorts: Cohort A (50 participants) will be treated with omalizumab for 8 weeks followed by 24 weeks of treatment with placebo. Cohort B (50 participants) will be treated with omalizumab for 8 weeks followed by dupilumab for 24 weeks. Cohort C (10 participants) will be treated with placebo for 8 weeks, followed by 24 weeks treatment with dupilumab. Participants will be stratified at randomization by two or three food allergens within each cohort. Participants will be dosed according to the appropriate dosing schedule every 2 weeks or every 4 weeks with the appropriate medication according to their blinded treatment assignment. All participants will be observed for 2 hours after the first 3 omalizumab injections they receive in clinic and 30 minutes thereafter between weeks 0-8. It is currently unknown if the administration of live vaccines during treatment with Dupilumab impacts the safety or effectiveness of these vaccines. Participants must complete the DTaP, MMR, Varicella or IPV vaccine series, at least four weeks prior to your Randomization visit. The Comirnaty® (BioNTech/Pfizer), Moderna, and Johnson & Johnson COVID-19 vaccines are not live vaccines.

Initial Dose Escalation Day (Week 8/IDED) At week 8, all participants will undergo an Initial Dose Escalation Day (IDED) for all foods chosen (2 or 3 foods), starting at a dose of 1 mg protein of each FA and escalating to 10 mg, 50 mg, 100 mg, 210 mg, 420 mg, and 1,000 mg. Participants that tolerate the 1,000 mg dose of each FA will continue on that dose until week 32. Participants that fail to reach the 1,000 mg dose of each FA, will receive the highest tolerated dose on IDED as their home dose and then return to the clinic in two weeks for up dosing to the next step. Participants may return to the clinic the next day (IDED+1) for an observed dose if deemed necessary by the Investigator. If the participant can start the home dosing the day after the IDED (i.e. IDED+1) they do not need to take that dose in clinic as they have already had that dose effectively observed. If the first home dose cannot be taken the day after IDED (i.e., IDED+2 or greater) the first dose will be an observed dose in clinic. If a participant does not tolerate 1 mg of each FA at their IDED they will be deemed a treatment failure.

Dupilumab/placebo and OIT (Week 8 – 32): Cohort A will receive placebo injections over the next 24 weeks. Cohort B will receive dupilumab every 2 to 4 weeks for 24 weeks. Cohort C will receive dupilumab every 2 to 4 weeks for 24 weeks. At week 8 participants will begin their OIT. Participants that tolerate the 1,000 mg dose per food will continue on that dose until week 32. Participants that fail to reach the 1,000 mg dose of each food allergen will receive the highest tolerated dose on IDED as their home dose and then return to the clinic in two weeks for up dosing to the next step. Participants may return to the clinic the next day (IDED+1) for an observed dose if deemed necessary by the Investigator. If the participant can start the home dosing the day after the IDED (i.e. IDED+1) they do not need to take that dose in clinic as they have already had that dose effectively observed. If the first home dose cannot be taken the day after IDED (i.e., IDED+2 or greater) the first dose will be an observed dose in clinic. These attempts will continue until week 30 or until they reach 1,000 mg of each FA, whichever occurs first, while receiving dupilumab or placebo every 2 to 4 weeks. The Dupilumab/placebo injection can be dyssynchronous from the OIT dosing if necessary (Appendix 4).

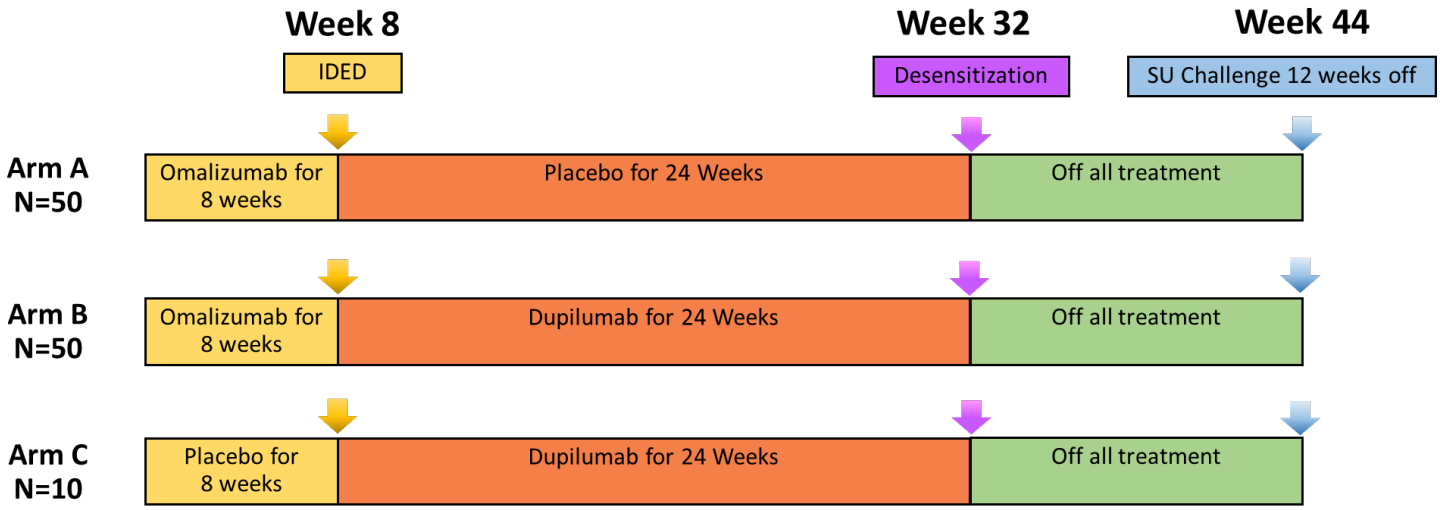
Maintenance Phase (Week 30-32 minimum): Participants must escalate to 1,000 mg each FA on/before the end of the week 30 visit otherwise they will be deemed a treatment failure. The maintenance phase starts when the participant reaches 1,000 mg each FA until the end of their week 32 DBPCFCs (after which they stop OIT dosing and enter sustained unresponsiveness phase).

First DBPCFC (Week 32): At the conclusion of the maintenance phase (week 32), participants will undergo DBPCFCs for each FA in their OIT on separate days (Please also see section on assessment of cross desensitization)**.** If the participant fails all DBPCFCs evidenced by not tolerating ≥1,043 mg protein for all food allergens, they are deemed a treatment failure and will be withdrawn from the study. Participants who tolerate at least one food challenge at cumulative dose of ≥1,043 mg will continue into the withdrawal phase. No participant will repeat a food challenge at week 44 that was not tolerated at week 32.

Withdrawal Phase

(Week 32 to Week 44): A discontinuation (i.e. withdrawal from OIT) will occur for 12 weeks, from week 32 to week 44. This withdrawal phase is designed to examine mechanisms underlying sustained unresponsiveness (SU). At week 44, after 12 weeks of withdrawal, participants will undergo DBPCFCs on separate days**.** Participants that pass their food challenges with no or mild objective reactions to a cumulative ≥1,043 mg of each eligible FA in their OIT at the end of this phase (secondary outcome) will be considered tolerant (i.e. sustained unresponsiveness or SU).

Figure 1. Study Design of a Prospective Phase 2 Study to Test the Efficacy of Omalizumab and Dupilumab Combination in multi-OIT



Please note that placebo refers to placebo for either biologic (Omalizumab in the first 8 weeks of the study; Dupilumab in weeks 10-32 of the study)

End of study (Week 44): The DBPCFCs at week 44 will mark the completion of the withdrawal phase and end of study (EOS). Participants can exit the trial at Week 44 to meet the study completion criteria.

Assessment of Cross Desensitization Effect as Exploratory Endpoint:

Participants will be allowed to perform optional food challenges to explore whether one type of food allergen given in oral immunotherapy (like walnut) can provide cross desensitization effects to a similar protein (like pecan). The specific cross desensitization (or 'bystander') pairs we will be exploring are walnut/pecan and cashew/pistachio. These optional food challenges (pecan and/or pistachio) can be opted into anytime as a series of DBPCFCs occur throughout the study (screening, week 32, week 44). Exploring whether there are possible bystander effects may help us to improve the design of future clinical trials.

This phase 2 clinical trial is aiming to study safety and efficacy of treating FA patients with omalizumab-dupilumab combination with their OIT. In addition, the clinical trial would provide understanding of B cell and immunoglobulin (Ig) responses and alterations induced by multi-OIT in patients with multiple food allergies. It also will allow the characterization of the immunophenotypic and functional changes induced by multi-OIT in total and allergen-specific T cells. After initial screening and enrollment, there are four phases of the study (Figure 1):

- Intervention Phase
  - Blockade of IgE
  - Dose escalation and blockage of IL4/IL13 signaling
  - Maintenance dosing
- Withdrawal phase

Overall, 110 subjects who are eligible will undergo the Initial Dose Escalation Day (IDED) for their specific FAs. Subsequent up dosing visits concomitant with dupilumab or placebo treatment will occur every 2 to 4 weeks as part of the build-up phase. They will continue to updose until they reach 1,000 mg of each FA protein daily.

Figure 2. Study Flow Chart/Schedule of Events

	Screen	Omalizumab or placebo 8 weeks	Initial Dose Escalation Day (IDED)	Day After Initial Dose Escalation Day (IDED+1)	Buildup Phase w/ Dupilumab or placebo 24 weeks	Maintenance Phase	Withdrawal Phase 12 weeks
Time	*Day -270 – 0*	*Every 2-4 wks (Week 0 – 8)*	*Week 8*	*1 day after IDED (week 8, day 1)*[4]	*Every 2 wk (Weeks 10 - 32)*	*Week 32*	Week 44 *End of Study*
Visit Window	*±12 weeks*	*±7 days*	*± 7 days*	*+ 6 days*	*± 7 days*	*± 14 days*	*±14 days*
Informed Consent	X						
Medical History	X						
Physical	X	X[3]	X	X	X	X	X
Con Meds	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Specific IgE/IgG4	X						X
Skin prick testing	X					X	X
CBC with	X		X			X	X
Blood for mechanistic	X	X	X			X	X
Serum pregnancy	X						

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Lung Function	X		X	X	X	X	X
Diaries		X	X	X	X	X	X
Inject Epi training	X						X
Omalizumab or Dupilumab[1]Injectio		X	X		X		
Optional samples [2]	X		X			X	X
DBPCFC	X					X Test desensitization	X Test SU
OIT			X	X	X	X	
Questionnaires	X		X			X	X

[1]omalizumab or placebo will be given every 2 or 4 weeks from week 0 until week 8. Dupilumab or placebo will be given every 2 to 4 weeks from week 10 to week 32.
[2]Optional Samples include: buccal swabs, skin swabs, saliva samples, fecal samples, urine samples
[3]Symptom-directed physical assessment
[4]IDED+1 procedures to be done if dosing is performed in clinic (as applicable)

Treatment Failures:

A treatment failure will be defined as:

- A participant who does not tolerate 1mg of each FA at week 8/IDED
- A participant who has not escalated to 1,000 mg each food by the end of visit at week 30
- A participant deemed a treatment failure at any time prior to week 32 by the PI
- A participant who demonstrates moderate or severe clinical reactivity (objective) at <1,043 mg protein to all foods at week 32 DBPCFCs for all foods tested, at which point they will be withdrawn from the study.

A treatment failure will not receive any more study therapy nor further food challenges. Participant disposition is specified in Appendix 4.

If the participant passes the week 32 food challenge to at least one food, they are not treatment failures and will proceed to the next phase. At week 44, they will be challenged only to the foods they were desensitized to at week 32 (Appendix 4).

Sustained Unresponsiveness Failures:

A sustained unresponsiveness failure will be defined as:

- A participant who demonstrates moderate or severe clinical reactivity (objective) at <1,043 mg protein each food at week 44 DBPCFCs for all foods tested.

A sustained unresponsiveness failure will be advised to follow-up with their allergist for further instructions.

Treatment failures and SU failures will be considered in statistical analyses of the intent-to-treat population.

Integration with mechanistic science program: This is a prospective, phase 2 clinical trial aiming to study safety, efficacy, and multi-OIT with adjuvant treatment with omalizumab and/or dupilumab. In addition, the clinical trial's mechanistic purpose is to obtain fundamental understanding of human immune cell responses in patients with multiple food allergies, and to analyze the alterations induced by multi-food allergen oral immunotherapy. It is also aiming to characterize the immunophenotypic and functional changes induced by multi-OIT in total and allergen-specific lymphocytes. We will analyze the modulation over time of specific cellular subsets during immunotherapy to elucidate whether these changes are associated with successful treatment responses.

Study Design Safety Considerations

The design considers important safety issues:

- All updosing visits will be supervised in a clinical setting where trained study physicians are available.
- Standing orders from an MD are provided for all clinical study personnel (RN, NP, PA, etc.) to initiate treatment of reactions immediately (i.e., prior to MD notification), including IM administration of epinephrine, based on their own clinical judgment.
- A crash cart with pediatric and adult equipment is available in close proximity of all participant rooms or bays.
- Dosing symptoms and adverse events will be captured throughout the study.
- Subjects will be prescribed an epinephrine auto-injector (if not prescribed by a treating clinician previous to study entry) and all subjects will be trained in its use. If he/she cannot afford one, an epinephrine auto-injector will be provided to the participant.

Subjects will be cautioned against consuming any foods containing the FAs they are being treated for, other than study-supplied food allergen while on study.

3.2 Primary Endpoint(s)/Outcome(s)

There are three co-primary endpoints (via hierarchical design): i) the success rates of passing a peanut DBPCFC, ii) the success rates of passing a DBPCFC to peanut and at least one other FA, and iii) the success rates of passing a DBPCFC to peanut and two other FAs, where for all three endpoints, success is defined as passing a cumulative dose of $\geq$ 1,043 mg at the Week 44 DBPCFC if the subject has no or mild objective reactions.

The primary endpoints would be compared between cohort A and cohort B.

3.3 Secondary Endpoint(s)/Outcome(s)

Clinical Endpoints:

- Proportion of participants who successfully pass DBPCFCs to a cumulative dose of $\geq$1,043 mg protein to 1, 2, or 3 FAs when applicable at week 44 (SU).
- Proportion of participants who successfully pass DBPCFCs to a cumulative dose of $\geq$2,043 mg to 1, 2, or 3 FAs when applicable at week 32.
- Proportion of participants who pass DBPCFCs for each FA at a cumulative dose of $\geq$1,043 mg, $\geq$2,043 mg, or $\geq$4,043 mg at week 32 and/or week 44.

- Proportion of participants who have a 10-fold change in the cumulative tolerance dose for each FA at weeks 32 and/or week 44, compared to baseline.

3.4 Exploratory and Mechanistic Endpoint(s)/Outcome(s)

- Differences in immunological responses, as measured by allergen-specific and non-specific markers, such as free allergen-specific IgE, specific IgG4, total IgE, IgG4/IgE ratios, basophil activation tests (BAT), basophil phenotyping, BCR (B cell receptor) repertoire features, B cell phenotyping, TCR (T cell receptor) levels, T cell phenotyping, and other immune-related cells measured at:
  - Baseline
  - IDED at week 8
  - End of maintenance phase at week 32
  - End of withdrawal (sustained unresponsiveness) phase at week 44
  - As needed per investigators discretion during unscheduled visits
- Quality of life questionnaire at baseline, week 32, and week 44.
- Time to maintenance by arm and by number of FAs

3.5 Safety Endpoints

- Frequency of AEs, SAEs, and safety events in each cohort during the first 32 weeks of treatment.
- Frequency of AEs, SAEs, and safety events among treatment cohorts after completing their mOIT withdrawal to week 44 or end of study.

3.6 Stratification, Randomization, and Blinding/Masking

Stratification: This is a Phase 2, randomized, placebo-controlled study that is stratified for treatment combination with omalizumab and dupilumab. Participants will be randomly stratified to one of 3 cohorts:

- Cohort A – omalizumab treatment for 8 weeks followed by 24 weeks of placebo treatment and multi oral immunotherapy (mOIT);
- Cohort B – omalizumab treatment for 8 weeks followed by 24 weeks of adjuvant dupilumab treatment with mOIT;
- Cohort C – placebo treatment for 8 weeks followed by 24 weeks of adjuvant dupilumab treatment with mOIT;

Randomization: Statistician will generate the randomization list where participants will be randomized at a 5:5:1 ratio into one of the three treatment cohorts. Within each cohort, participants will be stratified to either two or three foods. Randomization lists are maintained in a secured area (the pharmacy) by the individuals responsible for maintaining the blind (the unblinded pharmacists). The Stanford unblinded pharmacist will determine treatment cohort and number of food stratification for the enrolled participant, and assign a study ID.

Blinding/Masking: Placebo control and randomization will be the main methods to minimize bias in this trial. DBPCFCs will be performed during screening, at week 32 and at week 44. During DBPCFC, the order of food

allergen protein powders and placebo (oat) powder will be randomly permuted and both the participant and study staff will be blinded to the randomized order and the allergen involved in the specific challenge. Omalizumab and its placebo (normal saline) will be dispensed in syringes and labeled in a fashion that maintains the blind. Both omalizumab and normal saline are clear, colorless solutions identical in appearance. The viscosity of omalizumab is higher and may feel slightly different to those administering when compared to the saline. Dupilumab and its placebo (normal saline) will be dispensed in syringes and labeled in a fashion that maintains the blind. Dupilumab is a clear solution ranging from clear to very light yellow and should be difficult to differentiate from normal saline unless directly compared side by side.

3.6.1 Procedure for Unblinding/Unmasking

This is a double-blind study where the participants and the research team including the PI are blinded to the strata. The pharmacist who maintains the randomization lists, is unblinded to the treatment groups.

In the case of unscheduled unblinding or the removal of the randomization lists from the secured pharmacy binder, the CRA will verify that the site Principal Investigator and the NIAID Medical officer have been notified and that a written account has been completed and forwarded to these individuals.

Unblinding must be approved by the NIAID Medical Officer unless an immediate life-threatening condition has developed, and the Medical Officer is not accessible. The emergency unblinding will also be reported to the Data and Safety Monitoring Board (DSMB).

A full account of the event will be recorded, including the date and time of the unblinding, the reason for the decision to unblind, and the name of the individual who made the decision and the names of the NIAID Medical Officer and others who were notified. The reasons for unblinding of a participant's treatment will be included in the final study report.

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

4 Selection of Participants and Clinical Sites/Laboratories

4.1 Rationale for Study Population

The lower cutoff of 4 years of age was selected to include children where there is some guidance for dosing and to include only participants with sufficient blood volumes to support mechanistic investigations. The upper age limit of 55 years was selected because it is important to study the adult population with multiple food allergies. The prevalence of food allergy has been increasing over the last 30 years, so a significant number of young adults are food allergic (1 in 10),[35] whereas it is a rarer condition in middle-aged and older adults. Our previous studies have not shown age differences in the ability to become desensitized and it will be important to understand if immune mechanisms of desensitization and sustained unresponsiveness are similar in adults and children.

We anticipate enrolling 110 participants with multi food allergies. Participants must have either food specific IgE > 4kU/L for each allergen or a skin test reactivity to each food allergen ≥ 6mm wheal diameter. In addition, participants must be able to be adequately dosed with omalizumab based on the tables for this protocol, a clinical reaction during a double blind placebo controlled food challenge (DBPCFC) with food protein/powder to establish sensitivity to given food protein/powder (peanut, cashew, hazelnut, egg, walnut, sesame seed, wheat, almond, shellfish, fish, soy, or milk) and no clinical reaction during placebo (oat) challenge.

4.2 Inclusion Criteria

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

1. Subject and/or parent guardian must be able to understand and provide informed consent.
2. Written informed consent from adult participants.
3. Written informed consent from parent/guardian for minor participants.
4. Written assent from minor participants as appropriate (e.g., at and above the age of 7 years).
5. Age 4 through 55 years (inclusive).
6. Clinical history of peanut allergy **and** allergy to 1 or 2 additional foods from the following foods: cashew, hazelnut, egg, walnut, sesame seed, wheat almond, shellfish, fish, soy, or milk; allergy to milk and egg is defined as unable to tolerate both cooked and uncooked forms.
7. Positive allergy test determined by:
   - ImmunoCAP serum IgE level >4 kUA/L for each allergen within the past 12 months OR
   - Skin prick test (SPT) ≥6 mm wheal diameter to each allergen
8. A clinical reaction during a DBPCFC to small doses of food defined as a cumulative dose of =/ <444 mg food protein.
9. No clinical reaction observed during the placebo (oat) challenge.
10. For women of childbearing potential, must agree to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods (barrier methods or oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy) during the treatment period and for 60 days after the last dose of study drug.

4.3 Exclusion Criteria

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

1. History of cardiovascular disease, including uncontrolled or inadequately controlled hypertension
2. Individuals less than 15 kg in weight at start of the study
3. History of severe anaphylaxis to participant-specific foods that will be used in this study, defined as neurological compromise or requiring intubation
4. History of chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that is, or is at significant risk of becoming, unstable or requiring a change in chronic therapeutic regimen.

5. History of eosinophilic esophagitis (EoE), other eosinophilic gastrointestinal disease, chronic, recurrent, or severe gastroesophageal reflux disease (GERD), symptoms of dysphagia (e.g., difficulty swallowing, food "getting stuck"), or recurrent gastrointestinal symptoms of undiagnosed etiology.
6. Severe asthma (NAEPP EPR-3 Medication Criteria Steps 5 or 6, appendix 1)[30]
7. Mild or Moderate asthma (NAEPP EPR-3 Medication Criteria Steps 1-4, appendix 1), if uncontrolled or difficult to control.
8. Uncontrolled asthma as evidenced by:
   - FEV1 < 80% of predicted, or ratio of FEV1 to forced vital capacity (FEV1/FVC) < 75% of predicted, with or without controller medications. (only for age 6 or greater and able to do spirometry reliably. If unable to do spirometry, PEF of >80% is acceptable) or;
   - One overnight admission to a hospital in the past year for asthma or,
   - Emergency room (ER) visit for asthma within six months prior to screening.
9. Inability to tolerate biological (antibody) therapies
10. Use of immunomodulator therapy (not including corticosteroids).
11. Use of beta-blockers (oral), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB) or calcium channel blockers.
12. Unable to be adequately dosed with omalizumab based on the tables used for this study.
13. Current participation or within the last 4 months in any other interventional study.
14. Pregnancy or lactation.
15. Allergy to oat (placebo in DBPCFC).
16. Use of investigational drugs within 16 weeks of participation.
17. In build-up phase of immunotherapy for aeroallergens or venom
18. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements, or that may impact the quality or interpretation of the data obtained from the study.
19. Known hypersensitivity to omalizumab or any of its excipients
20. Known hypersensitivity to dupilumab or any of its excipients

4.4 Selection of Clinical Sites/Labs

Additional clinical sites will be assessed as needed.

5 Known and Potential Risks and Benefits to Participants

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

Please see package insert for Xolair (omalizumab), DUPIXENT (dupilumab), and see **IND** [redacted] (Andrew Long, PharmD) for the different foods.

Omalizumab:

Omalizumab is approved by the European Commission and US FDA for patients with moderate to severe

persistent asthma 6 years of age or older, in adults and adolescents 12 years of age and older with chronic idiopathic urticaria who remain symptomatic despite H1 antihistamine treatment, and as an add-on maintenance treatment in patients 18 years of age and older for chronic rhinosinusitis with nasal polyps with inadequate response to nasal corticosteroids. As of 16February 2024, omalizumab has been approved by the FDA for IgE-mediated food allergy in adult and pediatric patients aged 1 year and older for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods; omalizumab is to be used in conjunction with food allergen avoidance.

The most common adverse reactions in asthma clinical studies with adult and adolescent patients ≥12 years of age were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. In clinical studies with pediatric patients 6 to <12 years of age, the most common adverse reactions were nasopharyngitis, headache, pyrexia, upper abdominal pain, pharyngitis streptococcal, otitis media, viral gastroenteritis, arthropod bites, and epistaxis. In chronic spontaneous urticarial trials, the most common adverse reactions (≥2% omalizumab-treated patients and more frequent than in placebo) included the following: nausea, nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, arthralgia, headache, and cough. In patients with IgE-mediated food allergy, ≥ 3% of patients had injection site reactions and pyrexia.

Additional risks include (see package insert):

- Anaphylaxis: Signs and symptoms have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening.
- Malignancy: Malignancies have been observed in clinical studies and the possibility of a relationship between omalizumab and cancer could not be ruled out.
- Eosinophilic conditions: Eosinophilia, vasculitic rash, vasculitis consistent with Churg-Strauss syndrome, worsening pulmonary symptoms, cardiac complications, and/or neuropathy
- Fever, Arthralgia, and Rash: signs and symptoms are similar to those seen in patients with serum sickness
- Parasitic (Helminth) Infection
- Cardiovascular and cerebrovascular events
- Immunogenicity (antibodies to omalizumab)
- Hematologic: Severe thrombocytopenia has been reported

Dupilumab:
Dupilumab has been approved in the US, the EU, and several other countries including Japan for the treatment of 6 months and older with moderate-to severe atopic dermatitis (AD), patients age 12 years and older with chronic rhinosinusitis with nasal polyps as an add-on maintenance treatment, and in patients with moderate-to-severe asthma aged 6 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma as an add-on maintenance treatment. It has been approved in patients 1 year and older (15 kg+) for eosinophilic esophagitis, for the treatment of adult patients with prurigo nodularis, and as an add-on maintenance treatment of adult patients with inadequately controlled chronic obstructive pulmonary disease (COPD) and an eosinophilic phenotype.
Most common adverse reactions (incidence ≥1%) observed in AD trials are injection site reactions, conjunctivitis, blepharitis, oral herpes, hand-foot-and-mouth disease, warts, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye. Most common adverse reactions (incidence ≥1%) in asthma studies are injection site reactions, oropharyngeal pain, and eosinophilia. Most common adverse reactions

(incidence ≥1%) in chronic rhinosinusitis with nasal polyposis are injection site reactions, conjunctivitis, arthralgia, gastritis, insomnia, eosinophilia and toothache.

Additional risks include (see package insert):

- Hypersensitivity: Hypersensitivity reactions include urticaria, rash, erythema nodosum, anaphylaxis, and serum sickness)
- Conjunctivitis and Keratitis
- Eosinophilic Conditions: vasculitic rash, worsening pulmonary symptoms, and/or neuropathy
- Parasitic (Helminth) Infections
- Immunogenicity (antibodies to dupilumab)
- Facial rash or redness
- Cardiovascular: Eosinophilic granulomatosis with polyangiitis, thromboembolic complications, vasculitis
- Arthralgia
- Upper respiratory infection
- For prurigo nodularis indication: Nasopharyngitis, oral herpes, other herpes simplex virus, dizziness (dizziness postural, vertigo, and vertigo positional), myalgia (musculoskeletal pain and musculoskeletal chest pain), diarrhea, antibody development (binding and neutralizing)
- For COPD: injection site reactions, viral infection, headache, nasopharyngitis, back pain, diarrhea, arthralgia, urinary tract infection, local administration reaction, rhinitis, eosinophilia, toothache, and gastritis

Oral Immunotherapy:
Daily food OIT dosing may cause normal allergic reactions, including anaphylaxis. Participants will be prescribed Injectable epinephrine and trained in their use and they will have emergency plans in place with instructions to go to an emergency department in the event of an acute allergic reaction. The likelihood of a subject experiencing allergic symptoms will be lessened by the OIT protocol, starting at small amounts of the FA proteins for dosing under close medical supervision in the Stanford Food Allergy Clinical Research Unit (SNP-CTRU). Escalations are aborted at the first sign of an allergic reaction with equipment and medications (IV fluids, steroid, antihistamine, epinephrine) immediately available to treat allergic reactions. In the previous OIT studies, milder reactions like oral pruritus or abdominal pain have successfully been managed by decreasing the rate of increase of OIT dosing and the use of antihistamines.

Ingesting an offending food allergen on a regular basis may worsen food allergy and result in allergic reactions to the offending food allergy such as hives, stomach pain, vomiting, diarrhea, runny nose, or cough. It may also worsen skin allergy (eczema) or cause decreased weight gain, which will be monitored. Ingesting food allergens may also delay or prevent outgrowing the offending food allergy. The long-term effects of daily offending food allergen ingestion on growth have not been reported. Interruption of daily OIT (missed doses) may also result in the return of allergic reactions.

Food products used for Oral Food Challenges and OIT: the food products used in this study for OIT and oral food challenges are made from commercially available food powders. The powders are not treated. They are tested for bioburden and meet the standards as established by the USP-NF. Mold has been seen in these products. Mold in foods have the possibility of causing an allergic or other adverse events.

Complications of oral immunotherapy: During the initial desensitization period subjects may experience generally mild allergic reactions to the multi-food OIT. Although rare, the risk of severe anaphylaxis to OIT exists. In a recent review of over 352 subject undergoing OIT to peanut, Wasserman et al., reported that 95 subjects required the use of epinephrine at some point in their treatment[28]. However, all cases resolved with the use of epinephrine and none escalated and needed further treatment suggesting that severe reactions during OIT are recognized promptly and treated appropriately.

5.2 Risks of Investigational Product or Intervention cited in Medical Literature

Omalizumab:

To the best of our knowledge, no other risks of omalizumab were cited in the medical literature other than those described in section 5.1 .

Dupilumab:

To the best of our knowledge, no other risks were cited in the medical literature other than those described in section 5.1.

Oral Immunotherapy:

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

EoE is a chronic immune disorder mediated by antigen exposure and is defined by clinical and histopathological criteria, in the absence of other causes. Clinical symptoms may include the following: reflux-like symptoms, abdominal pain and/or vomiting that is refractory to reflux treatment, dysphagia and/or food impaction. These symptoms occur in conjunction with histological evidence of dense eosinophilic infiltration of the mucosa [>15 eosinophils per high-power field (eos/hpf)]. A meta-analysis[31] and a recent retrospective review[32] estimated the incidence of EoE during OIT at rates of 2.7% and 5.1%, respectively. However, OIT-induced EoE-like symptoms resolve with discontinuation of OIT in most affected patients, so that individuals do not undergo an esophagogastroduodenoscopy with esophageal biopsies. A definitive diagnosis of EoE cannot be made without histologic evidence.[33, 34]

There was a recent report of a fatal reaction to rush OIT to milk in a facility in Japan (Gordon Research Conference, Ventura, CA 2018).

The buildup and daily maintenance doses of food OIT may cause allergic symptoms including sneezing, rhinorrhea, urticaria, angioedema, flushing, flares of eczema, ocular, nasal, oral and/or throat pruritus, nausea, vomiting, abdominal discomfort, cough, wheezing and/or shortness of breath in addition to severe

anaphylaxis. Although no subject will be allowed to enroll who carries the diagnosis of eosinophilic disorder, the risk of eosinophilic esophagitis during OIT will be evaluated during the study. The likelihood of a subject experiencing any allergic symptoms is expected to be lessened by initiating dosing at small amounts of characterized food allergen and by buildup dosing under observation in a clinical setting until the maintenance dose is achieved.

Accidental food allergen exposures:
There may be a risk that during participation in the trial subjects may decrease their vigilance against accidental food allergen ingestion because they believe they are protected from them. This phenomenon has been reported in previous trials, and subjects in the trial will be warned that they should continue to practice their usual vigilance against accidental ingestion of these foods.

5.3 Risks of Other Protocol Specified Medications

Epinephrine injection – Common side effects of epinephrine when used properly include anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties. Heart problems and stroke, particularly in the elderly and people with health problems, have been seen. Rare cases of serious skin and soft tissue infections have been reported at the injection site following epinephrine injection in the thigh.
It is very important to use proper techniques when giving epinephrine to avoid injury to the person administering the epinephrine or to the person receiving the injection. In addition to the common side effects above, accidental injection into the finger, hand or foot may result in loss of blood flow to the area causing paleness; coldness; numbness; bruising; bleeding; redness or damage to the bones. Epinephrine should not be injected into the buttocks and has resulted in cases of gas gangrene.

Anti H-1 blockers (e.g., cetirizine, loratadine, fexofenadine), and H-2 antagonists (famotidine) may be used orally according to manufacturer's instructions approximately one hour prior to, or one hour post-ingestion of each food allergen dose at home. The risks of these medications include:

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

5.4 Risks of Study Procedures

Initial Dose Escalation Day Procedure

A potential risk associated with the Initial dose day procedure, up dosing procedure, and oral food challenges is the risk of anaphylaxis. Symptoms of anaphylaxis may include:

- Pruritus
- Wheezing
- Emesis

- Urticaria
- Angioedema
- Cough
- Dyspnea
- Diarrhea
- hypotension that may progress to hypotensive shock.

The potential discomforts with the initial dose day procedure, up dosing procedure, and oral food challenges are no more than when eating the suspected food in the past. The major risks involved include respiratory distress and rarely anaphylactic shock or death. Symptoms are usually transient (lasting less than 2 hours) and include:

- pruritus
- urticaria
- nausea
- abdominal discomfort
- rhinitis
- sneezing
- emesis
- diarrhea
- wheezing

Medication, personnel, and equipment are immediately available in the SNP-CTRU to treat allergic reactions. Subjects will be provided a prescription for an EpiPen or EpiPen, Jr. or equivalent to have with them at all times and to use in case of an allergic reaction.

Risks associated with phlebotomy or insertion of an intravenous catheter include:

- Infection
- Syncope
- Localized Pain
- Stinging
- Bleeding
- Contusions

These risks are associated with the phlebotomy site where the needle is inserted into the vein.

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

Oral food challenges:

Oral food challenges may induce allergic reactions. Allergic reactions can be severe including life-threatening reactions; however, the risk of an allergic reaction is reduced by initiating the challenge with a very small amount of the food, gradually increasing the dose, and stopping the challenge at the first sign of a reaction. If subjects have an allergic reaction during the challenges, they may need oral, intramuscular, or intravenous medications. Subjects may have an IV catheter placed before the DBPCFCs if they have a history of anaphylaxis with hypotension requiring IV fluid resuscitation. Additionally, IV catheters may be placed, at physician discretion for any visit, based on factors such as previous reactions, recent clinical history, and clinical status observed during the visit. Trained personnel, including a study physician, as well as medications and equipment, will be immediately available to treat any reaction. The anticipated rate of life threatening anaphylactic reactions is < 0.1%.

5.5 Potential Benefits

There are no guaranteed benefits to participating in this study. The only possible direct benefit to the participants is, for those participants who develop desensitization as a result of OIT, an ability to decrease their reactions to the offending allergen(s). The likelihood of this is unknown.

6 Investigational Agent/Device/Intervention

6.1 Investigational Agents/Devices/Interventions

Placebo for Omalizumab and Dupilumab

Placebo for biologics will consist of normal saline obtained through each clinical site's medical supplier, either as a vial that is drawn into a syringe prior to administration or as a pre-filled syringe primed to appropriate volumes. Each blinded dose will be prepared by the unblinded staff. Beyond-use dating of final compounded doses will follow guidelines established by USP chapter 797 for compounded sterile preparations. The prepared syringe(s) will be dispensed to and administered by an unblinded injector in a fashion that maintains the blind (i.e., shielded from the view of participants, visitors, and all other blinded individuals). Used syringes will be discarded per site policy in a fashion that maintains the blind.

6.1.1 Omalizumab (Xolair®)

Omalizumab is manufactured by Novartis/Genentech and will be purchased from a commercial vendor.

6.1.1.1 Formulation, Packaging, Labeling, and Storage

Please refer to package insert on omalizumab (Xolair) for formulation, packaging and labeling information. Omalizumab (Xolair®) is available as a 150 mg/mL or 75 mg/ 0.5 mL pre-filled syringe (PFS). It is a clear and colorless solution and should not be used if the liquid contains visible particulate matter or is discolored. The original PFSs should be stored at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. If necessary, pre-filled syringes may be kept at room temperature up to 77°F (25°C) for a cumulative period not exceeding 4 hours. A syringe may be taken out to be warmed up but placed back into the fridge for use at a later time; however, this may not be done more than once, and the cumulative time at room temperature may not exceed 4 hours. Do not expose the syringe to heat or direct sunlight.

6.1.1.2 Dosage, Preparation, and Administration

Omalizumab will be prepared and dispensed by the Lucile Packard Children's Hospital pharmacy. Dosing will follow the Omalizumab Global Dosing schedule as outlined below (per Table 1 and Table 2). Each dose of omalizumab will be dispensed to and administered by an unblinded injector in a fashion that maintains the blind (i.e., shielded from the view of participants, visitors, and all other blinded individuals). Used syringes will be discarded per site policy in a fashion that maintains the blind.

Table 1. Omalizumab Global Dosing Schedule - Omalizumab doses (milligrams/ dose) administered by subcutaneous injection every 2 weeks

Screening IgE (IU/mL)	Body weight (kg)/ Study drug dose (mg)										
	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**	**91-125kg**	**126-150 kg**
101-200										225	300
201-300							225	225	225	300	375
301-400					225	225	225	300	300	450	525
401-500				225	225	300	300	375	375	525	600
501-600				225	300	300	375	450	525	600	
601-700			225	225	300	375	450	525	600		
701-800	225	225	225	300	375	450	450	600			
801-900	225	225	225	300	375	450	525				
901-1000	225	225	300	375	450	525	600				
1001-1100	225	225	300	375	450	600					
1101-1200	300	300	300	450	525	600					
1201-1300	300	300	375	450	525						
1301-1500	300	300	375	525	600						
1501-2000	375mg	450	600	600	600						

Table 2. Omalizumab Doses - Administration every 4 WEEKS - Omalizumab doses (milligrams/ dose) administered by subcutaneous injection every 4 weeks

Screening IgE (IU/mL)	Body weight (kg)/ Study drug dose (mg)										
	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**	**91-125 kg**	**125-150 kg**
30-100	75 mg	75mg	75mg	75mg	150mg	150mg	150mg	150mg	150mg	300mg*	300mg
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									

*225 mg would be sufficient, however 300 mg is recommended per XOLAR asthma prescribing information table.

6.1.2 Dupilumab (DUPIXENT®)

Dupilumab is manufactured by Regeneron Pharmaceuticals, Inc. and will be purchased from a commercial vendor.

6.1.2.1 Formulation, Packaging, Labeling

Please refer to the dupilumab (Dupixent®) package insert for full information on formulation, labeling, packaging, and storage. Dupilumab (Dupixent®) is available as a 300 mg/2 mL or 200 mg/1.14 mL solution in single-dose, PFSs. It is a clear to slightly opalescent, colorless to pale yellow solution and should not be used if the liquid contains visible particulate matter or is discolored or cloudy (other than clear to slightly opalescent, colorless to pale yellow). The original PFSs should be stored at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. If necessary, pre-filled syringes may be kept at room temperature up to 77°F (25°C) for a

maximum of 14 days. Do not store above 77°F (25°C). After removal from the refrigerator, the product must be used within 14 days or discarded. Do not expose the syringe to heat or direct sunlight.

6.1.2.2 Dosage, Preparation, and Administration

Dupilumab will be dosed according to the following algorithm:

- Participants aged 4-17 years old:
  - ≥15kg to <30kg will receive dupilumab 300 mg or placebo SC every 4 weeks following a loading dose of 600 mg at Week 10
  - ≥30kg to <60kg will receive dupilumab 200 mg or placebo SC every 2 weeks following a loading dose of 400 mg at Week 10
  - ≥60kg will receive dupilumab 300 mg or placebo SC every 2 weeks following a loading dose of 600 mg at Week 10

- Participants aged 18 years or older will receive dupilumab 300 mg or placebo SC every 2 weeks following a loading dose of 600 mg at Week 10

Dupilumab will be prepared for dispensing by unblinded pharmacy staff. All PFSs will only be used for a single participant.

Each dose of dupilumab will be dispensed to and administered by an unblinded injector in a fashion that maintains the blind (i.e., shielded from the view of participants, visitors, and all other blinded individuals). Dupilumab will be dosed a maximum of 24 weeks as per the randomized arms. Used syringes will be discarded per site policy in a fashion that maintains the blind.

6.1.3 Multi-OIT (Food Proteins)

SNP Food Allergy Manufacturing Facility: with cross reference to IND [redacted] (Andrew Long, PharmD).

6.1.3.1 Formulation, Packaging, and Labeling

A CMC (Chemistry, Manufacturing and Controls) section is available for each food allergen (see **IND [redacted],** Andrew Long, PharmD).

6.1.3.2 Dosage, Preparation, and Administration

Any food powder will be obtained from the Sean N. Parker Food Allergy Manufacturing Facility and will be stored as per SNP Food Allergy Manufacturing Facility's SOPs. Research staff will administer food powder to the participant orally in an age-appropriate food vehicle. Dosage will be done per the protocol as set forth above.

All food powder products are prepared and fully characterized under SNP Food Allergy Manufacturing conditions.

6.2 Drug Accountability

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

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed. The Pharmacy will keep the unused Xolair®(omalizumab)/Dupixent®(dupilumab) syringes, and used omalizumab/dupilumab syringes will be discarded and not returned to pharmacy. All drug material will be released and recorded by the personnel. All records regarding the disposition of the investigational product will be available for inspection.
The participant will be asked to bring back unused OIT doses and study staff will reconcile OIT accountability.

6.3 Assessment of Participant Compliance with Investigational Agent

Participants (and families) will document daily dosing and any reaction from at-home dosing on diary logs. For food OIT-related symptoms participants will be reminded to report: itching of the tongue or mouth, tongue/mouth/throat pain, lip/tongue/throat swelling, stomach pain, nausea/vomiting, nasal itching or congestion, runny nose, and hives around the mouth or face. For specific symptoms related to the study injection, participants will be reminded to report: injection site pain, redness, tenderness, and swelling. Parents or caregivers should fill out the diary daily for children less than 12 years old. Children 12 years old and above may fill out the diary themselves with parent or caregiver supervision. Monitoring of compliance will be performed by reviewing the participant's diary and monitoring and counting their returned study medication. Unused food allergen OIT doses will be brought back to the SNP-CTRU with each visit and collected by study staff for reconciliation of remaining IP product.

6.4 Toxicity Prevention and Management

Reactions to Omalizumab Injections

Anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of omalizumab. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, participants will be observed closely for two hours after the first 3 omalizumab administrations and 30 minutes thereafter. The research staff will be prepared to manage anaphylaxis that can be life-threatening. We will inform participants of the signs and symptoms of anaphylaxis and will provide them immediate medical care should symptoms occur. A study physician will be present on the unit floor.

Potential risk of fever, arthralgia, and rash due to biologics (Omalizumab and/or Dupilumab)

Some omalizumab-treated participants have experienced arthritis/arthralgia, rash, fever and lymphadenopathy with an onset 1 to 5 days after the first or subsequent injections of omalizumab. These signs and symptoms, similar to those observed in patients with serum sickness due to biologics (monoclonal

antibodies), have recurred after additional doses in some patients. Investigational product will be discontinued if a participant develops these signs and symptoms.

Potential risk for eosinophilic conditions

- Participants with asthma receiving omalizumab or dupilumab may present with serious systemic eosinophilia. These study subjects may present with clinical features of vasculitis consistent with Churg-Strauss syndrome.
- Subjects will be actively monitored for early development of EoE by soliciting for symptoms at each study visit such as gastroesophageal reflux, nausea, vomiting, abdominal pain, dysphagia, choking or gagging with meals, and food impaction *(if participant shows symptoms indicative of early development of EoE, will use the validated pediatric Eosinophilic Esophagitis Symptom Score (PEESS) v2.0 questionnaire (Franciosi et al, BMC Gastroenterology, 2011) to assist with characterization of EoE in pediatric subjects who report gastrointestinal symptoms).* Information on all diagnosed biopsy-confirmed EoE and on the number of subjects who discontinue from the study due to gastrointestinal (GI) symptoms possibly, probably and definitely associated with EoE will be documented. All participants with symptoms concerning EoE will be followed until resolution of clinical symptoms.
- For chronic/recurrent GI symptoms, especially upper GI symptoms, the investigator will refer to a GI specialist for evaluation of suspected EoE when:
  - *Any participant withholds OIT dosing for > 7 days due to GI AEs and is still having GI AEs*
  - *Any participant who develops chronic/recurrent GI AEs as defined by experiencing symptoms for >6 weeks despite dosing adjustments and use of proton pump inhibitors (PPIs)*

In our experience of giving Omalizumab to children and adults with food allergy and/or asthma over the past 11 years at Stanford and Stanford clinics, we have not seen any increase in risk for anaphylaxis, malignancy, cardiovascular, fever, arthralgia, or blood eosinophilia or eosinophilic conditions. Nonetheless, safety will be monitored carefully in pediatric and adult participants. If any symptoms are noted by our trained personnel, we will refer the participants immediately for the care by the appropriate specialist and possibly terminate the participant from the study.

Potential risk for injection site reactions (ISR) persisting longer than 24 hours

Based on the SC mode of administration as well as a higher incidence of local ISRs observed for dupilumab in general, severe ISRs lasting longer than 24 hours are considered as a potential risk. Any severe ISR that persists longer than 24 hours will be recorded.

Potential risk for drug-drug interactions

The clinical significance of the limited in vitro findings for IL-4 and IL-13 involvement in the CYP regulation reported in the literature, and the impact of dupilumab on CYP enzymes are not fully understood. As a precautionary measure, during the study treatment and up to the end of follow-up, caution should be used for drugs with a narrow therapeutic index that are metabolized via the CYP isoforms. The Investigators are advised to use close clinical observation and/or laboratory monitoring, as applicable, to enable early detection of potential toxic manifestations or lack of activity/efficacy of these narrow therapeutic index drugs, followed by dose adjustment or withdrawal if needed.

Reactions to OIT During Initial dose day

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

1. Extend time interval between dosing (up to an additional 30 minutes).

2. Discontinue protocol.

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

For *mild symptoms*, defined as:

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

The action should be either to advance to the next dose in 30-60 minutes, or stop dosing depending on the physician's discretion.

For *moderate symptoms*, defined as:

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

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

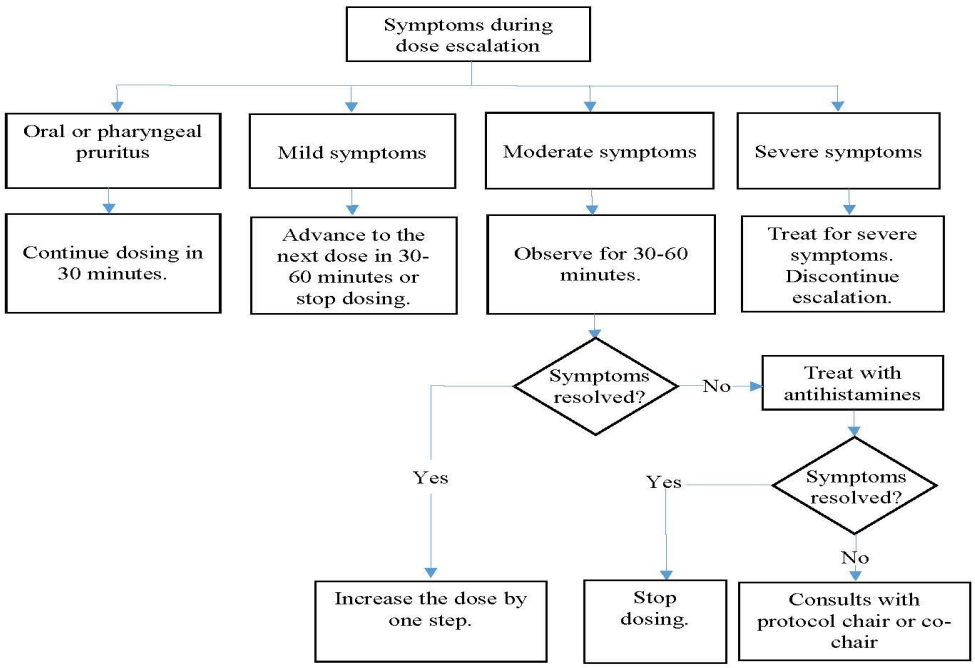
For *severe symptoms*, defined as:

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

The initial escalation dose should be discontinued, and the appropriate rescue medications administered. If the subject requires treatment for symptoms with antihistamines on one occasion during the initial escalation protocol, then the rest of the protocol may be followed. If the subject requires more than one medication (e.g., albuterol, diphenhydramine, epinephrine, or others) or multiple doses of antihistamines, the initial escalation protocol should be terminated. A study physician trained in the protocol will be present on the unit floor.

The PI will be available for questions and decision making for any questions related to the study protocol. All subjects will be observed for a minimum of 2 hours following administration of the final dose and will be discharged only when deemed clinically stable by a study physician.

Figure 3. Management of Symptoms during Initial Dose Escalation Day



Reactions to OIT During Build-up or Maintenance Phase

To be eligible for an up dosing or maintenance dose visit, subjects cannot have active wheezing, spirometry (as per manual of procedures) demonstrating FEV_1 <80% predicted, or a current flare of atopic dermatitis that contraindicates up dosing in the clinical judgment of the study physician. As needed, subjects will be maintained on their current dose of study product until their flare of asthma or atopic dermatitis is resolved. If spirometry is unavailable, peak flow is acceptable.

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

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

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

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

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

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

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

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

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

If, at any point in the study, the subject complains of new onset vomiting, dysphagia, chronic abdominal pain, and/or difficulty swallowing for more than 2 weeks despite use of daily anti acids the subject will be given daily proton pump inhibitors (dosed per age and weight) and if no relief occurs in 2 weeks, they will be referred to a gastroenterologist for assessment of possible gastroenterological disorders associated with food allergy (i.e., eosinophilic esophagitis). The study MOP for managing persistent gastrointestinal symptoms related to OIT dosing will be followed. If at any point, side effects develop from the use of antacids or PPIs, the subject will be discontinued for the concomitant medication and referred to a GI specialist.

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

6.5 Premature Discontinuation of Investigational Agent

Study therapy (omalizumab, dupilumab, or placebos) will be prematurely discontinued for any participant if:

- Significant hypersensitivity to omalizumab or dupilumab develops per investigator decision.
- If the investigator believes that the study treatment is no longer in the best interest of the participant.

Participant may follow up for food challenges and biosample collection.

Study therapy (mOIT) may also be prematurely discontinued for any participant under circumstances that include, but not limited to, the following:

I. Poor control or persistent activation of secondary atopic disease (e.g., AD, asthma)

Circumstances (e.g., concurrent illness, such as gastroenteritis) requiring missed allergen OIT maintenance dosing of > 14 consecutive days

II. Non-adherence with home OIT dosing protocol (excessive missed days; i.e., > 10 consecutive days missed on 3 or more occasions) without consulting with study staff would be a safety issue warranting discontinuation

III. If the investigator believes that the study treatment is no longer in the best interest of the participant.

Participant may follow up for biosample collection.

Follow-up of Subjects Who Discontinue Treatment Only

Subjects who prematurely discontinue treatment with OIT may remain in the study until the end of study visit at Week 44. All willing subjects will come back for week 32 and 44 visits to monitor safety parameters and to obtain biosamples.

Subjects who initiate mOIT therapy (i.e., who do not fail the initial dose escalation day AND initiate home dosing) in this trial will not be replaced.

7 Other Medications

7.1 Concomitant Medications

Protocol-mandated

There is no protocol-mandated concomitant medication(s) to be administered during the study.

Other permitted concomitant medications

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

PPI use will be allowed as detailed under Reactions to OIT During Build-up or Maintenance Phase.

7.2 Prophylactic Medications

There will be no protocol-mandated prophylactic medication(s) to be administered during this study.

7.3 Prohibited Medications

Participants will be removed from the trial if any of the following meds are started:

- Omalizumab (Xolair) that is not part of the study procedure
- Dupilumab (Dupixent) that is not part of the study procedure
- Systemic (oral, IV, IM) corticosteroids used for any greater than 7 days at one time or longer than a total of 3 weeks (21 days) duration each year for asthma. If used, subjects must not be up-dosed until at least 3 days after ceasing the administration of oral steroids
- β-blockers

7.4 Rescue Medications

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

Generally, for mild and moderate symptoms, the subject should receive antihistamines, and for more severe symptoms, the subject should receive epinephrine, antihistamines, and then the other medications as indicated. If a Grade 4 anaphylactic reaction occurs at any time, as defined by Table 6, CoFAR Grading Scale for Systemic Allergic Reactions

v. 3.0, the participant will be terminated per individual stopping rules. All other cases will be discussed with the Protocol Chair/IND holder, Medical Monitor and DAIT/NIAID Medical Officer.

<u>Antihistamines</u>

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

<u>Epinephrine</u>

Any reaction (in SNP-CTRU or at home) that requires two or more doses of epinephrine will require evaluation by study team before further mOIT doses are administered. mOIT dose will be reduced and administered under observation in CTRU. In the event the participant is unable to return to clinic, the participant should contact study clinician for further guidance.

SNP-CTRU

If a single administration of epinephrine is required during in SNP-CTRU escalation, the dose should be reduced by one-two doses, and the subject continued on that dose for two weeks. After 2 weeks at the reduced dose, an escalation attempt may be tried in SNP-CTRU.
If a single administration of epinephrine is required a second consecutive time during this escalation attempt, the dose should be reduced by one-two doses, and the subject continued on that dose for 6-8 weeks. After 6-8 weeks at the reduced dose, an escalation attempt may be tried in SNP-CTRU.
If a single administration of epinephrine is required a third consecutive time during this escalation attempt, dosing will be discontinued, and further treatment or monitoring will be performed as per Appendix 4.

Home

If a single administration of epinephrine use occurs during dosing at home, this epinephrine use is not counted as one of the uses described above, unless severe anaphylaxis occurs at home. The subject should return to SNP-CTRU for an observed dose prior to resuming any dosing at home. In the event the participant is unable to return to clinic, the participant should contact study clinician for further guidance.

8 Study Procedures

8.1 Enrollment

The research study will be explained in lay terms to each potential research participant. If the potential participant is an adult, the participant or parent of a child participant will sign an informed consent form before undergoing any study procedures. Once the informed consent/assent has been signed, the participant is considered enrolled in the study. The purpose of enrollment is to complete the screening phase to determine eligibility. The participant then will be assigned a unique participant number after signing the informed consent/assent document(s).

8.2 Screening/Baseline Visit

The purpose of the screening period is to confirm eligibility to continue in the study. The Screening/Baseline assessments may take place over several visits. All assessments must be completed no more than 12 months (Figure 2) preceding initiation of FA treatment. Specifically, baseline/screening visits following requirements below, conducted under a different protocol within the past 6 months prior to IDED, can be used towards this study; IgE testing and DBPCFCs conducted within 12 months under a different protocol to a cumulative dosage of 444mg or less of food allergen can be used towards the study.
The following procedures, assessments, and laboratory measures will be conducted to determine participant eligibility:

- Consent and Assent
- Medical history, including review of all food allergies
- Physical Assessment
- Con meds and adverse events

- Blood draw for allergen-specific IgE and IgG4 measurement, CBC with differential, and mechanistic studies
- Skin prick test (SPT) to FA extracts (neat extract with no dilution, Greer Laboratories, Lenoir, NC)
- Spirometry
- Questionnaires
- Fecal and urine sample collection (optional)
- Skin swabs, saliva and buccal swab collection (optional)
- Epi training
- Pregnancy test, if subject is a female who has undergone menarche and is of childbearing potential (i.e., not otherwise incapable of having children from a previous medical condition, surgery, or other circumstance)
- DBPCFC to a cumulative 444 mg of each food allergen protein

Any of the above items may be repeated within the screening period preceding initiation of study treatment if warranted, in the opinion of the investigator, by changes in the subject's clinical status.
Once participant was determined eligible to participate in the study, s/he will be randomized to one of the 3 study cohorts in a 5:5:1 ratio. Randomization will occur within 2-4 weeks of eligibility confirmation.

The following procedures, assessments, will be conducted within 12 months prior to determine participant eligibility:

Double-Blind Placebo-Controlled Food Challenge (DBPCFC) During the Screening Process
Randomization and preparation of the challenge materials will be performed by trained study personnel in the SNP Food Allergy Manufacturing facility at Stanford. Prior to the food challenge, subjects will be asked to restrict the use of oral antihistamines (five half-lives), beta-agonists (12 hours), theophylline (12 hours), and cromolyn (12 hours).

The screening DBPCFC will consist of 6 doses given every 15-30 minutes in increasing amounts up to a cumulative total of =/<444 mg of FA protein. If the study team suspects a reaction may be developing, they may exercise their clinical judgment to separate doses by up to an additional 30 minutes (one hour maximum between doses). The other challenge will consist of placebo material given also in 6 doses. The doses will be 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, and 300 mg (see Table 3). Before each challenge, the subject will have a physical assessment administered by a trained physician's assistant, registered nurse, nurse practitioner, and/or physician of the study team who is blinded to the testing material. The supervising investigator will also be blinded to testing material.

Reactions will be scored using a Food Challenge Symptom Score sheet (see criteria in section 12.4.1). If the subject begins to have any objective symptoms or subjective symptoms deemed clinically significant, the food challenge will be terminated, and the subject will be given appropriate treatment. The subject will be observed for a minimum of two hours after the final administered dose and discharged only when deemed clinically stable by a study clinician. All food challenges will be performed under physician supervision. If the

subject has no symptoms related to allergic reactions to the food allergen ingestion with the DBPCFC, they will not be enrolled in the study.

Table 3: Dosing Regimen for DBPCFC at Screening and Week 32/44

Dose #	Screening Food Protein/Placebo (mg protein)	Week 32/44 Food Protein/Placebo (mg protein)
1	1	3
2	3	10
3	10	30
4	30	100
5	100	300
6	300	600
7		1,000
8		2,000

8.3 Study Visits or Study Assessments

Xolair/Placebo Pretreatment (weeks 0-8)

After enrollment, participants will be treated every two weeks or four weeks (per Table 1 and table 2. Omalizumab Global Dosing Schedules) with either omalizumab or placebo for 8 weeks. Diaries will be given at the randomization visit.

Allergen-Specific OIT Treatment Overview

Food allergen OIT administration will include an Initial dose escalation day (IDED) with oral immunotherapy dosing occurring at the Stanford SNP-CTRU.

A targeted history and physical assessment will be performed at each in person visit. Physical assessments performed in this protocol will be allergy focused and include the following systems: eyes, ears, nose, and throat; lungs; heart; abdomen; and skin. Subjects will be assessed for exacerbation of atopic dermatitis or asthma (as determined by active wheezing) prior to each in-SNP-CTRU dosing. In the presence of an exacerbation of atopic dermatitis, the study physician will use their professional judgment in deciding whether the exacerbation should preclude an attempt at up dosing. In the presence of wheezing noticed on exam the participant will remain at their current dose for two additional weeks. That day's dose may be administered in the SNP-CTRU and monitored.

In addition to dosing visits, subjects will return to the SNP-CTRU at designated visits (see Figure 2) for their DBPCFCs or other assessments/blood draws. A medical and diary review, and targeted physical assessment will also be performed at these visits. DBPCFCs will occur at screening, end of maintenance phase (Week 32), and end of study (Week 44).

Initial Dose Escalation Day (week 8, IDED)

At week 8, all participants will undergo an Initial Dose Escalation Day (IDED) for 2 or 3 foods chosen starting at a dose of 1 mg of protein of food allergen (FA) and escalating to 10 mg, 50 mg, 100 mg, 210 mg, 420 mg, and 1,000 mg (Table 4). Participants who tolerate the 1,000-mg dose per food will continue on that dose until week 32. Participants that fail to reach the 1,000-mg dose of each FA will receive the highest tolerated dose on IDED as their home dose and then return to the clinic in two weeks for up dosing to the next step. Participants may return to the clinic the next day (IDED+1) for an observed dose if deemed necessary by the Investigator. If the participant can start the home dosing the day after the IDED (i.e. IDED+1) they do not need to take that dose in clinic as they have already had that dose effectively observed. If the first home dose cannot be taken the day after IDED (i.e., IDED+2 or greater) the first dose will be an observed dose in clinic. These attempts will continue until week 30 and until they reach 1,000 mg of each FA, while receiving dupilumab or placebo every 2 to 4 weeks. At week 32, participants will discontinue dupilumab or placebo treatment and will undergo DBPCFCs. Participants who tolerate food challenges to any food with a cumulative dose of ≥1,043 mg with no or mild objective reactions of the FAs in their OIT at the DBPCFCs at week 32 will stop active OIT dosing and undergo DBPCFCs at week 44. Those with no or mild objective reactions to a cumulative dose of ≥1,043mg of the FAs at week 44 will be considered as achieving sustained unresponsiveness and will have successfully met the primary endpoint.

Table 4: IDED FA combined dose

2 allergens (1:1) dose (mg)	3 allergens (1:1:1) dose (mg)
2	3
20	30
100	150
200	300
420	630
840	1,260
2,000	3,000

The Initial Dose Escalation Day will be completed at the SNP-CTRU and will consist of OIT dosing, starting at a dose of 1 mg of protein of food allergen (FA) and escalating to 10 mg, 50 mg, 100 mg, 210 mg, 420 mg, and 1,000 mg. Participants will be given a total amount of protein multiplied equally by the number of allergens included in their OIT. Each food allergen is separately put in water or an appropriate food vehicle and then swallowed by the participant. The food vehicles that will be used are applesauce, chocolate pudding or vanilla pudding. The pudding does contain milk and will only be used for participants who are not allergic to cow's milk.

Subjects will not have active wheezing, spirometry demonstrating FEV1 <80% predicted, or a current flare of atopic dermatitis that contraindicates dosing in the clinical judgment of the study physician. If spirometry is unavailable, peak flow is acceptable. A physician will be present at all times during any of the SNP-CTRU food allergen OIT dosing visits and will be available to respond within 60 seconds to any allergic reaction.

Build Up Phase with Dupilumab or Placebo (Week 8 – 32)

Participants who tolerate the 1,000-mg dose per food will continue on that dose until week 32. Participants that fail to reach the 1,000-mg dose of each food allergen will receive the highest tolerated dose on IDED the next day as their home dose and then return to the clinic in two weeks for up dosing to the next step. Participants may return to the clinic the next day (IDED+1) for an observed dose if deemed necessary by the Investigator. If the participant can start the home dosing the day after the IDED (i.e. IDED+1) they do not need to take that dose in clinic as they have already had that dose effectively observed. If the first home dose cannot be taken the day after IDED (i.e., IDED+2 or greater) the first dose will be an observed dose in clinic. These attempts will continue until week 30 and/or until they reach 1,000 mg of each FA, while receiving dupilumab or placebo every 2 to 4 weeks. Diaries will be reviewed at each clinic visit.

Any up-dosing attempts may be postponed for 1-2 extra visits based on clinical judgment. However, an up-dosing attempt must be made within a maximum of 3 consecutive scheduled clinic visits.

Subjects should withhold their daily home dose and any prophylactic antihistamines on the in-SNP-CTRU up dosing day but should take all other prescribed medications. Note that the daily home dose should be taken as part of a meal at a consistent time (within 24±2 hours of the previous day's dose), and it is critical to take the dose every day. Doses should be separated by at least 12 hours. Subjects who require dosing reduction during the 2-week period due to illness will undergo an attempted up-dosing only after resuming their full dose for a minimum 3 days.

As stated above, an up-dosing attempt must be made within 3 clinic visits on a given dose, unless up dosing is delayed due to administration of epinephrine as defined in Section 7.4 or illness. If the subject fails to successfully increase up dosing for three consecutive attempts, up dosing will be halted at the last tolerated dose and the participant will be considered a treatment failure. Further treatment or monitoring will be performed per Appendix 4.

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

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

In the event of an epidemic/pandemic or other unforeseen circumstances during which the participant cannot come into clinic, we will plan to send OIT doses to their homes/residences, and/or perform home visits or telehealth visits. Subjects may be maintained on the previously tolerated OIT dose until a dose-escalation can be performed safely.

Placebo/Dupilumab and OIT (Week 8 – 32): Cohort A will receive placebo injections over the next 24 weeks. Cohort B will receive dupilumab every 2 to 4 weeks for 24 weeks. Cohort C will receive dupilumab every 2 to 4 weeks for 24 weeks. At week 8 participants will begin their OIT as above. Participants must escalate to 1,000mg each FA on/before the end of the week 30 visit otherwise they will be deemed a treatment failure. Further treatment or monitoring will be performed per Appendix 4. Based on our previous data we expect all subjects on active treatment to reach 1,000 mg of each FA between week 8 and week 24 visits.

Maintenance Phase (Week 30-32 minimum): The maintenance phase starts when the participant reaches 1,000 mg for each FA until the end of their week 32 DBPCFCs (after which they stop OIT dosing and enter sustained unresponsiveness phase). Even after tolerating the maintenance dose of 1,000 mg of each FA, it is possible that the activity of allergic cells (i.e., mast cells, basophils, eosinophils) will increase as the level of omalizumab/dupilumab/placebo decreases. Therefore, participants 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.

First DBPCFC (Week 32): At the conclusion of the maintenance phase (week 32), participants will undergo DBPCFCs for each FA in their OIT on separate days**.** The visit will also include a physical assessment, spirometry, optional samples (fecal, urine, buccal swab, skin swabs, saliva collection), and blood draw for mechanistic studies. If spirometry is unavailable, peak flow is acceptable. The subject's sensitivity to food allergen is defined as the dose at which the subject experiences allergic reactions. All symptoms and signs will be evaluated and rated per **Table 6**.

During or prior to the oral food challenge, there should be increased hydration (i.e. about 16 oz for an adult and a proportionate amount for a child).

Up dosing during the DBPCFCs will be stopped when the Principal Investigator (or study physician) finds symptoms and/or signs that indicate a definite allergic reaction (objective or subjective) has occurred based on clinically significant changes in reported symptoms, physical findings, or vital signs that the subject is experiencing to the challenge material. The challenge will consist of doses consistent with PRACTALL guidelines (mg protein of food allergen: 3, 10, 30, 100, 300, 600, 1,000, 2,000) (see Table 3). The FA proteins and oat protein will be concealed in a food that masks the taste. After the last dose of the DBPCFC, the subject will be monitored for 2 hours and then discharged home. Subjects will be considered to have tolerated the DBPCFC if they do not experience any objective reactions (see Table 6).

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

Participants that tolerate any foods included in the OIT mix with no or mild objective reactions (Table 6) to a cumulative dose of ≥1,043 mg of the FAs in their OIT at the DBPCFCs at week 32 will continue into the withdrawal phase. At week 44, participants will undergo DBPCFCs to the foods tolerated at week 32. If the participant fails all DBPCFC evidenced by not tolerating ≥1,043 mg of any protein at week 32, they are deemed a treatment failure and are discontinued from the study protocol and advised to follow-up with their allergist for further instructions.

Withdrawal Phase (Week 32 to Week 44): After the week 32 DBPCFCs, OIT will be discontinued and the

participants will be off OIT until week 44. This withdrawal phase is designed to examine mechanisms underlying sustained unresponsiveness (SU). At week 44, after 12 weeks off OIT, participants will undergo DBPCFCs on separate days only to those foods to which they were desensitized at week 32**.** The subject's sensitivity to food allergen is defined as the dose at which the subject experiences allergic reactions. All symptoms and signs will be evaluated and rated based on a standardized oral food challenge scoring system (see Table 6).

During or prior to the oral food challenge, there should be increased hydration (i.e. about 16 oz. for an adult and a proportionate amount for a child).

Up dosing during the DBPCFCs will be stopped when the Principal Investigator (or designee) finds symptoms and/or signs that indicate a definite allergic reaction (objective or subjective) has occurred based on clinically significant changes in reported symptoms, physical findings, or vital signs that the subject is experiencing to the challenge material. The challenge will consist of doses consistent with PRACTALL guidelines. The FA proteins and oat protein will be concealed in a food that masks the taste. After the last dose of the DBPCFC, the subject will be monitored for 2 hours and then discharged home. Subjects will be considered to have tolerated the DBPCFC if they have no or mild objective reactions (Table 6).

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

Participants who pass their food challenges with no or mild objective reactions (Table 6) to a cumulative dose of ≥1,043 mg of the food allergens in their OIT at the end of this phase will be considered to have achieved sustained unresponsiveness, and completed the study. If the participant fails a DBPCFC evidenced by not tolerating ≥1,043 mg each protein they are deemed a sustained unresponsiveness failure and are advised to follow-up with their allergist for further instructions.

The DBPCFC visits will include a physical assessment, spirometry, optional samples (fecal, urine, saliva, buccal swab and skin swabs sample collection), and blood draw for mechanistic studies. If spirometry is unavailable, peak flow is acceptable.

8.4 Unscheduled Visits

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

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

8.5 Visit Windows

Study visits should take place within the time limits specified below: the designated visit windows for each scheduled visit are also indicated on the Table 5 of Schedule of Events. A minimum of 10 days is required between doses of omalizumab/ placebo and a minimum of 7 days between doses of Dupilumab/placebo for participants that are on every two-week injections. For participants that are on every 4-week injections, a

minimum of 14 days is required between doses of omalizumab/placebo, and a minimum of 21 days between doses of Dupilumab/placebo.

Table 5. Visits window

Visit Type	Target Date	Visit Window
Screening/Baseline/Randomization	Day -168 to 0	+/- 12 weeks
Omalizumab/dupilumab/placebo Treatment	Week 0 to 8	+/- 7 days
Initial Dose Escalation Day (IDED)	Week 8	+/- 7 days
Dose Escalation visits	Every 2 weeks until week 32	+/-7 days
Desensitization DBPCFCs	Week 32	+/-14 days
Sustained Unresponsiveness DBPCFCs	Week 44	+/-14 days

9. Mechanistic Assays

9.1 Serum Assays

Panel	Volume needed for each sample collection
Specific IgE, IgG4, IgA anti-food allergen and the component-resolved testing where applicable	1 ml
Epitope Arrays	350 microliters

Expected Results for Serum Parameters

Parameter	Desensitization	Sustained Unresponsiveness (SU)
Specific IgE And Specific IgG4	Progressive decrease in specific IgE to food allergen (FA) and increase in specific IgG4	Low specific IgE and increased IgG4
Epitope Array for IgE for FA peptides—predictive marker for outcome	Progressive Inhibitory antibodies present in epitope array	Intermediate epitope spreading at baseline
Specific IgA	Progressive increases in specific IgA over time	Intermediate levels of specific IgA

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

9.2 Cell components for CyTOF

Expected Results for Cell Parameters

Parameter	Desensitization	Sustained Unresponsiveness (SU)
Th2	Progressive decrease in Th2 absolute numbers and ICS transcription factors and Th2 cytokines	Low Th2 cells and low ability to proliferate in response to FA
Th1	Progressive increase in Th1 absolute numbers and ICS transcription factors and Th1 cytokines	High Th1 cell numbers and ability to proliferate in response to FA
Th17	Do not expect change	Do not expect change
Treg	Progressive increase in absolute counts of Treg but then decline by 12 mo.	Intermediate Treg cell numbers and decreased ability to proliferate in response to FA
NKT	Progressive increase in absolute counts of NKT cells	Intermediate NKT cell numbers associated with desensitization
DC	Progressive decrease of TSLP receptor in mDCs, progressive increase in CD103 and CCR9 in DCs	Intermediate TSLP receptor expression in mDCs and intermediate DC expression of CD103 and CCR9
Cell death markers	Progressive increase in cell death of allergen-specific Th2 memory cells	Intermediate cell death of allergen-specific Th2 memory cells
Chemokine receptors	Progressive increase in CCR4 and CCR8 in Treg	Intermediate expression of CCR4 and CCR8 in Treg
Allergen specific cells	Switch from mostly Th2 to Th1 or Treg subset over course of therapy	Intermediate decrease in Th2 cytokines and trans factors

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

Up to six 10ml EDTA purple top tubes (about 60 ml whole blood) will be collected.

9.3 Sample Basophil Assay:

Expected Results for Basophil Activation Parameters

Parameter	Desensitization	Sustained Unresponsiveness (SU)
CD203c/CD63	During course of therapy, will see decrease in basophil reactivity sooner than lowering of specific IgE in participants	Basophil reactivity decreases.

4 ml of whole blood in a sodium heparin green top tube will be collected.

9.4 Sample B cell Repertoire Assay:

Expected Results for B cell Receptor Repertoire Features

Parameter	Desensitization	Sustained Unresponsiveness (SU)
IgG4 expression in members of clones containing IgE+ B cells	Increased numbers of IgE+ clones that contain IgG4-expressing B cell members	Further increased numbers of IgE+ clones that contain IgG4-expressing B cell members

No additional blood draw required as this will be part of the six 10 ml purple top tubes collected for the CyTOF assays.

Logistics: Blood samples will be collected at timepoints indicated in the schedule of events during the subject's participation in the study. Volumes collected will follow NIH guidelines (for children: 5 ml/kg at any single draw, no more than 9.5 ml/kg over an 8-week period; over 18 years old: the smaller of 10.5 ml/kg or 550 ml total at any single draw).

10. Biospecimen Storage

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

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

11.1 Participant Completion

Completion of the study will be defined as reaching the Week 44 visit.

11.2 Participant Stopping Rules and Withdrawal Criteria

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

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
3. The participant dies.
4. The Investigator no longer believes participation is in the best interest of the participant.
5. Individual safety stopping rules
    a. Anaphylaxis resulting in hypotension, neurological compromise or mechanical ventilation secondary to OIT dosing, injections, or any food challenge
    b. The subject develops biopsy-documented eosinophilic esophagitis (EoE) with synchronous symptoms or other eosinophilic gastrointestinal disease
    c. Any subject deemed to have severe allergic reactions and who receives aggressive therapy (e.g., mechanical ventilation, three or more doses of epinephrine for a life-threatening reaction) at any time should be discontinued from further therapy
6. Other circumstances including, but not limited to, the following:
    a. Poor control or persistent activation of secondary atopic disease (e.g., AD, asthma)
    b. Started on beta-blockers, or other prohibited medications, with no alternative medications available per the prescribing physician
    c. Pregnancy

11.3 Participant Replacement

Participants who withdraw or are withdrawn will not be replaced.

11.4 Follow-up after Early Study Withdrawal

Subjects who prematurely discontinue treatment with OIT may remain in the study until end of study visit at week 44. All willing subjects will be attempted to be followed and will be asked to come back at week 32 and 44 to monitor safety parameters. These visits will include skin testing and a blood draw for mechanistic studies.

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

11.5. Study Stopping Rules

The study may be prematurely terminated for the following reasons:

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

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

- Any death related to dosing or study procedure.
- More than three participants requiring more than two injections of epinephrine during a single OIT dosing
- More than 1 case of CoFAR Grade 4 AE (Table 6) related to food allergen dosing
- More than 2 cases of CoFAR Grade 4 AE (Table 6) related to oral food challenge
- More than 3 serious adverse events, related to investigational product or
- More than 3 cases of eosinophilic esophagitis with synchronous clinical symptoms and confirmatory biopsy findings

If any of the stopping rules listed below are met, injections will be paused and participants will remain on their current OIT dose pending expedited review of all pertinent data:

- More than one participant requiring more than two injections of epinephrine during a single omalizumab/placebo or dupilumab/placebo injection

12. Safety Monitoring and Reporting

12.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse Events (AEs) that are classified as serious and unexpected according to the definition of health authorities must be reported promptly (per Section 12.5, *Reporting of Serious Adverse Events and Adverse Events*) to the IND sponsor, Medical Monitor and the DAIT/NIAID Medical Officer. Appropriate notifications will also be made to site principal investigators (PIs), Institutional Review Boards (IRBs), and health authorities, as needed.

Information in this section complies with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6 (R2): Guideline for Good Clinical Practice (GCP): Integrated Addendum to ICH E6 (R1), 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. A study physician licensed to make medical diagnoses will be responsible for all trial-related medical decisions.

12.2 Definitions

12.2.1 Adverse Event

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

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

- All symptoms or events, that occur within two hours and that are expected according to the Protocol and related to administration of Multi-allergen OIT or oral food challenge will be recorded as a dosing reaction, not an AE. However, episodes in response to home dosing that are Grade 3 by Table 6 Criteria or that are classified as SAEs defined in Section 12.2.4 below, will be recorded on the AE/SAE CRF as appropriate.

Any symptom or event that occurs more than two hours after Multi-allergen OIT will be recorded as an AE on the AE eCRF but will not be identified as a dosing reaction.

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

Study therapy regimens:

Omalizumab/ Placebo
Dupilumab/ Placebo
In-Clinic OIT dosing
Home OIT Dosing
For the study-mandated procedures below, only the signs and symptoms listed under each procedure will be considered outside normal range and will be recorded as an AE. For all other study-mandated procedures, all AEs will be recorded.

Skin Prick Test

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

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

Blood Draw

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

- Syncope/vasovagal events
- Bruising at the puncture site larger than 2 cm diameter
- Bleeding from the puncture site lasting more than 30 minutes
- Induration/swelling at the puncture site larger than 2 cm diameter
- Allergic reaction to local skin anesthetic that requires rescue medications
- Infection at the puncture site

12.2.2 Suspected Adverse Reaction

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

12.2.3 Unexpected Adverse Event

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

"Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a).

12.2.4 Serious Adverse Event

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

- Death
- A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the PI or Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death

- Inpatient hospitalization or prolongation of existing hospitalization, (excludes hospitalization for continued observation of allergic reaction for potential of biphasic reaction).
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly or birth defect
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

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

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

12.3 Pregnancy Reporting

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

The PI/co-PI (Site PIs), shall report simultaneously via email to the Protocol Chair/Sponsor, Medical Monitor and the DAIT/NIAID Medical Officer all pregnancies within 24 hours of becoming aware of the event using the Pregnancy CRF. All pregnancies identified during the study shall be followed to conclusion. Follow-up information detailing the outcome of the pregnancy should be documented as it becomes available.

Information requested about the delivery shall include:

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

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

12.4 Grading and Attribution of Adverse Events

12.4.1 Grading Criteria

The study site will grade the severity of all non-allergic 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) Version 5.0. 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 or disabling.

Grade 4 = life-threatening or urgent intervention.

Grade 5 = death.

Events grade 1 or higher will be recorded on the appropriate AE paper case report form (CRF) for this study.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that does not meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

Table 6: CoFAR Grading Scale for Systemic Allergic Reactions v.3.0

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

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

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

Table 7. Clinical Criteria for Diagnosing Anaphylaxis (Sampson, HA, Et. Al, 2006[38])

DESCRIPTION		EXAMPLE SIGNS AND SYMPTOMS	TIMING OF ONSET
Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:			
1.	**Acute onset of an illness with involvement of the skin, mucosal tissue, or both AND AT LEAST ONE OF THE FOLLOWING:**	Generalized hives, pruritus or flushing, swollen lips-tongue-uvula	Minutes to several hours
a. Respiratory compromise		Dyspnea, wheeze-bronchospasm, stridor, reduced Peak expiratory flow (PEF), hypoxemia)	
b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction		Hypotonia [collapse], syncope, incontinence	
2.	**Two or more of the following that occur rapidly after exposure to a likely allergen for that patient**		Minutes to several hours
a. Involvement of the skin-mucosal tissue		Generalized hives, itch-flush, swollen lips-tongue-uvula	
b. Respiratory compromise		Dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia	
c. Reduced BP or associated symptoms		Hypotonia [collapse], syncope, incontinence	
d. Persistent gastrointestinal symptoms		Crampy abdominal pain, vomiting	
3.	**Reduced BP after exposure to known allergen for that patient**		Minutes to several hours
a. Infants and children		Low systolic BP* (age specific) or greater than 30% decrease in systolic BP	
b. Adults		Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline	

***Low Systolic BP is defined as less than (70 + [2 x age]) mm Hg**

12.4.2 Attribution Definitions

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

12.4.2 Attribution of Adverse Events

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

12.5 Collection and Recording of Adverse Events

12.5.1 Collection Period

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

12.5.2 Collecting Adverse Events

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

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

12.5.3 Recording Adverse Events

Throughout the study, the investigator will record all AEs and SAEs as described previously (Section 12.2) on the appropriate AE/SAE eCRF regardless of the relationship to study therapy regimen or study procedure.

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

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

12.6.1 Reporting of Serious Adverse Events, and Pregnancies

This section describes the responsibilities of the site investigators and the Sponsor to report SAEs and pregnancies to the FDA, Medical Monitor and the DAIT/NIAID Medical Officer. Timely reporting of AEs is required by 21 CFR and ICH E6 guidelines.

Site PIs/co-PIs will report all SAEs and/or pregnancies (see Sections 12.2 and 12.3), regardless of relationship or expectedness, via an email to the Protocol Chair/Sponsor, Medical Monitor and the DAIT/NIAID Medical Officer within 24 hours of discovering the event.

For SAEs, all requested information on the SAE form will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the SAE form will be updated and submitted. Initial SAE notification will include as much information as possible, but at a minimum must include the following:

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

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

12.6.2 Reporting to the FDA

After an SAE requiring 24-hour reporting (see Section 12.6.1, Reporting of Serious Adverse Event) or pregnancy is submitted via the SAE form by the site PI/co-PI, it will be assessed by the Medical Monitor, the Protocol Chair/IND Sponsor, and DAIT/NIAID Medical Officer. The IND Sponsor must report the event to the FDA using one of two categories.

12.6.2.1 Expedited Safety Reporting

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

- **Serious and unexpected suspected adverse reaction [SUSAR]** (see Sections 12.2.3 and 12.2.4 and 21 CFR 312.32(c)(1)).

  The IND Sponsor shall report any suspected adverse reaction (SAR) that is both serious and unexpected. The IND Sponsor shall report an SAE as a SAR only if there is evidence to suggest a causal relationship between the study drug and the SAE, such as:

  1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
  2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug
  3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the

study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

- **Any findings from studies that suggests a significant human risk**

  The IND Sponsor shall report any findings from other clinical, epidemiological studies, pooled analysis of multiple studies, or any finding from animal or *in vitro* testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, package insert, or other aspects of the overall conduct of the study.

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

12.6.2.2 Standard Reporting (report in the IND Annual Report)

The IND Sponsor, will include in the IND annual study report to the FDA all adverse events classified as:

o Serious, expected, suspected adverse reactions (see Section 12.2.2, *Suspected Adverse Reaction,*
and Section 12.2.3, *Unexpected Adverse Event*).

o Serious and not a suspected adverse reaction (see Section 12.2.2, *Suspected Adverse Reaction*).

o Pregnancies.

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

12.6.3 Reporting of Adverse Events to IRBs

Site PIs/Co-Is shall report AEs and SAEs in a timely fashion to their local IRB in accordance with applicable regulations and guidelines.

12.6.4 Reporting of Other Safety Information

The Protocol Chair/Sponsor shall promptly notify the Medical Monitor and DAIT/NIAID Medical Officer via email when an “unanticipated problem involving risks to participants or others” is identified, which is not otherwise reportable as an AE.

12.7 Review of Safety Information

12.7.1 Medical Monitor and DAIT/NIAID Medical Officer Review

The study Medical Monitor and DAIT/NIAID Medical Officer, shall receive monthly reports from the Sponsor compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the Clinical Trial Research Units (CTRUs) on appropriate CRFs.

In addition, the Medical Monitor shall review and make recommendations on the disposition of the SAE and pregnancy reports received by the Sponsor from all clinical sites (see Sections 12.6.1 and 12.3). The DAIT/NIAID Medical Officer may provide input to the Medical Monitor.

12.7.2 DSMB Review

12.7.2.1 Planned DSMB Reviews

The NIAID Allergy and Asthma Data and Safety Monitoring Board (DSMB) shall review safety data twice per year during planned DSMB Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs, major and non-major deviations, that will be created by the IND Sponsor.

12.7.2.2 Ad hoc DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for ad hoc reviews when a study stopping rule (Section 11.5) is met or if an event occurs that is of sufficient concern to the DAIT/NIAID Medical Officer, and/or the Medical Monitor and/or the IND Sponsor/Protocol Chair to warrant a DSMB review. The DSMB will be notified within 24-48 hours by the DAIT/NIAID Medical Officer and will promptly review any such event. After review, the DSMB will make recommendations regarding study conduct and/or continuation.

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

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

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

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

13. Statistical Considerations and Analytical Plan

13.1 Overview

This phase 2 study in multi-OIT concomitant with omalizumab and/or dupilumab treatment in participants ages 4-55 years that are allergic to multiple food including peanut, intends to identify immune mechanisms that explain the effect of multi-OIT in individuals who do or do not become clinically tolerant and to determine whether immune monitoring can predict safety and therapeutic outcomes in multi-OIT protocols. The primary analysis is an intent-to-treat comparison of sustained unresponsiveness success rates between participants who received omalizumab, placebo plus OIT (cohort A) vs. participants who received omalizumab, dupilumab plus OIT (cohort B), where sustained unresponsiveness success is defined by reaching and passing the DBPCFC at 44 weeks with no or mild objective reactions (Table 6). Each food allergen the participant is taking will be decided at baseline (screening phase) and documented in the chart and will not be changed throughout the immunotherapy process. Secondary endpoints will include the intent-to-treat comparisons of week 44 success rates and week 32 success rates among cohorts A, B, and C, with no or mild objective reactions (Table 6). Additional secondary endpoint include: 1) to compare the abilities among treatment cohorts to pass DBPCFCs for each FA at a cumulative dose of ≥1,043 mg, ≥ 2,043 mg, or ≥4,043 mg at week 32 and/or week 44; and 2) to compare the proportions of participants who have a 10-fold change in the cumulative tolerance dose for each FA at weeks 32 and/or week 44 compared to baseline across FAs within each cohort and across cohorts for each FA. Evaluation of the statistical significance of differences in desensitization or sustained unresponsiveness success rates between groups will be evaluated using a Pearson chi-square test. A Fisher's exact test will be used if expected cell counts are low (<5). The multivariable logistic regression will also be conducted as the supportive analysis. Additional tertiary mechanistic endpoints will be evaluated in the study, using immunological assays including those described in Section 9 above. A number of regression techniques will be applied to these assay results to address our aims. Specifically, we will utilize methods such as generalized linear mixed effects models (GLMMs) to estimate associations of interest, particularly when correlating changes in features over time to clinical phenotypes (e.g., achieving desensitization vs. SU). In addition, methods appropriate for right-censored data (time to achieving desensitization) such as the Cox proportional hazards model also will be considered. We also will use methods such as the Least Absolute Selective Shrinkage Operator (LASSO) to identify immunophenotypes that correlate with clinical outcomes and to identify epitopes and/or clonotypes associated with clinical phenotypes. Such methods are appropriate when jointly considering a large number of correlated features, as we anticipate with data generated from the CyTOF platform. Finally, we will consider hierarchical clustering techniques to explore the clustering of both mechanistic features and patients, to provide insight into whether mechanistic features can be used to describe clinical phenotypes of interest.

13.2 Endpoints/Outcomes

Primary Endpoint:

The primary endpoint (via hierarchical design) is: i) the success rates of passing a peanut DBPCFC, ii) the success rates of passing a DBPCFC to peanut and at least one other FA, and iii) the success rates of passing a DBPCFC to peanut and two other FAs, where for all three endpoints, success is defined as

passing a cumulative dose of ≥ 1,043 mg at the Week 44 DBPCFC if the subject has no or mild objective reactions.

Secondary Endpoints:

Clinical endpoints:

- Proportion of participants who successfully pass DBPCFCs to a cumulative dose of ≥1,043 mg protein to 1, 2, or 3 FAs when applicable at week 44 (SU).
- The proportion of participants who successfully pass DBPCFCs to a cumulative dose of ≥2,043 mg to 1, 2, or 3 FAs when applicable at week 32.
- Proportion of participants who pass DBPCFCs for each FA at a cumulative dose of ≥1,043 mg, ≥2,043 mg, or ≥4,043 mg at week 32 and/or week 44.
- Proportion of participants who have a 10-fold change in the cumulative tolerance dose for each FA at weeks 32 and/or week 44, compared to baseline.

Exploratory and Mechanistic Endpoints:

- Differences in immunological responses, as measured by allergen-specific and non-specific markers, such as free allergen-specific IgE, specific IgG4, total IgE, IgG4/IgE ratios, basophil activation tests (BAT), basophil phenotyping, BCR (B cell receptor) repertoire features, B cell phenotyping, TCR (T cell receptor) levels, T cell phenotyping, and other immune-related cells measured at:
  - Baseline
  - IDED at week 8
  - End of maintenance (desensitization) phase at week 32
  - End of withdrawal (sustained unresponsiveness) phase at week 44
- Quality of life questionnaire at baseline, week 32, and week 44.
- Time to maintenance by arm and by number of FAs

Safety Endpoints

- Frequency of AEs, SAEs, and safety events in each cohort during the first 32 weeks of treatment
- Frequency of AEs, SAEs, and safety events among treatment cohorts after completing their mOIT withdrawal to week 44.

13.3 Measures to Minimize Bias

This study will employ a randomized, double-blind, placebo-controlled design, with a placebo used for comparison to the biologic treatment groups (omalizumab plus dupilumab; omalizumab alone; or dupilumab alone), with all participants receiving OIT. We will also use centralized laboratories and /or masking of laboratory staff to minimize bias.

13.4 Analysis Plan

13.4.1 Analysis Populations.

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

- Per-protocol (PP) sample: Subjects who complete at least 75% of injections and at least 75% of OIT doses, and have non-missing value for the primary or secondary endpoint will comprise the PP sample.
- The Safety Sample (SS) is defined as all enrolled participants who receive at least one dose of OIT. Participants in the SS will be analyzed according to the treatment that they received. This sample will be utilized to assess differences in safety endpoints.

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

The primary analysis is an ITT comparison between arms A and B. A hierarchical endpoint analysis will be used, with peanut allergy as primary, to test the difference in proportions of participants who pass the peanut OFCs between arms A and B at week 44. If this test is significant, the subsequent comparison will be a test between the proportions who pass peanut and at least one other FA. If this second test is significant, a third comparison will be made between arms A and B of the proportion who pass all three OFCs.

Unevaluable tests or dropouts will be considered treatment failures (i.e. they will be imputed as allergic cases). The analysis will be performed using a two-sided Pearson chi-square test with an alpha level of 0.05. A Fisher's exact test will be used instead if expected cell counts are less than 5. If the exact test is used for first comparison, the subsequent comparison will also be the exact test. The success rate for each of the three co-primary endpoints in each arm will also be estimated, with 95% binomial confidence interval, or exact binomial confidence interval when using Fisher's exact test. If the hierarchical test does not allow the subsequent tests, the success rates and corresponding confidence intervals will be presented. We will perform multiple imputation and a tipping-point analysis to address bias resulting from missing data. If the second test is significant, it will also be stratified by the number of FAs (two FAs or three FAs) as a supplementary analysis.

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

A multivariable logistic regression will be conducted for each of the three co-primary endpoint comparisons between Cohort A and Cohort B. The model will be adjusted for important baseline demographic and clinical characteristics, such as age and number of original FAs that participants start with. If the first test uses exact logistic regression, the subsequent test will also be exact version.

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

The secondary endpoints for the treatment cohorts A, B, and C described in section 13.2 will be compared using logistic regression and ordinal logistic regression with a two-sided alpha level of 0.05, and 95% exact binomial confidence intervals. The multivariable logistic regression models will be conducted and adjusted for age and number of original FAs that participants

start with. The ordinal comparisons for number of allergies will also be adjusted by age and the 2 or 3 original FAs. The number of allergies will be modeled under the proportional odds assumption; however, this assumption will be tested, and a partial proportional odds model will be used if this assumption is violated.

We will calculate the proportion of participants who have a 10-fold change in the cumulative tolerated dose for each FA at weeks 32 and/or week 44, compared to baseline. The difference of the proportions across FAs will be compared within each cohort. The proportions for each food will also be compared across treatment arms. The analysis will be conducted using the chi-square test or Fisher's exact test.

Proportions of AEs and accidental FA exposure will be tabulated using the safety sample for each cohort.

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

The exploratory mechanistic endpoints will be compared among cohorts A, B and C. There are numerous questions of interest that involve the utility of data generated on a variety of platforms for predicting clinical response, or for describing other relevant clinical phenotypes that could provide insight into OIT. An important goal is to identify those with potential ability to discriminate across phenotypes relevant for characterizing and treating patients with significant FA. Thus, for each platform of interest, we will evaluate the roles of mechanistic features in predicting week 44 and week 32 success rates, and control the false discovery rate (FDR) to be no more than 5%. In addition to statistical testing, analyses (e.g., those that employ LASSO) will jointly evaluate features and identify those with relatively more importance with respect to the clinical phenotype of interest. Additionally, other analyses (such as hierarchical clustering) will provide graphical depictions of clustering of features and of subjects, providing insight into features within and across platforms and potentially meaningful clinical phenotypes. We will also evaluate the associations between clinical and lab characteristics with the clinical outcomes. Participant Quality of life (QoL) questionnaires will be compared between time points and between three cohorts. The QoL scores will be compared between cohorts using the Mann-Whitney U test, and between time points using the Wilcoxon signed-rank test. The time to maintenance will be compared by arm and by number of FAs, using the log-rank test and Kaplan-Meier plot.

13.4.6 Descriptive Analyses

Descriptive statistics will be presented and compared among cohorts A, B and C. Means, medians, standard deviations, and interquartile ranges will be presented for continuous variables. Frequency tables will be provided for categorical and discrete terms, such as family history and ethnicity. Graphical tools such as boxplots and histograms will be used to assess distributional properties of continuous variables.

13.4.7 Analysis for the PP sample

The primary and secondary endpoints will be explored in the PP samples.

13.6 Statistical hypotheses

For the three co-primary endpoint comparisons, the following will be tested:
i) The success rates of passing a peanut DBPCFC:

- Null hypothesis: The success rates of passing a peanut DBPCFC at week 44 are equal between Cohort A and Cohort B.
- Alternative hypothesis: The success rates of passing a peanut DBPCFC at week 44 differ between Cohort A and Cohort B.

ii) The success rates passing a DBPCFC to peanut and at least one other FA

- Null hypothesis: The success rates of passing a DBPCFC to peanut and at least one other FA at week 44 are equal between Cohort A and Cohort B.
- Alternative hypothesis: The success rates of passing a DBPCFC to peanut and at least one other FA at week 44 differ between Cohort A and Cohort B.

iii) The success rates of passing a DBPCFC to peanut and two other FAs

- Null hypothesis: The success rates of passing a DBPCFC to peanut and two other FAs at week 44 are equal between Cohort A and Cohort B.
- Alternative hypothesis: The success rates of passing a DBPCFC to peanut and two other FAs at week 44 differ between treatment groups

13.7 Sample Size Considerations

To carry out power calculations for the primary endpoint, successful sustained unresponsiveness (SU) at week 44 for omalizumab and placebo plus OIT (Cohort A) compared to omalizumab and dupilumab plus OIT (Cohort B) in the study, we used prior data from our published MTAX study. This study investigated multi-OIT facilitated by 16 weeks of omalizumab. SU testing occurred after a successful desensitization challenge at week 30, followed by 6 weeks of decreased maintenance dose or avoidance of multi-OIT. At the week 36 (SU visit), a significantly greater proportion of the participants on active OIT (34 [85%] of 40) versus discontinuation arm (11 [55%] of 20) passed double-blind, placebo-controlled food challenges to a CTD of 2 g protein for two or more of their offending foods (odds ratio 4.5, 95% CI 1.1–19.3, p=0.03). The MTAX study also showed, most foods had approximately equal rates of success (no clinical signs at food challenge: “no allergy”) at week 30 and week 36; therefore, we assumed that the foods would behave approximately similarly in response to drug and desensitization at both allergy assessments.

In this study, we apply the fixed-sequence procedure for three co-primary endpoints. Power and sample size calculation was conducted for each of the three tests based on simulation in R (version 3.6.0). From MTX study, the pairwise correlations between week 36 outcomes that passing peanut, peanut plus at least one FA, and peanut plus at least two FAs are between 0.64 to 0.84, we assume that the correlation between three endpoints in this study is somewhat in between, say 0.75. Based on the proportions of participants in the MTAX study who passed peanut and other FAs at the SU visit (after 6 weeks of avoidance), we expected that there would be 26% in arm A and 62% in arm B who

successfully pass peanut at week 44 SU testing in current study (after 12 weeks of avoidance). Given these effect sizes estimated for the primary comparison between cohorts A and B, 43 participants per arm would give us a superior power of 93% at alpha level of 0.05 using the two-sided chi-square test. Assuming the effect sizes of 25% vs 59% for arm A and arm B that pass peanut and at least one other FA in the subsequent test, 43 per arm would be sufficient to achieve an 86% of power. If subsequently fewer participants pass all three FAs, say 24% vs 58% for arm A vs B, we would have 81% of power to detect this difference. Considering a 15% dropout, 50 participants per arm would give us sufficient power to detect the above differences. When use Fisher's exact test, the power would be 88%, 79%, and 73% to detect the above effect sizes, respectively, if all tests are performed. The power calculation for the third test is based on the best scenario that all participants receive three FAs. It is unclear what proportion of subjects will have three FAs, while the expectation is that the clear majority of patients will, the power presented here represents a likely overestimate of power for the three FAs endpoint. The study will be positive with respect to the primary endpoint if the first test in the hierarchy reaches statistical significance, and the estimated power for this test is high.

14. Identification and Access to Source Data

14.1 Source Data

Source documents and source data are considered to be the original documentation where subject information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial. In this protocol, source data will be recorded onto paper CRFs at the time of collection. Skin test results will be recorded via adhesive tape transfer of the outline of any wheal(s) and/or erythema. Spirometry results will be recorded as printouts from the software package used to perform the testing. Peak flow data will be recorded.

14.2 Access to Source Data

The site investigators and site staff will make all source data available to the NIAID and PPD site monitors, as well as, to relevant health authorities, in this case, the FDA. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

15. Protocol Deviations

15.1 Protocol Deviation Definitions

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

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

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

15.2 Reporting and Managing Protocol Deviations

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

Upon determination that a protocol deviation has occurred, the study staff will a) notify the site PI/co-PI, b) notify the Protocol Chair/Sponsor, c) notify the NIAID Project Manager and NIAID Medical Officer, and c) will complete a Protocol Deviation form. Sites are permitted to use their own Protocol Deviation form templates as long as the form captures the information required on the eCRF. The NIAID Project Manager and Medical

Officer will make the decision as to whether the Deviation is major or not and what the impact of the Deviation on the study participant or the entire study may be. The study staff will submit the Protocol Deviation reports to the appropriate review bodies (IRB, DSMB, FDA etc.) and the NIAID Medical Officer will review and approve the corrective action plan submitted by the site PI, that will be implemented as a result of the Protocol Deviation.

16. Ethical Considerations and Compliance with Good Clinical Practice

16.1 Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* dated March 2018, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the IRB. Any amendments to the protocol or to the consent materials must first be approved by the NIAID and then approved by the IRB before they are implemented.

16.2 Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator, or study physician listed on the FDA 1572, will review the consent and answer questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.
The consent process will be ongoing. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

16.3 Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information.

17. Publication Policy

Publications will be reviewed with the Stanford and the NIAID teams.

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List of Tables

List of Figures

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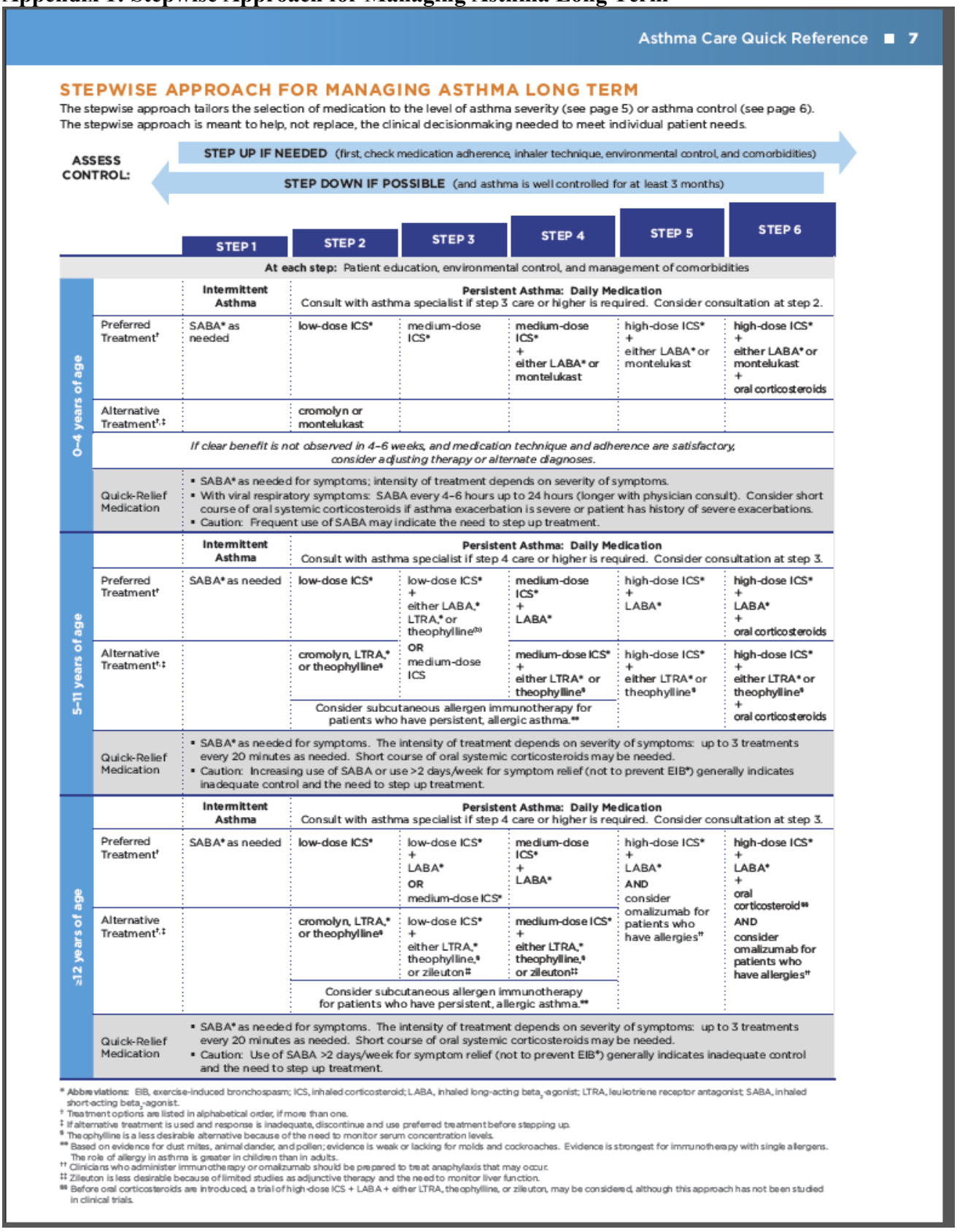
Appendix 1: Stepwise Approach for Managing Asthma Long Term



Asthma Care Quick Reference ■ 7

STEPWISE APPROACH FOR MANAGING ASTHMA LONG TERM

The stepwise approach tailors the selection of medication to the level of asthma severity (see page 5) or asthma control (see page 6). The stepwise approach is meant to help, not replace, the clinical decisionmaking needed to meet individual patient needs.

ASSESS CONTROL:

STEP UP IF NEEDED (first, check medication adherence, inhaler technique, environmental control, and comorbidities)

STEP DOWN IF POSSIBLE (and asthma is well controlled for at least 3 months)

		STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
		At each step: Patient education, environmental control, and management of comorbidities					
0–4 years of age		**Intermittent Asthma**	**Persistent Asthma: Daily Medication** Consult with asthma specialist if step 3 care or higher is required. Consider consultation at step 2.				
	Preferred Treatment†	SABA* as needed	low-dose ICS*	medium-dose ICS*	medium-dose ICS* + either LABA* or montelukast	high-dose ICS* + either LABA* or montelukast	high-dose ICS* + either LABA* or montelukast + oral corticosteroids
	Alternative Treatment†,‡		cromolyn or montelukast				
		If clear benefit is not observed in 4–6 weeks, and medication technique and adherence are satisfactory, consider adjusting therapy or alternate diagnoses.					
	Quick-Relief Medication	▪ SABA* as needed for symptoms; intensity of treatment depends on severity of symptoms. ▪ With viral respiratory symptoms: SABA every 4–6 hours up to 24 hours (longer with physician consult). Consider short course of oral systemic corticosteroids if asthma exacerbation is severe or patient has history of severe exacerbations. ▪ Caution: Frequent use of SABA may indicate the need to step up treatment.					
5–11 years of age		**Intermittent Asthma**	**Persistent Asthma: Daily Medication** Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.				
	Preferred Treatment†	SABA* as needed	low-dose ICS*	low-dose ICS* + either LABA,* LTRA,* or theophylline[§§] OR medium-dose ICS	medium-dose ICS* + LABA*	high-dose ICS* + LABA*	high-dose ICS* + LABA* + oral corticosteroids
	Alternative Treatment†,‡		cromolyn, LTRA,* or theophylline§		medium-dose ICS* + either LTRA* or theophylline§	high-dose ICS* + either LTRA* or theophylline§	high-dose ICS* + either LTRA* or theophylline§ + oral corticosteroids
			Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.**				
	Quick-Relief Medication	▪ SABA* as needed for symptoms. The intensity of treatment depends on severity of symptoms: up to 3 treatments every 20 minutes as needed. Short course of oral systemic corticosteroids may be needed. ▪ Caution: Increasing use of SABA or use >2 days/week for symptom relief (not to prevent EIB*) generally indicates inadequate control and the need to step up treatment.					
≥12 years of age		**Intermittent Asthma**	**Persistent Asthma: Daily Medication** Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.				
	Preferred Treatment†	SABA* as needed	low-dose ICS*	low-dose ICS* + LABA* OR medium-dose ICS*	medium-dose ICS* + LABA*	high-dose ICS* + LABA* AND consider omalizumab for patients who have allergies††	high-dose ICS* + LABA* + oral corticosteroid§§ AND consider omalizumab for patients who have allergies††
	Alternative Treatment†,‡		cromolyn, LTRA,* or theophylline§	low-dose ICS* + either LTRA,* theophylline,§ or zileuton‡‡	medium-dose ICS* + either LTRA,* theophylline,§ or zileuton‡‡		
			Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.**				
	Quick-Relief Medication	▪ SABA* as needed for symptoms. The intensity of treatment depends on severity of symptoms: up to 3 treatments every 20 minutes as needed. Short course of oral systemic corticosteroids may be needed. ▪ Caution: Use of SABA >2 days/week for symptom relief (not to prevent EIB*) generally indicates inadequate control and the need to step up treatment.					

* Abbreviations: EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist.
† Treatment options are listed in alphabetical order, if more than one.
‡ If alternative treatment is used and response is inadequate, discontinue and use preferred treatment before stepping up.
§ Theophylline is a less desirable alternative because of the need to monitor serum concentration levels.
** Based on evidence for dust mites, animal dander, and pollen; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.
†† Clinicians who administer immunotherapy or omalizumab should be prepared to treat anaphylaxis that may occur.
‡‡ Zileuton is less desirable because of limited studies as adjunctive therapy and the need to monitor liver function.
§§ Before oral corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton, may be considered, although this approach has not been studied in clinical trials.

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Appendix 2: Sample Serious Adverse Event Form

Serious Adverse Event Form
Date of Report: _____
MM/DD/YYYY
□ Initial Report
□ Follow-up Report *(if follow-up complete participant identification and then only enter new/revised information)*
Initial Report Date: _____
MM/DD/YYYY

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

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

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

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

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

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

_____ _____

Name and Signature of Principal Investigator or co-PI Date

Appendix 3: Injectable Epinephrine Training Form

Injectable Epinephrine Training Form

By signing the Injectable Epinephrine training form, I acknowledge being appropriately trained and demonstrate understanding in the use and proper storage of Injectable epinephrine 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

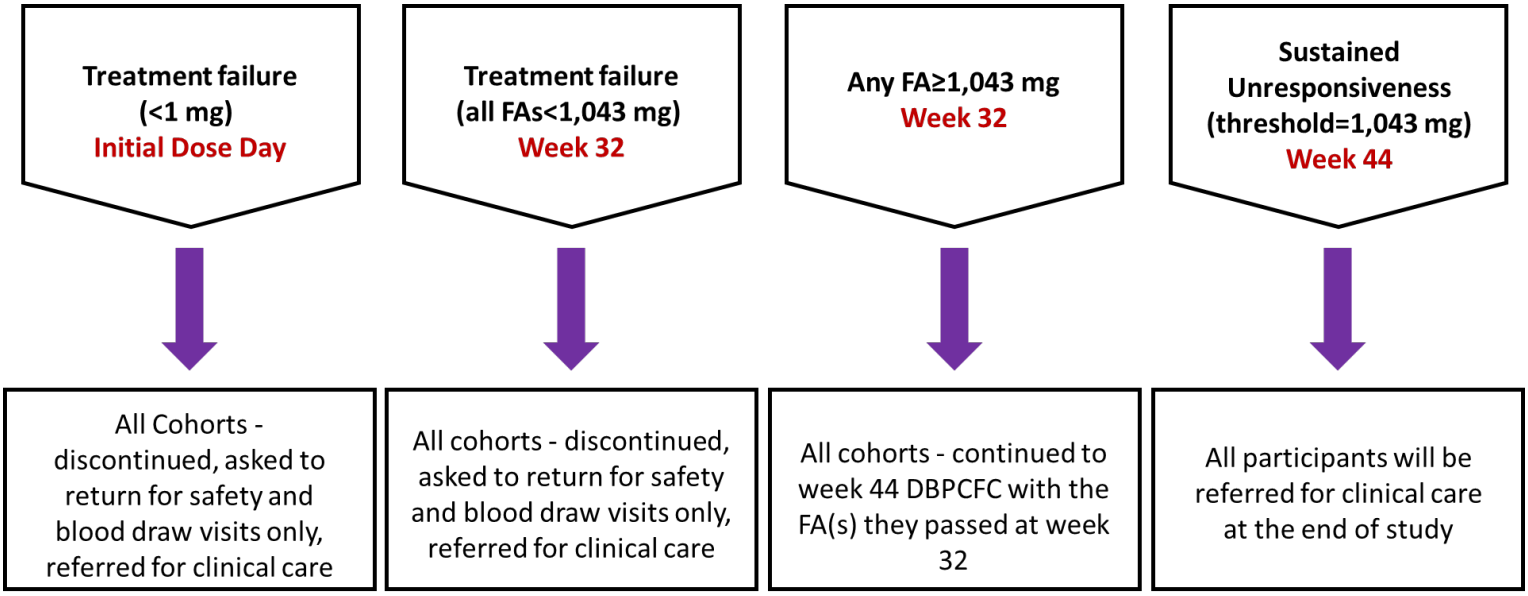
- ❑ **Epinephrine Autoinjector 0.3 mg**
- ❑ **Epinephrine Autoinjector 0.15 mg**
- ❑ **Epinephrine Autoinjector 0.10 mg**

ANAPHYLAXIS INFORMATION (All boxes must be checked)

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

Protocol AADCRC-STAN-004 COMBINE

Appendix 4: Participant Disposition



Protocol AADCRC-STAN-004 COMBINE

Appendix 5: Definition of Dose-Limiting Symptoms

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

Mild:

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

Moderate:

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

Severe:

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