Long Title: Phase 2 Randomized Controlled Trial using Biologics to Improve Multi OIT Outcomes

Short Title: COMBINE

Statistical Analysis Plan (SAP)

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Title: Phase 2 Randomized Controlled Trial using Biologics to Improve Multi OIT Outcomes (COMBINE Study)

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Investigator Agreement

- □ All statistical analyses included in an abstract or manuscript should reflect the work of the biostatistician(s) listed on this SAP. No changes or additional analyses should be made to the results or findings without discussing with the project biostatistician(s).
- □ All biostatisticians on this SAP should be given sufficient time to review the full presentation, abstract, manuscript, or grant and be included as co-authors on any abstract or manuscript resulting from the analyses.
- □ If substantial additional analysis is necessary or the aims of the project change, a new SAP will need to be developed.

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☐ I have reviewed the SAP and understand that any changes must be documented.

Acknowledged by:

Lead Principal Investigator:

_____

Date: _____

Lead Biostatistician:

_____

Date: _____

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Contents

1. Study Overview

1.1 Background/Introduction:

Food allergy (FA) is a serious public health concern that can cause life threatening reactions in affected patients. The prevalence of food allergy in the United States has increased and now affects 15 million patients: 4-8% of children (6 million children, 30% with multiple food allergies) and about 9% of adults. One treatment for food allergies is oral immunotherapy (OIT). OIT involves exposing the immune system to progressively larger amounts of an allergen to induce sustained unresponsiveness /tolerance. Unfortunately, a significant proportion of food allergic patients cannot tolerate OIT or fail to be desensitized. One specific limitation to OIT is that with allergen dose increases, food-allergen-specific lgE on mast cells can trigger allergic reactions and limit the ability to rapidly increase doses with minimal side effects. Omalizumab could potentially make OIT more effective because it inhibits the binding of IgE to the high-affinity IgE receptor on the surface of mast cells and basophils and reduces levels of free IgE in the blood. However, omalizumab with OIT alone has not been demonstrated to improve the ability of OIT to maintain tolerance of an allergic food in the absence of continued OIT. Dupilumab - a fully human monoclonal antibody - has also been shown to reduce IgE levels over time but not to the extent of omalizumab. This study investigates if the combination of omalizumab and dupilumab with OIT improves sustained clinical tolerance to allergens in participants compared to participants who only received omalizumab with OIT. Participants will have allergies to at least two out of the thirteen following allergens – almond, cashew, egg, salmon, cod, hazelnut, milk, peanut, sesame, shrimp, soy, walnut and wheat. However, our primary aim is to determine if omalizumab followed by the combination of OIT with dupilumab will increase the ability to sustain clinical tolerance to **peanut** allergen in the absence of continued therapy relative to OIT plus omalizumab alone

1.2 Study Aims and Hypothesis

1.2.1 Primary Aims

Primary Aim 1: To determine if omalizumab followed by the combination of OIT with dupilumab will increase the ability to sustain clinical tolerance to **1,043 mg of peanut** in the absence of continued therapy relative to OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals with a peanut allergy.

Hypothesis: We hypothesize that a combination treatment with dupilumab, omalizumab and OIT will increase the likelihood of sustained unresponsiveness to peanut allergy over OIT with omalizumab alone.

Primary Aim 2: To determine if omalizumab followed by the combination of OIT with dupilumab will increase the ability to sustain clinical tolerance to **1,043 mg each of peanut plus one other allergen** in the absence of continued therapy relative to OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals with a peanut allergy.

Hypothesis: We hypothesize that a combination treatment with dupilumab, omalizumab and OIT will increase the likelihood of sustained unresponsiveness to peanut plus one other allergen over OIT with omalizumab alone.

Primary Aim 3: (Only applies to cohort subgroup that had allergies to peanuts and two other allergens.) To determine if omalizumab followed by the combination of OIT with dupilumab will increase the ability to sustain clinical tolerance to **1,043 mg each of peanuts plus two other allergens** in the absence of continued therapy relative to OIT plus omalizumab alone (without dupilumab) ***solely among individuals with a peanut allergy and two other allergies.***

Hypothesis: We hypothesize that a combination treatment with dupilumab, omalizumab and OIT will increase the likelihood of sustained unresponsiveness to peanut plus two other allergens over OIT with omalizumab alone among those allergic to peanuts and at least two other allergens

1.2.2 Secondary Aims

Secondary Aim 1: To determine whether omalizumab followed by the combination of OIT with dupilumab will increase the ability to sustain clinical tolerance to at least **one allergen** at **1,043 mg at week 44** in the absence of continued therapy relative to OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals.

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance to one allergen that may not be peanut over OIT with omalizumab alone.

Secondary Aim 2: To determine whether omalizumab followed by the combination of OIT with dupilumab will increase the ability to sustain clinical tolerance to at **least two allergens 1,043 mg at week 44** that may or may not include peanut in the absence of continued therapy relative to OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals.

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance to at least two allergens that may not include peanut relative to OIT with omalizumab alone.

Secondary Aim 3: To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood **of tolerating 2,043 mg of one allergen at week 44** relative to participants who received OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals.

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance at week 44 at a cumulative dose of 2,043 mg for one allergen relative to OIT treatment with omalizumab alone.

Secondary Aim 4: To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood **of tolerating 2,043 mg each of at least two allergens at week 44** relative to participants who received OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals.

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance at week 44 at a cumulative dose of 2,043 mg for each of two different allergens relative to OIT treatment with omalizumab alone.

Secondary Aim 5: (Only applies to cohort subgroup that had allergies to peanuts and two other allergens.) To determine if participants assigned to receive omalizumab in combination with OIT and dupilumab have an increased likelihood **of tolerating 2,043 each mg of all three allergens at week 44** relative to participants assigned to OIT plus omalizumab alone (without dupilumab) **among multi-allergic individuals with at least three allergies.**

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance at week 44 at a cumulative dose of 2,043 mg for each of three different allergens relative to OIT treatment with omalizumab alone.

Secondary Aim 6: To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood **of tolerating 4,043 mg of one allergen at week 44** relative to participants who received OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals.

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance at week 44 at a cumulative dose of 4,043 mg for one allergen relative to OIT treatment with omalizumab alone.

Secondary Aim 7: To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood **of tolerating 4,043 mg each of at least two allergens at week 44** relative to participants who received OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals.

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance at week 44 at a cumulative dose of 4,043 mg for each of two different allergens relative to OIT treatment with omalizumab alone.

Secondary Aim 8: (Only applies to cohort subgroup that had allergies to peanuts and two other allergens.) To determine if participants assigned to receive omalizumab in combination with OIT and dupilumab have an increased likelihood **of tolerating 4,043 each mg of all three allergens at week 44** relative to participants assigned to OIT plus omalizumab alone (without dupilumab) **among multi-allergic individuals with at least three allergies.**

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance at week 44 at a cumulative dose of 4,043 mg for each of three different allergens relative to OIT treatment with omalizumab alone.

Secondary Aim 9: To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood **of tolerating 4,043 mg of one allergen at week 32** relative to participants who received OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals.

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance at week 32 at a cumulative dose of 4,043 mg for one allergen relative to OIT treatment with omalizumab alone.

Secondary Aim 10: To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood **of tolerating 4,043 mg each of at least two allergens at week 32** relative to participants who received OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals.

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance at week 32 at a cumulative dose of 4,043 mg for each of two different allergens relative to OIT treatment with omalizumab alone.

Secondary Aim 11: (Only applies to cohort subgroup that had allergies to peanuts and two other allergens.) To determine if participants assigned to receive omalizumab in combination with OIT and dupilumab have an increased likelihood **of tolerating 4,043 each mg of all three allergens at week 32** relative to participants assigned to OIT plus omalizumab alone (without dupilumab) **among multi-allergic individuals with at least three allergies.**

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance at week 32 at a cumulative dose of 4,043 mg for each of three different allergens relative to OIT treatment with omalizumab alone.

Secondary Aim 12: To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood of having a **10-fold change in cumulative tolerance amount for at least one allergen at week 44** compared to their baseline allergen tolerance relative to participants who received OIT plus omalizumab alone (without dupilumab).

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of having a 10-fold change in cumulative tolerance amount for one allergen at week 44 compared to their baseline allergen tolerance relative to OIT treatment with omalizumab alone.

Secondary Aim 13: To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood of having a **10-fold change in cumulative tolerance amount for each of at least two different allergens at week 44** compared to their baseline allergen tolerance relative to participants who received OIT plus omalizumab alone (without dupilumab).

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of having a 10-fold change in cumulative tolerance amount for each of two different allergens at week 44 compared to their baseline allergen tolerance relative to OIT treatment with omalizumab alone.

Secondary Aim 14: (Only applies to cohort subgroup that had allergies to peanuts and two other allergens.) To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood of having a **10-fold change in cumulative tolerance amount for each of all three different allergens at week 44** compared to their baseline allergen tolerance relative to participants who received OIT plus omalizumab alone (without dupilumab) **among multi-allergic individuals with at least three allergies.**

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of having a 10-fold change in cumulative tolerance amount for each of three different allergens at week 44 compared to their baseline allergen tolerance relative to OIT treatment with omalizumab alone.

Secondary Aim 15: To determine if participants who received omalizumab in combination with OIT and dupilumab have an **increased tolerance to peanut allergen, even if that tolerance level does not reach the clinical level of 1,043 mg (primary outcome)**, relative to participants who received OIT plus omalizumab alone (without dupilumab).

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase tolerance to peanut allergen, even if that tolerance level does not reach the clinical level relative to OIT treatment with omalizumab alone.

Secondary Aim 16: To determine if participants who received omalizumab in combination with OIT and dupilumab have a **smaller wheel diameter after a peanut skin prick test at week 44** relative to participants who received OIT plus omalizumab alone (without dupilumab).

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will result in smaller wheel diameters after a peanut skin prick test compared to OIT treatment with omalizumab alone.

Secondary Aim 17: To determine if participants who received omalizumab in combination with OIT and dupilumab have a **less total IgE** relative to participants who received OIT plus omalizumab alone (without dupilumab).

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will result in less total IgE compared to OIT treatment with omalizumab alone.

Secondary Aim 18: To determine if participants who received omalizumab in combination with OIT and dupilumab have a **less total peanut-specific IgE** relative to participants who received OIT plus omalizumab alone (without dupilumab).

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will result in less peanut-specific IgE compared to OIT treatment with omalizumab alone.

Secondary Aim 19: To determine if participants who received omalizumab in combination with OIT and dupilumab have a **less total walnut-specific IgE** relative to participants who received OIT plus omalizumab alone (without dupilumab).

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will result in less walnut-specific IgE compared to OIT treatment with omalizumab alone.

Secondary Aim 20: To determine if participants who received omalizumab in combination with OIT and dupilumab have a **less total cashew-specific IgE** relative to participants who received OIT plus omalizumab alone (without dupilumab).

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will result in less cashew-specific IgE compared to OIT treatment with omalizumab alone.

Secondary Aim 21: To determine if participants who received omalizumab in combination with OIT and dupilumab have a **more specific IgG4** relative to participants who received OIT plus omalizumab alone (without dupilumab).

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will result in less specific IgG4 compared to OIT treatment with omalizumab alone.

Secondary Aim 22: To determine if participants who received omalizumab in combination with OIT and dupilumab have a **larger IgG4/IgE ratio** relative to participants who received OIT plus omalizumab alone (without dupilumab).

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will result in a larger IgG4/ IgE ratios compared to OIT treatment with omalizumab alone.

1.2.3 Safety Aims

Safety Aim 1: This is a descriptive aim to understand the difference in the number of safety events across the three treatment arms - omalizumab followed by the combination of OIT with dupilumab, omalizumab followed by the combination of OIT alone, and OIT and dupilumab alone.

Hypothesis: We expect participants who received omalizumab followed by the combination of OIT with dupilumab will have a smaller number of safety events compared to the other two treatment groups.

Safety Aim 2: To determine if the omalizumab and dupilumab group is **less likely to drop out from the study due to adverse events**, we will compare dropout rates between the arms.

Hypothesis: The omalizumab and dupilumab group is less likely to drop out of the study due to adverse events compared to the omalizumab only group.

Safety Aim 3: To determine if the omalizumab and dupilumab group **has less GI Symptoms per OIT dose** compared with the omalizumab only group, we will compare symptoms that impact the GI system between the arms.

Hypothesis: Participants in the omalizumab and dupilumab group have fewer GI Symptoms per OIT dose compared to the omalizumab only group.

Safety Aim 4: To determine if the omalizumab and dupilumab group **has the same amount of non-GI Symptoms per OIT dose** compared with the omalizumab only group, we will compare symptoms that impact non-GI systems between the arms.

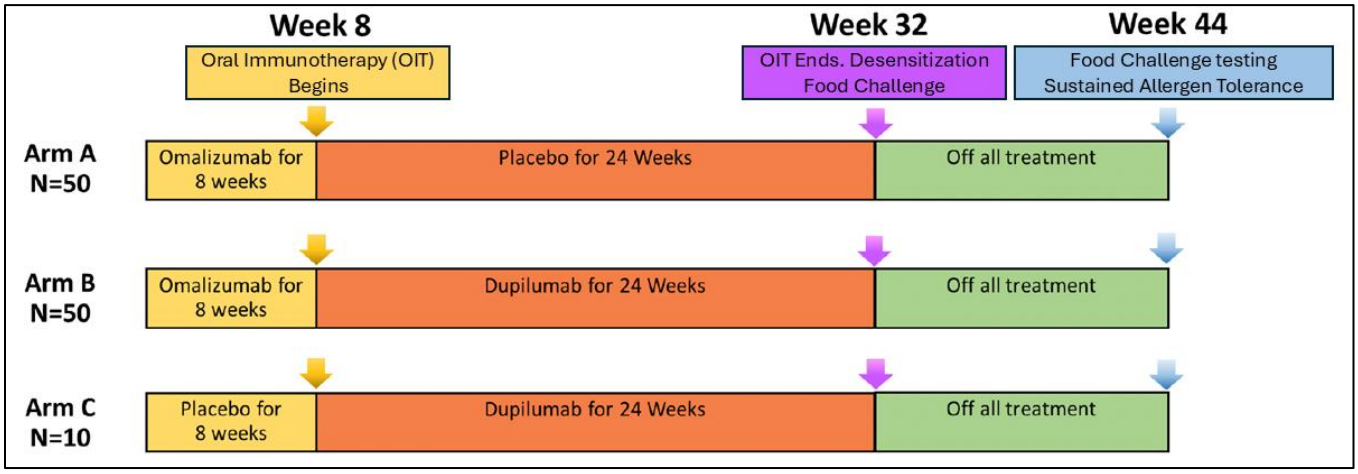
Hypothesis: Participants in the omalizumab and dupilumab group will have similar rates of non-GI symptoms per OIT dose as the omalizumab only group.

2. Study Population

Our target population is individuals (ages 4 – 55) with at least 2 allergies, one of which is peanut. Detailed description of the inclusion and exclusion criteria can be found in the appendix.

Study Design: This is a prospective Phase 2, multi-allergen clinical trial that includes participants with proven allergies to at least 2 different foods in which one must be peanut.

Study Design



Randomization: Individuals are randomized to one of three arms in double blinded fashion in a 5:5:1 randomization scheme. Study Arm A (50 participants) will be treated with omalizumab for 8 weeks followed by 24 weeks of treatment with placebo plus OIT. Study Arm B (50 participants)– our experimental treatment arm of interest -- will be treated with omalizumab for 8 weeks, followed by 24 weeks of treatment with dupilumab plus OIT. Study Arm C (10 participants) will be treated with placebo for 8 weeks followed by 24 weeks treatment with dupilumab. All arms will receive multi-food allergen oral immunotherapy.

Treatment arms: There will be three study arms, all will be double blinded: Study Arm A (50 participants) will be treated with omalizumab for 8 weeks followed by 24 weeks of treatment with placebo. Study Arm B (50 participants) will be treated with omalizumab for 8 weeks, followed by 24 weeks of treatment with dupilumab. Study Arm C (8 participants) will be treated with placebo for 8 weeks followed by 24 weeks treatment with dupilumab. All arms will receive multi-food allergen oral immunotherapy.

Analysis Populations:

Intent-to-Treat: Our intent to treat population includes those randomized to Arm A or Arm B - the 100 participants randomized to either the combination treatment arm or the omalizumab only arm regardless of their adherence to protocol or withdrawal status in the study (although regarding the latter they will only be included in the population up until the time that they withdraw consent). Subjects who are lost to follow up will be considered failures.

Per-Protocol Population: Our per-protocol population consists of all those randomized who completed the food challenges in both week 32 and week 44 without withdrawing consent (this includes treatment failures and those who discontinued study visits due to treatment failure) and only excludes those who moved away or withdrew consent for non-disease/treatment purposes.

Safety Population: Our safety population includes those randomized to Arms A, B, or C – all 108 participants. Participants will be analyzed according to the treatment that they received. This sample will be utilized to assess differences in safety endpoints.

Data source / how the data were collected: Source documents and source data are considered 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 Case Report Forms 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.
Contact information for team member responsible for data collection / acquisition: 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.
Data or version (if downloaded, provide date):
Data transfer method and date:
Where dataset is stored: Source documents and REDCap

Notes*: include any additional details that give information about how this data set is acquired.*
Description:
The data set for this clinical trial is initially collected through paper source documentation, after which the data are electronically captured and transcribed into the REDCap platform via the Stanford University instance. REDCap is a secure, web-based application designed for data collection and management. Participants are enrolled at three clinical sites, each using paper copies of the case report forms for data collection, which are then entered and managed in the REDCap system hosted by Stanford University. Data export from REDCap is typically facilitated through the platform's built-in export functionality, which allows to download data in various formats such as CSV, Excel, or XML.

3. Outcomes, Exposures, and Additional Variables for Interest

3.1 Primary Outcomes

CTD: Cumulative Tolerated Dose
DBPCFC: Double Blind Placebo Controlled Food Challenge

Primary Outcomes	Description	Variables and source	Specifications
Peanut_O1 Passing Peanut DBPCFC with a CTD≥ 1,043 mg at Week 44 with no or mild reactions	Binary variable 1: participant passed the peanut DBPCFC at week 44 for peanut 0: participant failed (peanut CTD < 1043)	Source: REDCap Study arm CTD	Missing values due to loss to follow up are treated as failures for the intent-to-treat population and as missing for the per-protocol population
Peanut_O2 Passing Peanut +1 allergen DBPCFC with a CTD ≥ 1,043 mg at Week 44 with no or mild reactions	Binary variable 1: participant passed the peanut and one other allergen DBPCFC at week 44 0: participant failed (peanut + 1 allergen CTD < 1043)	Source: REDCap Study arm CTD	If the patient failed the peanut test (peanut_O1 = 0), their value for this variable will also be 0. Missing values due to loss to follow up are treated as failures for the intent-to-treat population and as missing for the per-protocol population
Peanut_O3 Passing Peanut +2 allergen DBPCFC with a CTD≥ 1,043 mg at Week 44 with no or mild reactions	Binary variable 1: participant passed the peanut and two other allergen DBPCFC at week 44 0: participant failed (peanut + 2 allergen CTD < 1043)	Source: REDCap Study arm CTD	**This variable is only measured among those who have allergies to peanut and at least two other allergens**. If the patient failed the peanut+1 test (peanut_O2 = 0), their value for this variable will also be 0. However, participants who had allergies to only peanut and one other allergen will have a null value for this variable – it is a null value not a missing value.

Mock data are included here to demonstrate how DBPCFC results relate to the primary peanut outcomes. Notice that subject 2 does not have a Peanut_O3 value because they only have two allergies.

ID	Arm	Time	Peanut	Almond	Cashew	Hazelnut	Walnut	**Peanut_O1**	**Peanut_O2**	**Peanut_O3**
1	A	0	50	45	5	2500	NA	---	---	---
1	A	32	1000	1000	350	---	---	---	---	---
1	A	44	1043	1043	---	---	---	1	1	0
2	B	0	50	50	---	---	---	---	---	---
2	B	32	1000	1000	---	---	---	---	---	---
2	B	44	1000	1000	---	---	---	1	1	NA
3	A	0	50	---	35	35	1000	---	---	---
3	A	32	1000	---	1000	35	---	---	---	---
3	A	44	30	---	1000	---	---	0	0	0
Data Legend: Peanut Challenges Outcomes (peanut_O1, peanut_O2, peanut_O3)										

***NA here means Not Available. This is not a missing value. Participants who are treated for less than three allergens will not have values for Peanut_O3.**

3.2 Secondary Outcome

3.2.1 Secondary Aims 1 - 2: Number of Allergens passed at Week 44 endpoint

CTD: Cumulative Tolerated Dose
DBPCFC: Double Blind Placebo Controlled Food Challenge

Secondary Outcome	Description	Variables and source	Specifications
Allergen_O1 Passing any one allergen (peanut or other) DBPCFC with a CTD≥ 1,043 mg at Week 44 with no or mild reactions	Binary variable 1: participant passed the one allergen DBPCFC at week 44 0: participant failed (CTD < 1043)	Source: REDCap Study arm CTD	Missing values due to loss to follow up are treated as failures for the intent-to-treat population and as missing for the per-protocol population.
Allergen_O2 Passing any two allergens (peanut or other) DBPCFC with a CTD≥ 1,043 mg at the Week 44 DBPCFC with no or mild reactions	Binary variable 1: participant passed the two allergen DBPCFC at week 44 1043mg cut off for any of their two allergens 0: participant failed (CTD < 1043)	Source: REDCap Study arm CTD	If the patient failed the first allergen test (Allergen_O1 = 0), their value for this variable will also be 0. Missing values due to loss to follow up are treated as failures for the intent-to-treat population and as missing for the per-protocol population

Mock data are included here to demonstrate how DBPCFC results relate to secondary outcomes. These mock data also show how the Primary outcomes (Peanut_O1 and Peanut_O2) are different from the secondary outcomes (Allergen_O1 and Allergen_O2).

ID	Time	Peanut CTD	Almond CTD	Cashew CTD	**Peanut_O1**	**Peanut_O2**	**Peanut_O3**	**Allergen_O1**	**Allergen_O2**
1	44	1043	1043	1043	1	1	1	1	1
2	44	1043	50	50	1	0	0	1	0
3	44	1043	1043	50	1	1	0	1	1
4	44	1043	1043	NA	1	1	NA	1	1
5	44	1043	50	NA	1	0	NA	1	0
6	44	50	50	50	0	0	0	0	0
7	44	50	1043	1043	0	0	0	1	1
8	44	50	1043	50	0	0	0	1	0
9	44	50	50	NA	0	0	NA	0	0
10	44	50	1043	NA	0	0	NA	1	0

***NA here means Not Available. This is not a missing value. Participants who are treated for less than three allergens will not have values for Peanut_O3.**

3.2.2 Secondary Aims 3 - 5: Number of Allergens passed at 2043mg Week 44 endpoint

CTD: Cumulative Tolerated Dose
DBPCFC: Double Blind Placebo Controlled Food Challenge

Secondary Outcome	Description	Variables and source	Specifications
Allergen1_2043_w44 Passing any one allergen (peanut or other) DBPCFC with a CTD≥ 2,043 mg at Week 44 with no or mild reactions	Binary variable 1 = participant passed the one DBPCFC at week 44 at 2043 mg cutoff 0= participant failed (CTD < 2043)	Source: REDCap Study arm CTD	
Allergen2_2043_w44 Passing any two allergens (peanut or other) DBPCFC with a CTD≥ 2,043 mg at Week 44 with no or mild reactions	Binary variable 1: participant passed the two DBPCFC at week 44 0: participant failed (CTD < 2043)	Source: REDCap Study arm CTD	If the patient failed the first allergen test (Allergen1_2043_w44= 0), their value for this variable will also be 0.
Allergen3_2043_w44 Passing any 3 allergens DBPCFC with a CTD≥ 2,043 mg at Week 44 with no or mild reactions	Binary variable 1: participant passed the three DBPCFC at week 44 0: participant failed (CTD < 2043)	Source: REDCap Study arm CTD	**This variable is only measured among those who have allergies to peanut and at least two other allergens**. If the patient failed the two allergens test (Allergen2_2043_w44= 0), their value for this variable will also be 0. Participants who have two allergens will have null value, not a missing value, for this comparison.

Mock data are included here to demonstrate how DBPCFC results related to the secondary outcomes.

ID	Arm	Time	Peanut	Almond	Cashew	Hazelnut	**Allergen1_2043_w44**	**Allergen2_2043_w44**	**Allergen3_2043_w44**
1	A	0	50	45	5	2500	---	---	---
1	A	32	1043	2043	350	---	1	0	0
2	B	0	50	50	---	---	---	---	---
2	B	32	2043	2043	---	---	1	1	NA
3	A	0	50	---	35	35	---	---	---
3	A	32	2043	---	2043	35	1	1	0

Data Legend: Allergen Challenge Outcomes at Week 32 (All_W32_O1, All_W32_O2, All_W32_O3).

***NA here means Not Available. This is not a missing value. Participants who are treated for less than three allergens will not have values for Allergen_W32_O3.**

3.2.3 Secondary Aims 6 - 8: Number of Allergens passed at 4043mg Week 44 endpoint

CTD: Cumulative Tolerated Dose
DBPCFC: Double Blind Placebo Controlled Food Challenge

Secondary Outcome	Description	Variables and source	Specifications
Allergen1_4043_w44 Passing any one allergen (peanut or other) DBPCFC with a CTD≥ 4,043 mg at Week 44 with no or mild reactions	Binary variable 1 = participant passed the one DBPCFC at week 44 at 4043 mg cutoff 0= participant failed (CTD < 4043)	Source: REDCap Study arm CTD	
Allergen2_4043_w44 Passing any two allergens (peanut or other) DBPCFC with a CTD≥ 4,043 mg at Week 44 with no or mild reactions	Binary variable 1: participant passed the two DBPCFC at week 44 0: participant failed (CTD < 4043)	Source: REDCap Study arm CTD	If the patient failed the first allergen test (Allergen1_4043_w44= 0), their value for this variable will also be 0.
Allergen3_4043_w44 Passing any 3 allergens DBPCFC with a CTD≥ 4,043 mg at Week 44 with no or mild reactions	Binary variable 1: participant passed the three DBPCFC at week 44 0: participant failed (CTD < 4043)	Source: REDCap Study arm CTD	**This variable is only measured among those who have allergies to peanut and at least two other allergens**. If the patient failed the two allergens test (Allergen2_4043_w44= 0), their value for this variable will also be 0. Participants who have two allergens will have null value, not a missing value, for this comparison.

3.2.4 Secondary Aims 9 - 11: Number of Allergens passed at 4043mg Week 32 endpoint

CTD: Cumulative Tolerated Dose
DBPCFC: Double Blind Placebo Controlled Food Challenge

Secondary Outcome	Description	Variables and source	Specifications
Allergen1_4043_w32 Passing any one allergen (peanut or other) DBPCFC with a CTD≥ 4,043 mg at Week 32 with no or mild reactions	Binary variable 1 = participant passed the one DBPCFC at week 32 at 4043 mg cutoff 0= participant failed (CTD < 4043)	Source: REDCap Study arm CTD	
Allergen2_4043_w32 Passing any two allergens (peanut or other) DBPCFC with a CTD≥ 4,043 mg at Week 32 with no or mild reactions	Binary variable 1: participant passed the two DBPCFC at week 32 0: participant failed (CTD < 4043)	Source: REDCap Study arm CTD	If the patient failed the first allergen test (Allergen1_4043_w32= 0), their value for this variable will also be 0.
Allergen3_4043_w32 Passing any 3 allergens DBPCFC with a CTD≥ 4,043 mg at Week 32 with no or mild reactions	Binary variable 1: participant passed the three DBPCFC at week 32 0: participant failed (CTD < 4043)	Source: REDCap Study arm CTD	**This variable is only measured among those who have allergies to peanut and at least two other allergens**. If the patient failed the two allergens test (Allergen2_4043_w32= 0), their value for this variable will also be 0. Participants who have two allergens will have null value, not a missing value, for this comparison.

3.2.5 Secondary Aims 12 - 14: Tenfold change in cumulative tolerance of allergen protein compared to baseline

CTD: Cumulative Tolerated Dose

DBPCFC: Double Blind Placebo Controlled Food Challenge

FA: Food Allergy

FC: Fold Change

Secondary Outcome	Description	Variables and source	Specifications
FC_W44_O1 participant has a 10-fold change in the cumulative tolerance dose compared to baseline at week 44 respectively for one allergen (peanut or other)	Binary variable 1: participant's ratio between week 44 and baseline CTD is equal to greater than 10 for one allergen 0: participant's ratio between week 44 and baseline CTD is less than 10 for one allergen	Source:REDCap Study arm CTD	Missing values due to loss to follow up are treated as failures for the intent-to-treat population and as missing for the per-protocol population.
FC_W44_O2 participant has a 10-fold change in the cumulative tolerance dose compared to baseline at week 44 respectively for two allergens (peanut or other)	Binary variable 1: participant's ratio between week 44 and baseline CTD is equal to greater than 10 for two allergens 0: participant's ratio between week 44 and baseline CTD is less than 10 for two allergens	Source:REDCap Study arm CTD	If the patient failed the first allergen test (FC_W44_O1 = 0), their value for this variable will also be 0. All allergens are considered for this combination.
FC_W44_O3 participant has a 10-fold change in the cumulative tolerance dose compared to baseline at week 44 respectively for 3 allergens (peanut or other)	Binary variable 1: participant's ratio between week 44 and baseline CTD is equal to greater than 10 for three allergens 0: participant's ratio between week 44 and baseline CTD is less than 10 for three allergens	Source:REDCap Study Arm CTD	**This variable is only measured among those who have allergies to peanut and at least two other allergens**. If the patient failed the second allergen test (FC_W44_O2= 0), their value for this variable will also be 0. Participants with two allergies will have a null value, not a missing value.

ID	Arm	Time	Peanut	Almond	Cashew	**FC_W32_O1**	**FC_W32_O2**	**FC_W32_O3**	**FC_W44_O1**	**FC_W44_O2**	**FC_W44_O3**
1	A	0	50	45	5	---	---	---	---	---	---
1	A	32	1043	2043	350	1	1	1	---	---	---
1	A	44	1043	2043	---	---	---	---	1	1	0
2	B	0	304	50	---	---	---	---	---	---	---
2	B	32	1043	2043	---	1	0	NA	---	---	---
2	B	44	1043	1043	---	---	---	---	1	0	NA
3	A	0	300	---	300	---	---	---	---	---	---
3	A	32	1043	---	1043	0	0	NA	---	---	---
3	A	44	1043	--	1043	--	--	--	0	0	NA

***NA here means Not Available. This is not a missing value. Participants who are treated for less than three allergens will not have values for FC_W32_O3 or FC_W44_O3.**

3.2.6 Secondary Aims 15 - 22: SPT, Time to Fail, and IgE

Secondary Outcome	Description	Variables and source	Specifications
SPT Wheel Diameter (mm)	For each allergen for each time point for each participant	redcap	SPT will be coded as a continuous variable based on the wheel diameter.
Week 32 Peanut CTD		redcap	(for time to fail analysis)
Week 44 Peanut CTD		redcap	(for time to fail analysis)
Total IgE	Total IgE for each participant at baseline and Week 44	redcap	
Peanut Specific IgE	Total Peanut specific IgE for each participant at baseline and Week 44	redcap	
Walnut Specific IgE	Total walnut specific IgE for each participant at baseline and Week 44	redcap	
Cashew Specific IgE	Total cashew specific IgE for each participant at baseline and Week 44	redcap	
Total IgG4	Total IgG4 for each participant at baseline and Week 44	Needs to be included in redcap	
IgE/IgG4 ratio	Calculated for each participant at baseline and week 44.		

3.2.7 Safety Endpoints:

SAE: Severe Adverse Event
AE: Adverse Event
OIT: Oral Immunotherapy

Outcome	Description	Variables and source	Specifications
Number of AE during first 32 weeks	Per subject	Source: REDCap	
Number of SAE during first 32 weeks	Per subject	Source: REDCap	
Number of AE between 32 week and week 44	Per subject	Source: REDCap	
Number of SAE between 32 week and week 44 or end of study	Per subject	Source: REDCap	
Number of drop outs due to AE	Per arm	redcap	
Rate of GI-symptoms/ OIT dose	Per subject	redcap	
Rate of non-GI symptoms/ OIT dose	Per subject	redcap	

3.3 Additional Variables of Interest

SPT: Skin Prick Test

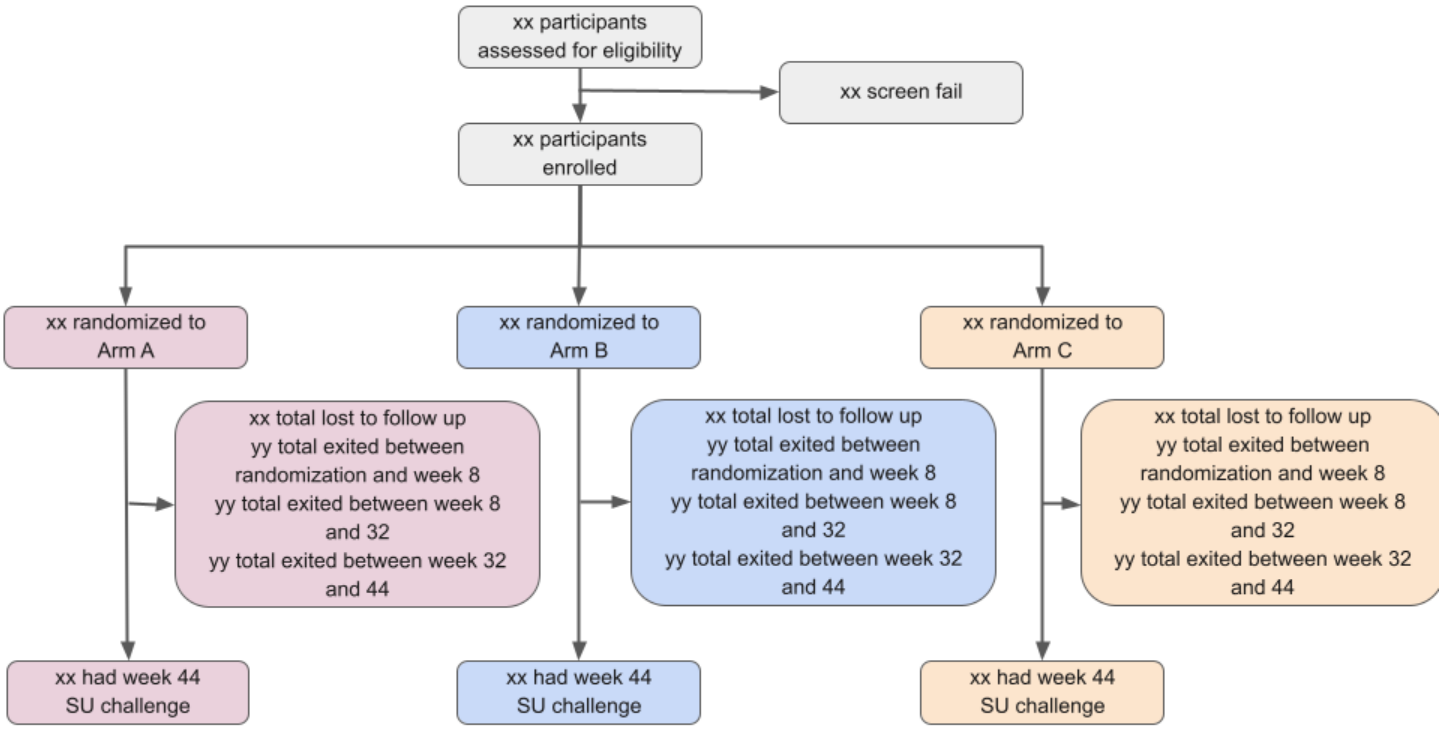
Outcome	Description	Variables and source	Specifications
Week_32_peanut_pass: Did the participant pass peanut protein tolerance at Week 32 immediately after OIT. (CTD > 1043mg)	Binary variable 1: Participant tolerated peanut at week 32 (CTD > 1043) 0: Participant could not tolerate peanut at week 32 (CTD < 1043mg for peanut)	Redcap	If a subject does not tolerate 1043 mg of peanut protein at week 32, then they are considered failures. The subject is then considered a failure for all peanut food challenges at week 44. These subjects are following the protocol.
Week_32_allergen_pass: Did the participant pass allergen tolerance at Week 32 immediately after OIT for any other allergen (peanut or other) (CTD > 1043mg)	Binary variable 1: Participant tolerated any allergen protein (peanut or other) at week 32 (CTD > 1043) 0: Participant could not tolerate any allergens (peanut or other) at week 32 (CTD < 1043mg)	Redcap	If a subject does not tolerate 1043 mg of any allergen protein at week 32, then they are considered failures. The subject is then considered a failure for all allergen food challenges at week 44. These subjects are following the protocol.
SPT Wheel Diameter (mm)	For each allergen for each time point		SPT will be coded as a continuous variable based on the wheel diameter.

4. Approach for Addressing Aims

4.0 Baseline Demographic and Clinical Characteristics

4.0.1 Consort Diagram

We will use a consort diagram to describe how our study arms were established.



4.0.2 Demographic Table

Descriptive statistics (proportions and frequency distributions (for categorical variables), means and standard deviations or medians and interquartile ranges (for continuous variables) will be presented, including baseline and demographic characteristics, use of medications,

Mock Table 1

	Total (n = 110)	Omalizumab (n = 50)	Omalizumab+ Dupilumab (n = 50)	Dupilumab (n = 10)
Sex				
Male n (%)	55 (50%)	25	25	5
Female n (%)	55 (50%)	25	25	5
Age in years, median (range)	20 (6 – 52)	20 (6 – 52)	20 (6 – 52)	20 (6 – 52)
4 years – 10 years 11 mo (n)	44	20	20	4
11 years – 17 years 11 mo (n)	44	20	20	4
≥18 years old (n)	22	10	10	2
Atopic Disorder History				
Allergic Rhinitis n (%)	21 (19%)	10	10	1
Asthma n (%)	21 (19%)	10	10	1
Atopic Dermatitis n (%)	21 (19%)	10	10	1
Number of Allergens Administered during OIT				
2 foods	67	30	30	7
3 foods	43	20	20	3
Participants with certain food in OIT, n (%)				
Peanut	110 (100%)	50	50	10
Almond	10 (9.1%)	3	5	2
Cashew	50 (45%)	27	22	1
Egg	10 (9.1%)	3	5	2
Hazelnut	10 (9.1%)	3	5	2
Milk	10 (9.1%)	3	5	2
Pecan	10 (9.1%)	3	5	2
Sesame	3 (2.7%)	1	1	1
Walnut	50 (45%)	27	22	1

4.1 Primary Aims Analysis Plan

To achieve our study goals, we will largely compare Arm A (OIT plus omalizumab alone) with our experimental arm of interest, Arm B (omalizumab followed by the combination of OIT with dupilumab).

Primary Aim 1: To determine if omalizumab followed by the combination of OIT with dupilumab will increase the ability to sustain clinical tolerance to **peanuts** in the absence of continued therapy relative to OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals with a peanut allergy.

Primary Aim 2: To determine if omalizumab followed by the combination of OIT with dupilumab will increase the ability to sustain clinical tolerance to **peanuts plus one other allergen** in the absence of continued therapy relative to OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals with a peanut allergy.

Primary Aim 3: To determine if omalizumab followed by the combination of OIT with dupilumab will increase the ability to sustain clinical tolerance to **peanuts plus two other allergens** in the absence of continued therapy relative to OIT plus omalizumab alone (without dupilumab) solely among multi-allergic individuals with a peanut allergy and two other allergies.

Mock Data

While the real data will have more subjects, we made mock data for 12 participants. There are 6 subjects in Arm A (omalizumab) and 6 subjects in Arm B (Omalizumab and Dupilumab). All participants will have values for Week 32, Peanut_O1, and Peanut_O2. This is because all participants have an allergy to peanuts and one more allergen. Only participants who have 3 allergies will have a value for Peanut_O3. In this mock data example 3 participants in Arm A and 5 participants in Arm B have an allergy to peanuts and two more allergens. Failing is an absorbing state. Therefore, once a subject fails a food challenge, they remain a failure for the remainder of the study. Participants can move from Pass to Fail but cannot move from Fail to Pass.

ID	Arm	Week 32	Peanut_O1	Peanut_O2	Peanut_O3
1	A	1	1	1	0
2	A	1	1	1	NA*
3	A	1	0	0	0
4	A	1	1	0	NA*
5	A	1	0	0	NA*
6	A	1	1	1	1
7	B	0	0	0	0
8	B	1	0	0	0
9	B	1	0	0	NA*
10	B	1	1	1	1
11	B	1	1	0	0
12	B	1	1	1	1

***NA here means Not Available. This is not a missing value. Participants who are treated for less than three allergens will not have Peanut_O3 values.**

Data Visualization of Food Challenges

First, we will leverage a Sankey plot to describe the various outcome pathways among patients randomized to Arms A and B in the intent-to-treat analysis population. Below is a Mock Sankey plot based off the following mock data.

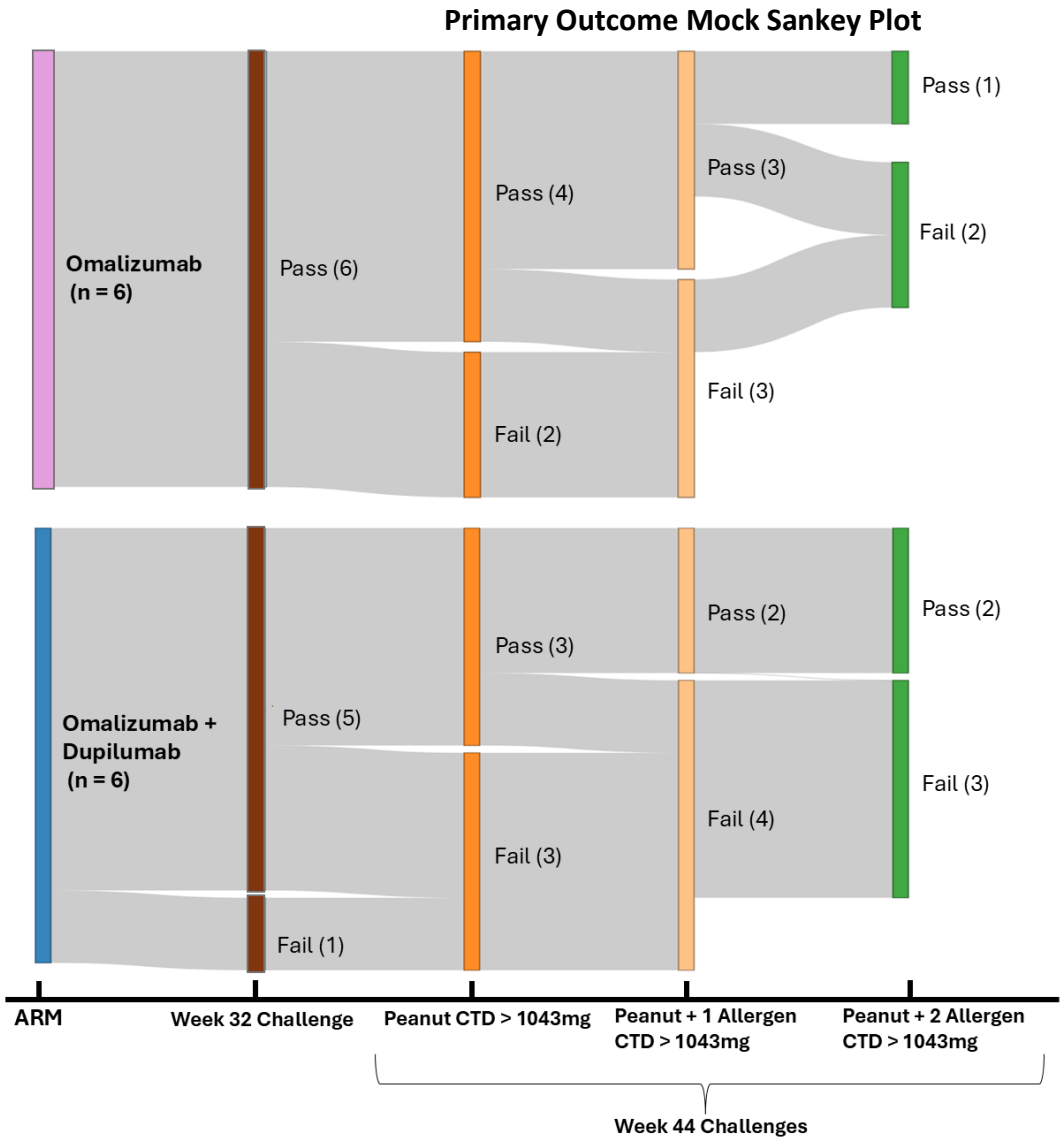


Figure Legend: The number of participants within each group are displayed within the parenthesis. CTD: Cumulative tolerated dose.

Mock Interpretation of Plot:
Although Arm B had more participants fail the Week 32 test, more participants tolerated 1043 mg of peanut and two other allergens compared to Arm A. More participants who were randomized to Study Arm B had sustained unresponsiveness to peanut and two other allergens compared to those participants who only received OIT and omalizumab.

PLEASE NOTE: The following primary hypothesis testing procedure is a revision/ update from the protocol.

Section 13.4.2 of the Protocol states "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."

We will instead use Fisher's exact test for all hypothesis tests to avoid switching between tests.

Primary Hypothesis Test

To address whether the combination therapy (Study Arm B) is superior to Study Arm A, we compare the rate of sustained unresponsiveness at Week 44 using the intent-to-treat analysis population. To that end, **we assume those who are lost to follow up are failures and will have a value of 0 (fail) for the remaining food challenges they do not participate in.** Subjects that only have an allergy to peanuts and one other allergen will not have any value for Peanut + 2 Food Challenge, even if they are lost to follow up. Further, we will use a fixed sequencing testing procedure to assess the differences between the two treatment arms. A two-sided Fisher's exact test with an **alpha level of 0.05** will be performed at the following three steps described below in hierarchical fashion. If we reject the null hypothesis corresponding to the first test, we will then test the next hypothesis. However, if we fail to reject, we will not test the next step. The success rate for each of the three co-primary endpoints in each arm will also be estimated, with exact binomial confidence interval.

The order of tests is as follows:
1: Is there a difference between the proportion of participants who had sustained unresponsiveness to **peanut** between Arms A and B at Week 44
2. Is there a difference between the proportion of participants who had sustained unresponsiveness to **peanut plus one other allergen** between Arms A and B at Week 44
3. Among those with at least three allergens (including peanut), is there a difference between the proportion of participants who had sustained unresponsiveness to **peanut plus two other allergens** between Arms A and B at Week 44

Imputation Procedure

We assume those who are lost to follow up are failures and will have a value of 0 (fail) for the remaining food challenges they do not participate in. We do not anticipate missingness within the covariates but will consider multiple imputation procedure if we do find missingness.

Primary Hypothesis Step 2 Test: Sensitivity Analysis (Assess Sensitivity of Our Findings to Adjustment of Potential Confounder – the Number of Food Allergies – by Stratification)

If the first test is significant, we will also perform a Fisher – Freeman – Halton test stratifying by 2 vs 3 food allergies on the second step to determine the sensitivity of findings to how the confounder of the number of food allergies is handled. If appropriate to combine tables and yield a summary odds ratio, we will compare our resulting point estimate along with confidence intervals to that obtained from our primary analysis. If not appropriate to combine tables (i.e., there is a strong suggestion of heterogeneity of treatment effect), we will describe the respective odds ratios and compare these to the primary findings, although a large difference will already have been discovered in the heterogeneity of treatment effect and noted.

Primary Hypothesis Test: Sensitivity Analysis (Assess Sensitivity of Our Findings to Adjustment of Age and Atopy as Potential Confounder by Regression)

To additionally assess sensitivity of findings to adjustment of potential confounders – age and atopy – we will use a logistic regression model with an interaction term by stratifying by the following 4 categories (< 11, absence of atopy; <11 presence of atopy; 11+, absence of atopy; 11+ presence of atopy) and assessing differences in the primary outcome between Arm A and Arm B. If appropriate to combine tables and yield a summary odds ratio, we will compare our

resulting point estimate along with confidence intervals to that obtained from our primary analysis. If not appropriate to combine tables (i.e., there is a strong suggestion of heterogeneity of treatment effect), we will describe the respective odds ratios and compare these to the primary findings, although a large difference will already have been discovered in the heterogeneity of treatment effect and noted.

Odds Ratios

An odds ratio with 95% binomial confidence interval will be calculated for each of the three co-primary endpoints. Exact binomial confidence interval will be used when using Fisher's exact test.

Mock Odds Ratio Table for Primary Outcomes (Written Description Version)

	Sustained clinical tolerance to peanut	Sustained clinical tolerance to peanut plus one allergen	Sustained clinical tolerance to peanut plus two allergens
Arm B (Omilizumab + Dupilumab)	Number of people in Arm B who tolerated 1043mg of peanut / Number of people in Arm B who did not tolerate 1043mg of peanut	Number of people in Arm B who tolerated 1043mg each of peanut and one other allergen / Number of people in Arm B who did not tolerate 1043mg each of peanut and one other allergen	Number of people in Arm B who tolerated 1043mg each of peanut and two other allergens / Number of people in Arm B who did not tolerate 1043mg each of peanut and two other allergens
Arm A (Only Omalizumab)	Number of people in Arm A who tolerated 1043mg of peanut / Number of people in Arm A who did not tolerate 1043mg of peanut	Number of people in Arm A who tolerated 1043mg each of peanut and one other allergen / Number of people in Arm A who did not tolerate 1043mg each of peanut and one other allergen	Number of people in Arm A who tolerated 1043mg each of peanut and two other allergens / Number of people in Arm A who did not tolerate 1043mg each of peanut and two other allergens
	OR (CI) q	OR (CI) q	OR (CI) q

Mock Odds Ratio Table for Primary Outcomes with Fake Data

	Sustained clinical tolerance to peanut	Sustained clinical tolerance to peanut plus one allergen	Sustained clinical tolerance to peanut plus two allergens
Arm B (Omilizumab + Dupilumab)	35/10	25/20	15/10
Arm A (Omilizumab)	25/25	15/35	3/12
	OR (CI) = 3.5 (1.43, 8.57) P = 0.003	OR (CI) = 2.92 (1.25, 6.78) P = 0.006	OR (CI) = 6 (1.34, 26.81) P = 0.009

Mock interpretation of Odds Ratio (NOT REAL): In our study, participants in arm B (who received omalizumab and dupilumab) were more than three times as likely to have a sustained tolerance to peanuts after being off all treatment for 12 weeks compared to participants in Arm A, who only received dupilumab (p=0.003). Those who received omalizumab and dupilumab were almost 3 times more likely to have sustained tolerance to peanuts and one other allergen after a 12 week break from treatment compared to those who only received dupilumab (p = 0.006). Finally, among those with at least three allergens (N=35), the odds ratio of sustained tolerance in Arm B vs A was 6, with a 95% CI of 1.34 to 26.81).

Per Protocol Population: Sensitivity Analysis

Within the intent to treat population, participants who were lost to follow up are imputed as failures. We will evaluate the superiority of Arm B relative to Arm A using the per protocol analysis population. These are ONLY the subjects that did not withdraw, were not lost to follow up, and followed the protocol to the end. For discussion, we will acknowledge the potential bias that can be introduced into this sensitivity analysis that challenges the intent to treat assumption.

MOCK RESULTS

ITT Population	**Omalizumab + Dupilumab** number of participants who passed / number of participants who failed	**Omalizumab** number of participants who passed / number of participants who failed	**Odds Ratio** (Confidence Interval)
Peanut Food Challenge	Xx/yy	Xx/yy	OR (CI) = 3.5 (1.43, 8.57) P = 0.003
Peanut + 1 Food Challenge	Xx/yy	Xx/yy	OR (CI) = 2.92 (1.25, 6.78) P = 0.006
Peanut + 2 Food Challenge	Xx/yy	Xx/yy	OR (CI) = 6 (1.34, 26.81) P = 0.009
PP Population			
Peanut Food Challenge	Xx/yy	Xx/yy	OR=2.56, 95% CI: 2.4-3.6, P-value = 0.045
Peanut + 1 Food Challenge	Xx/y	Xx/yy	OR=1.1, 95% CI: 0.85-1.2, p=0.67
Peanut + 2 Food Challenge	Xx/yy	Xx/yy	

Mock Interpretation: Our findings are comparable for the first test where we reject the null hypothesis (OR=2.56, 95% CI: 2.4-3.6, P-value = 0.045). However, unlike our primary analysis, we did not provide sufficient evidence to reject the second test that Arm B was superior to Arm A in sustaining unresponsiveness at Week 44 for peanut and another allergen (OR=1.1, 95% CI: 0.85-1.2, p=0.67). Thus, the third test was not performed. These findings demonstrate that among those who were able to adhere to protocol and complete our study, there was sufficient evidence of the combination therapy in sustaining effects for peanut, but not sufficient evidence to draw conclusions about additional allergens.

Tipping Point Analysis

Within the intent to treat population, participants who were lost to follow up are imputed as failures. To evaluate the impact of the missing data from lost to follow ups, a tipping point analysis will be conducted. The tipping point analysis will only be performed on the first primary outcome (ie tolerating 1043mg of peanut protein at week 44). Imputed fail outcomes will be systemically varied between pass and fail for participants with missing data until there is no statistically significant difference in the likelihood of passing the week 44 peanut food challenge between those who received omalizumab and dupilumab and those who only received omalizumab. A two sided Fisher's exact test with an alpha level of 0.05 will be leveraged to test for significance. This is intended to understand how rigorous our results are to the missing data and to understand how the results would change if we imputed missing data as food challenge passes. We will report the threshold for which results lost their significance.

Mock Interpretation: The proportion of patients who were lost to follow up was comparable across the two arms (XX% and YY% for Arms A and B, respectively). Recall that our primary analysis assumed these individuals did NOT have sustained tolerance to peanut at Week 44. Tipping point analysis demonstrated that the treatment effect lost

significance when assuming more than 50% of missing participants in the control treatment group did have sustained clinical tolerance to peanut allergen at week 44, highlighting some sensitivity to missing data assumptions.

4.2 Secondary Aims 1 – 14 Analysis Plan

The main goal for secondary aims is to determine if the combined experimental treatment of omalizumab + dupilumab increased the likelihood of sustained clinical tolerance for any allergen, not just peanut relative to the only receiving omalizumab.

Secondary Aim 1: Is there a difference in the proportion of participants who sustained clinical tolerance to **one allergen** at week 44 between Arms A and B.
Secondary Aim 2: Is there a difference in the proportion of participants who sustained clinical tolerance to **at least two allergens** at week 44 between Arms A and B.
Secondary Aim 3: Is there a difference in the proportion of participants who **tolerated 2,043 mg of one allergen at week 44** between Arms A and B.
Secondary Aim 4: Is there a difference in the proportion of participants who **tolerated 2,043 mg of two different allergens at week 44** between Arms A and B.
Secondary Aim 5: Is there a difference in the proportion of participants who **tolerated 2,043 mg of three different allergens at week 44** between Arms A and B.
Secondary Aim 6: Is there a difference in the proportion of participants who **tolerated 4,043 mg of one allergen at week 44** between Arms A and B.
Secondary Aim 7: Is there a difference in the proportion of participants who **tolerated 4,043 mg of two different allergens at week 44** between Arms A and B.
Secondary Aim 8: Is there a difference in the proportion of participants who **tolerated 4,043 mg of three different allergens at week 44** between Arms A and B.
Secondary Aim 9: Is there a difference in the proportion of participants who **tolerated 4,043 mg of one allergen at week 32** between Arms A and B.
Secondary Aim 10: Is there a difference in the proportion of participants who **tolerated 4,043 mg of two different allergens at week 32** between Arms A and B
Secondary Aim 11: Is there a difference in the proportion of participants who **tolerated 4,043 mg of three different allergens at week 32** between Arms A and B.
Secondary Aim 12: Is there a difference in the proportion of participants who had a **10-fold change in cumulative tolerance amount for one allergen at week 44** between Arms A and B.
Secondary Aim 13: Is there a difference in the proportion of participants who had a **10-fold change in cumulative tolerance amount for two allergens at week 44** between Arms A and B.
Secondary Aim 14: Is there a difference in the proportion of participants who had a **10-fold change in cumulative tolerance amount for three allergens at week 44** between Arms A and B.

Hypothesis Testing Analysis

For each of the following secondary outcomes, we will first calculate the odds ratio and the 95% confidence interval to compare the experimental treatment group (omalizumab + dupilumab) with the control group (omalizumab alone). We will assess the significance of the difference between the groups by using a two-sided Fisher's exact test. We will adjust for false discovery rate using Benjamini-Hochberg procedure. We will also add a forest plot to visualize the odds ratios.

	Omalizumab + Dupilumab number of people who passed (value of 1) / number of people who failed (value of 0)	**Omalizumab** number of people who passed (value of 1) / number of people who failed (value of 0)	**Odds Ratio** (Confidence Interval)	**P value**	**Adjusted p value**
Secondary Aim 1: Allergen_O1					
Secondary Aim 2: Allergen_O2					
Secondary Aim 3: Allergen1_2043_w44					
Secondary Aim 4: Allergen2_2043_w44					
Secondary Aim 5: Allergen3_2043_w44					
Secondary Aim 6: Allergen1_4043_w44					
Secondary Aim 7: Allergen2_4043_w44					
Secondary Aim 8: Allergen3_4043_w44					
Secondary Aim 9: Allergen1_4043_w32					
Secondary Aim 10: Allergen2_4043_w32					
Secondary Aim 11: Allergen3_4043_w32					
Secondary Aim 12: FC_w44_o1					
Secondary Aim 13: FC_w44_o2					
Secondary Aim 14: Fc_w44_o3					

4.3 Secondary Aims 15 and 16 Analysis Plan

The main goal for the mechanistic aims is to determine if the combined experimental treatment of omalizumab + dupilumab increased tolerance levels for any allergen, even if the tolerance level did not reach clinical significance, relative to a treatment of omalizumab alone.

Secondary Aim 15: To determine if participants who received omalizumab in combination with OIT and dupilumab have an **increased tolerance to peanut allergen, even if that tolerance level does not reach the clinical level**, relative to participants who received OIT plus omalizumab alone (without dupilumab).
Secondary Aim 16: To determine if participants who received omalizumab in combination with OIT and dupilumab have a **smaller wheel diameter after a peanut skin prick test at week 44** relative to participants who received OIT plus omalizumab alone (without dupilumab).

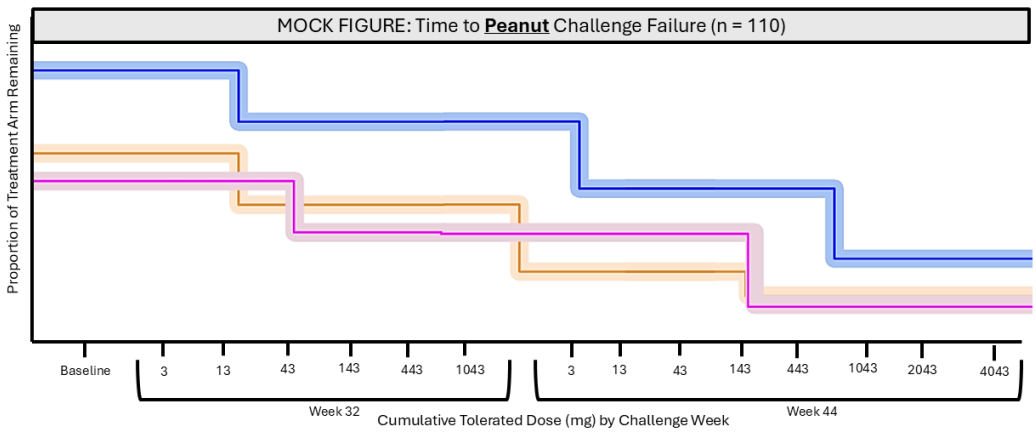
Time to Failure for Peanut

We will display time to fail curves for peanut cumulative tolerated dose (mg) for each of the three arms. This will help us understand at what peanut protein dose level participants in each arm failed at. Week and cumulative tolerated dose will be considered jointly. We will show all three arms for transparency. **We will calculate the hazard ratio and the 95% confidence interval for the comparison between arm A and B.**

UPDATE: To compare the distribution of dose-to-event, we will also calculate log rank test between all three arms and between arms A and B.

Below is a MOCK figure of that displays the survival curves for the cumulative tolerated dose of peanut allergen for all three treatment groups. **We will repeat the same analysis for the next top four allergens.** The top four allergens are likely cashew, walnut, egg, and milk. This will result in five out of thirteen allergens having the described time-to-failure analysis.

Mock Interpretation: Participants who received only omalizumab or only dupilumab had a lower cumulative tolerated dose for peanut allergen compared to the participants who received the omalizumab and dupilumab combination. The hazard ratio is 0.75, showing that the treatment group has a decreased risk in failing their food challenges. In other words, the treatment group is able to tolerate more peanut protein before having an adverse event.



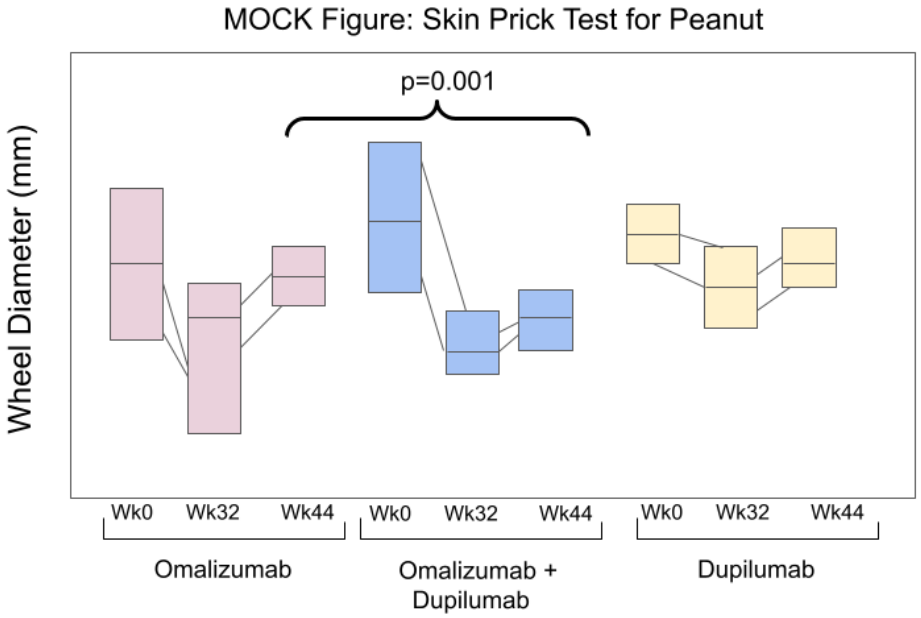
Number of Participants at Risk of Failing Peanut Challenge

Omalizumab + Dupilumab	**50**	**50**	**50**	**45**	**40**	**39**	**38**	**38**	**20**	**19**	**19**	**12**	**8**	**7**	**2**
Omalizumab	50	50	45	42	41	37	33	32	25	22	12	6	6	3	1
Dupilumab	10	10	10	10	8	7	5	5	4	4	3	2	2	0	0

Skin Prick Test: Peanut Wheel Diameter Analysis

The figure below displays the peanut skin prick test wheel diameter mean for each treatment group and food challenge time point. Lines are to connect individual participant wheel diameter values across the three time points. For transparency, we will show skin prick test results at all three time points. However, we are only interested in looking at the difference in wheel diameter at week 44 between Arms A and B to understand if combination therapy decreased the likelihood of allergic reactions. Therefore, we will perform a Student's t-test to determine if there is a statistical difference in wheel diameter mean at week 44 between participants who received omalizumab and dupilumab and participants who received only omalizumab. Performing a Student's t-test on wheel diameters at week 0 between arms A and B should result in a p-value > 0.05 because this is a randomized control trial.

We will repeat this analysis on cashew, walnut, milk, and egg.



Mock Interpretation: Participants who received the combination treatment of omalizumab and dupilumab had a smaller wheel diameter after a peanut skin prick test at week 44 compared to participants who only received omalizumab as treatment (p = 0.001).

Skin Prick Normalization

We will normalize SPT wheel size by subtracting the negative control.

4.4 Secondary Aims 17 - 22 Analysis Plan (IgE IU/mL and IgG4 Aims)

Secondary Aim 17: To determine if participants who received omalizumab in combination with OIT and dupilumab have a **smaller total IgE** relative to participants who received OIT plus omalizumab alone (without dupilumab).

Secondary Aim 18: To determine if participants who received omalizumab in combination with OIT and dupilumab have a **smaller total peanut-specific IgE** relative to participants who received OIT plus omalizumab alone (without dupilumab).

Secondary Aim 19: To determine if participants who received omalizumab in combination with OIT and dupilumab have a **smaller total walnut-specific IgE** relative to participants who received OIT plus omalizumab alone (without dupilumab).

Secondary Aim 20: To determine if participants who received omalizumab in combination with OIT and dupilumab have a **smaller total cashew-specific IgE** relative to participants who received OIT plus omalizumab alone (without dupilumab).

Secondary Aim 21: To determine if participants who received omalizumab in combination with OIT and dupilumab have a **higher specific IgG4** relative to participants who received OIT plus omalizumab alone (without dupilumab).

Secondary Aim 22: To determine if participants who received omalizumab in combination with OIT and dupilumab have a **larger IgG4/IgE ratio** relative to participants who received OIT plus omalizumab alone (without dupilumab).

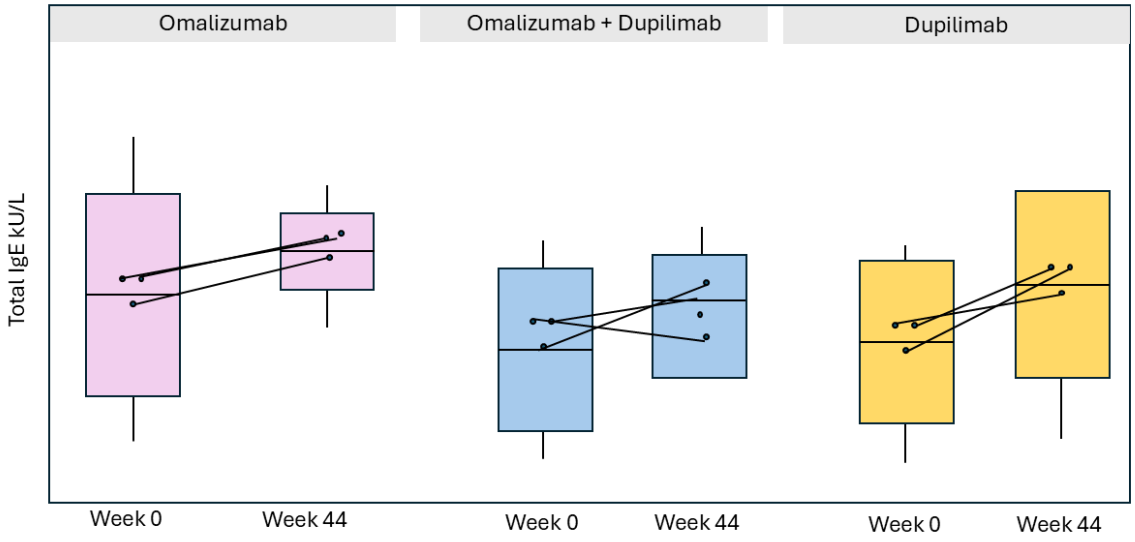
Total IgE Analysis

We will use a mixed model as analysis for total IgE. The model will include fixed effects for Time point (a binary indicator for Week 44), a Time * Intervention term at Week 44, and a random intercept for participant. The model is specified as follows:

$$total\ IgE_{ij} = \beta_0 + \beta_1 \cdot \text{Time}_j + \beta_2 \cdot \text{Intervention}_i \cdot \text{Time}_j + u_i + \epsilon_{ij}$$

where:

- $total\ IgE_{ij}$ = Total IgE for subject i at time point j
- Time_j= Time point indicator (1 = Week 44, 0 = Week 0)
- Intervention_i= Intervention arm for subject i (1 = Oma + Dupi, 0 = Oma)
- u_i = Random intercept for subjects
- ϵ_{ij} = Residual error



The treatment effect can be obtained from the regression coefficient for the interaction between the intervention variable and time (the overall treatment effect over time; $\boldsymbol{\beta_2}$ in equation). **The coefficient β_2 refers to the additional change in IgE over time for the Omalizumab and Dupilumab group compared to the Omalizumab only group.** We will show the coefficient value, the 95% Confidence Interval, and the p-value. We will also plot the Week 0 and Week 44 values for all three groups for transparency.

We will repeat this analysis on peanut specific IgG4 (secondary aim 21), peanut specific IgG4/IgE ratio (secondary aim 22), peanut-specific IgE (secondary aim 18), walnut-specific IgE (secondary aim 19), cashew-specific IgE (secondary aim 20).

Multiple Comparison Adjustment (Aims 17 – 22)

We will adjust for false discovery rate using Benjamini-Hochberg procedure.

Data Transformation (Aims 17 – 22)

If data is skewed, we will do a log transformation.

4.5 Safety Outcomes Analysis Plan

This aim is to understand the difference in the number of safety events between the three treatment arms - omalizumab followed by the combination of OIT with dupilumab, omalizumab followed by the combination of OIT alone, and OIT and dupilumab alone. We expect participants who received omalizumab followed by the combination of OIT with dupilumab will have a smaller number of safety events compared to the other two treatment groups.

Safety Aim 1: This is a descriptive aim to understand the difference in the number of safety events across the three treatment arms - omalizumab followed by the combination of OIT with dupilumab, omalizumab followed by the combination of OIT alone, and OIT and dupilumab alone.

Hypothesis: We expect participants who received omalizumab followed by the combination of OIT with dupilumab will have a smaller number of safety events compared to the other two treatment groups.

Safety Aim 2: To determine if the omalizumab and dupilumab group is **less likely to drop out from the study due to adverse events**, we will compare dropout rates between the arms.

Hypothesis: The omalizumab and dupilumab group is less likely to drop out of the study due to adverse events compared to the omalizumab only group.

Safety Aim 3: To determine if the omalizumab and dupilumab group **has less GI Symptoms per OIT dose** compared with the omalizumab only group, we will compare symptoms that impact the GI system between the arms.

Hypothesis: Participants in the omalizumab and dupilumab group have fewer GI Symptoms per OIT dose compared to the omalizumab only group.

Safety Aim 4: To determine if the omalizumab and dupilumab group **has the same amount of non-GI Symptoms per OIT dose** compared with the omalizumab only group, we will compare symptoms that impact non-GI systems between the arms.

Hypothesis: Participants in the omalizumab and dupilumab group will have similar rates of non-GI symptoms per OIT dose as the omalizumab only group.

Adverse Events Figure

We will first make a figure showing the times at which a dose reaction or an adverse event occurred for each participant.

Mock Adverse Event Plot

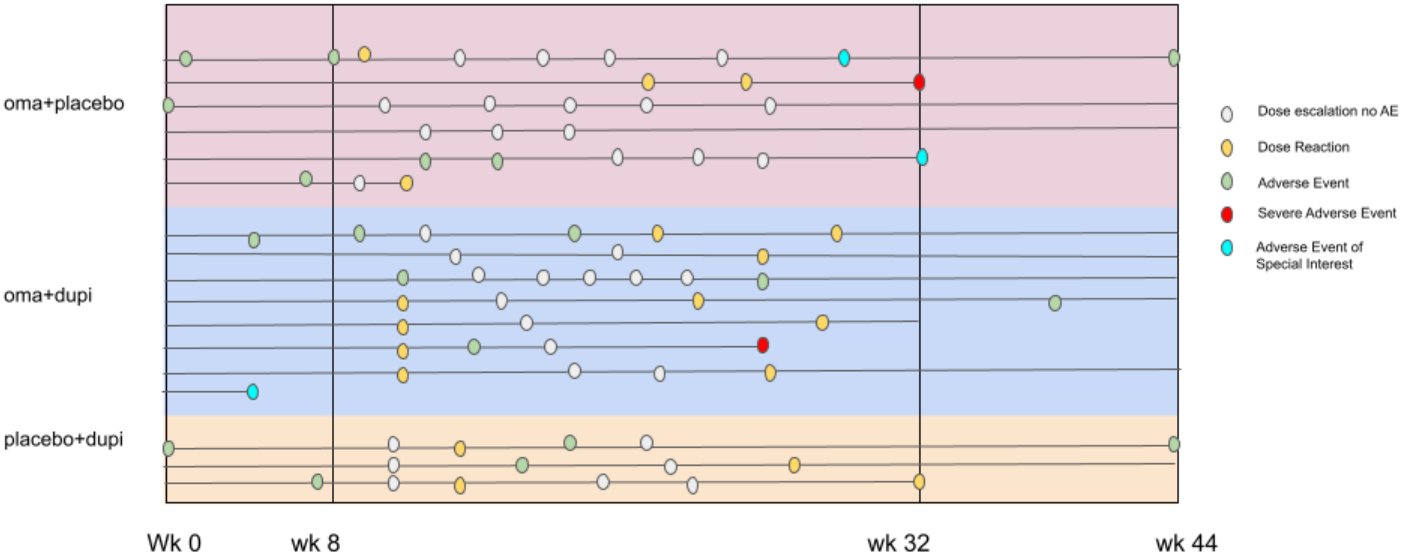


Figure legend: Only related and possibly related safety events are recorded. Lines indicate a single participant over time. Actual plot will be much denser.

Adverse Events Table

We will fill out the tables below to understand how many participants had adverse events during the study. The table will show each treatment arm and each time point. We will perform a Fisher – Freeman – Halton test each of the time frames (week 0 -8, week 8-32, week 32 – 44) to compare number of participants who had an adverse event between the three groups. The Fisher – Freeman – Halton test is an extension of the Fisher's exact test to use when contingency tables are larger than 2 x2. We will do the same analysis for dose reactions.

MOCK TABLE: Number and percentage of participants that experienced Adverse Events (AE) by week range and treatment arm

Treatment Arm and Time Period	Number of participants in phase and arm	Number of participants who had an AE (% of Total)	Organ System				AE Grade					P-value
			GI # (%)	General # (%)	Resp # (%)	Skin # (%)	1 # (%)	2 # (%)	3 # (%)	4 # (%)	5 # (%)	
Week 0 – 8												
Omalizumab + Dupilumab	50	10 (20%)	5 (10%)	1 (2%)	4 (8%)	6 (12%)	9 (18%)	7 (14%)	2 (4%)	2 (4%)	2 (4%)	0.001
Omalizumab	50	15 (30%)	8 (16%)	4 (8%)	10 (20%)	2 (4%)	12 (24%)	4 (8%)	4 (8%)	4 (8%)	4 (8%)	
Dupilumab	10	5 (50%)	2 (20%)	3 (30%)	5 (50%)	1 (10%)	3 (30%)	3 (30%)	2 (20%)	0	0	
Week 8 – 32												
Omalizumab + Dupilumab	45	25 (55%)										
Omalizumab	45	30 (67%)										
Dupilumab	8	8 (100%)										
Week 32 – 44												
Omalizumab + Dupilumab	40	20 (50%)										
Omalizumab	40	25 (63%)										
Dupilumab	6	5 (83%)										

GI: Gastrointestinal

Resp: Respiratory

Other indicates eye, nervous system, or vascular reactions

MOCK TABLE: Number and percentage of participants that experienced Dose Reactions (DR) by week range and treatment arm

Treatment Arm and Time Period	Number of participants in phase and arm	Number of participants who had an DR (% of Total)	Organ System				DR Grade		P-value
			GI # (%)	General # (%)	Resp # (%)	Skin # (%)	1 # (%)	2 # (%)	
Week 0 – 8									
Omalizumab + Dupilumab									
Omalizumab									
Dupilumab									
Week 8 – 32									
Omalizumab + Dupilumab									
Omalizumab									
Dupilumab									
Week 32 – 44									
Omalizumab + Dupilumab									
Omalizumab									
Dupilumab									

GI: Gastrointestinal

Resp: Respiratory

Other indicates eye, nervous system, or vascular reactions

Safety Aim 2: AE dropout rates

To test this, we will first calculate the odds ratio and the 95% confidence interval to compare the experimental treatment group (omalizumab + dupilumab) with the control group (omalizumab alone). We will assess the significance of the difference between the groups by using a two-sided Fisher's exact test.

ITT Population	**Omalizumab + Dupilumab**	**Omalizumab**	**Odds Ratio** (Confidence Interval)
number of participants who dropped out due to Adverse events (XX) / number of participants in the arm(yy)	Xx/yy	Xx/yy	OR (CI) = XXX (XX, XX) P = XXX

Safety Aim 3: GI Symptoms per OIT dose

We will perform a one-sided Wilcoxon test to determine if there is a statistical difference in the GI symptoms per OIT dose rate between the omalizumab and dupilumab group and the omalizumab only group. Itchy mouth symptoms will be excluded.

Safety Aim 4: non-GI Symptoms per OIT dose

We will perform a two-sided Wilcoxon test to determine if there is a statistical difference in the non-GI symptoms per OIT dose rate between the omalizumab and dupilumab group and the omalizumab only group. Itchy mouth symptoms will be excluded.

5. Limitations

All design and analysis limitations (this will grow as you do the study and should be included in the report)

6. Addendum for Additional Analyses

All post-hoc analyses should be described here. If minor changes are made to the main analysis (e.g. adding a covariate to the model), this can be changed in the main analysis section above and a note should be added to the activity log.

Additional Secondary aim:

We will calculate the Odds ratio for these aims. However they will not be included in statistical significance testing. Therefore results should not be used to infer treatment effect.

Other Secondary Aim 1: To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood **of tolerating 2,043 mg of one allergen at week 32** relative to participants who received OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals.

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance at week 32 at a cumulative dose of 2,043 mg for one allergen relative to OIT treatment with omalizumab alone.

Other Secondary Aim 2: To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood **of tolerating 2,043 mg each of at least two allergens at week 32** relative to participants who received OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals.

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance at week 32 at a cumulative dose of 2,043 mg for each of two different allergens relative to OIT treatment with omalizumab alone.

Other Secondary Aim 3: (Only applies to cohort subgroup that had allergies to peanuts and two other allergens.) To determine if participants assigned to receive omalizumab in combination with OIT and dupilumab have an increased likelihood **of tolerating 2,043 each mg of all three allergens at week 32** relative to participants assigned to OIT plus omalizumab alone (without dupilumab) **among multi-allergic individuals with at least three allergies.**

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance at week 32 at a cumulative dose of 2,043 mg for each of three different allergens relative to OIT treatment with omalizumab alone.

Other Secondary Aim 4: To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood of having a **10-fold change in cumulative tolerance amount for at least one allergen at week 32** compared to their baseline allergen tolerance relative to participants who received OIT plus omalizumab alone (without dupilumab).

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of having a 10-fold change in cumulative tolerance amount for one allergen at week 32 compared to their baseline allergen tolerance relative to OIT treatment with omalizumab alone.

Other Secondary Aim 5: To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood of having a **10-fold change in cumulative tolerance amount for each of two different allergens at week 32** compared to their baseline allergen tolerance relative to participants who received OIT plus omalizumab alone (without dupilumab).

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of having a 10-fold change in cumulative tolerance amount for each of two different allergens at week 32 compared to their baseline allergen tolerance relative to OIT treatment with omalizumab alone.

Other Secondary Aim 6: (Only applies to cohort subgroup that had allergies to peanuts and two other allergens.) To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood of having a **10-fold change in cumulative tolerance amount for each of three different allergens at week 32** compared to their baseline allergen tolerance relative to participants who received OIT plus omalizumab alone (without dupilumab) **among multi-allergic individuals with at least three allergies.**

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of having a 10-fold change in cumulative tolerance amount for each of three different allergens at week 32 compared to their baseline allergen tolerance relative to OIT treatment with omalizumab alone.

Other Secondary Aim 7: To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood **of tolerating 1,043 mg of one allergen at week 32** relative to participants who received OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals.

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance at week 32 at a cumulative dose of 1,043 mg for one allergen relative to OIT treatment with omalizumab alone.

Other Secondary Aim 8: To determine if participants who received omalizumab in combination with OIT and dupilumab have an increased likelihood **of tolerating 1,043 mg each of at least two allergens at week 32** relative to participants who received OIT plus omalizumab alone (without dupilumab) among multi-allergic individuals.

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance at week 32 at a cumulative dose of 1,043 mg for each of two different allergens relative to OIT treatment with omalizumab alone.

Other Secondary Aim 9: (Only applies to cohort subgroup that had allergies to peanuts and two other allergens.) To determine if participants assigned to receive omalizumab in combination with OIT and dupilumab have an increased likelihood **of tolerating 1,043 each mg of all three allergens at week 32** relative to participants assigned to OIT plus omalizumab alone (without dupilumab) **among multi-allergic individuals with at least three allergies.**

Hypothesis: We hypothesize that treatment with dupilumab, combined with omalizumab and OIT will increase the likelihood of sustained unresponsiveness tolerance at week 32 at a cumulative dose of 1,043 mg for each of three different allergens relative to OIT treatment with omalizumab alone.

FC_W32_O1 participant has a 10-fold change in the cumulative tolerance dose compared to baseline at week 32	Binary variable 1: participant's ratio between week 32 and baseline CTD is equal to greater than 10 for one allergen	Source:REDCap Study arm CTD		Missing values due to loss to follow up are treated as failures for the intent-to-treat population and as

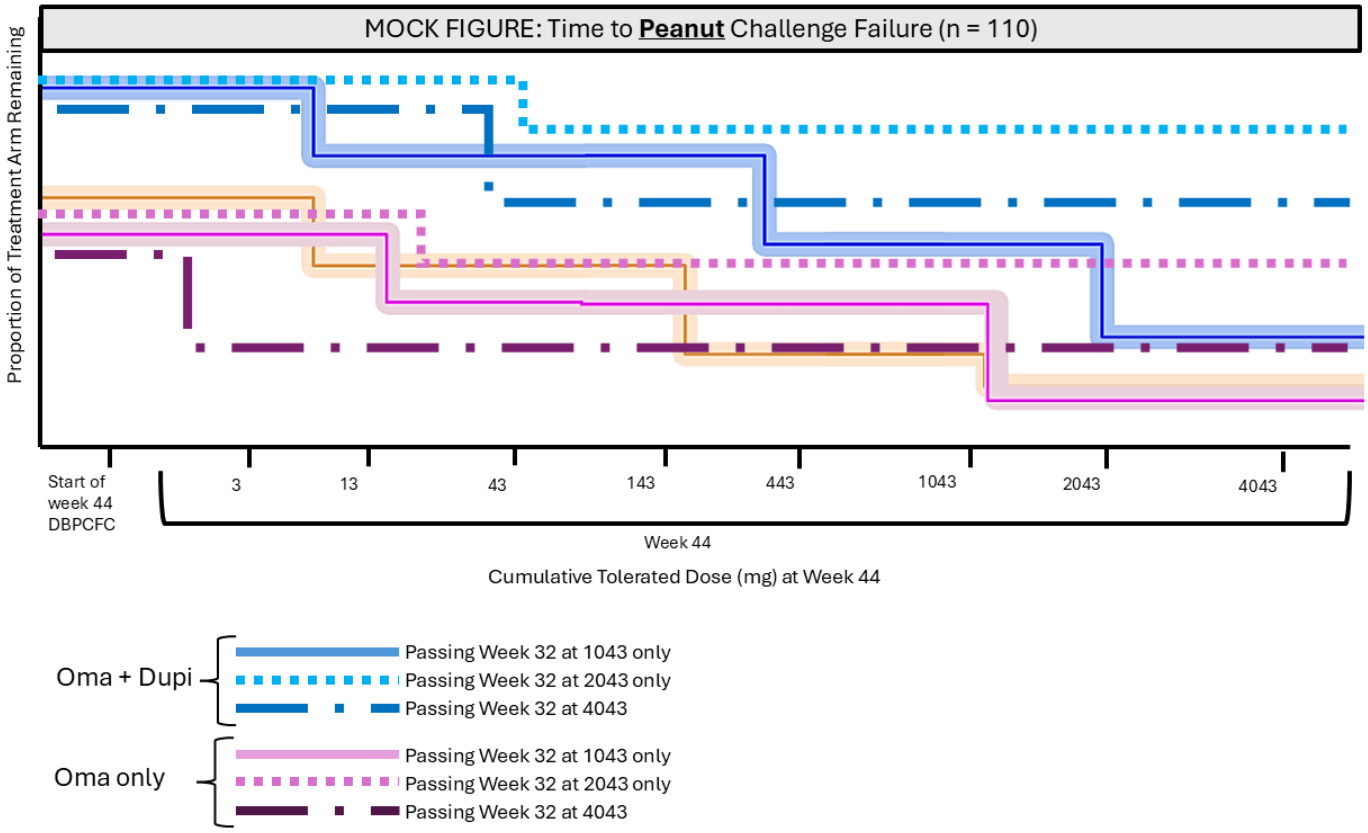
respectively for any one allergen (peanut or other)	0: participant's ratio between week 32 and baseline CTD is less than 10 for one allergen			missing for the per-protocol population.
FC_W32_O2 participant has a 10-fold change in the cumulative tolerance dose compared to baseline at week 32 respectively for 2 allergens (peanut or other)	Binary variable 1: participant's ratio between week 32 and baseline CTD is equal to greater than 10 for two allergens 0: participant's ratio between week 32 and baseline CTD is less than 10 for two allergens	Source:REDCap Study arm CTD		If the patient failed the first allergen test (FC_W32_O1 = 0), their value for this variable will also be 0. All allergens are considered for this combination.
FC_W32_O3 participant has a 10-fold change in the cumulative tolerance dose compared to baseline at week 32 respectively for three allergen (peanut or other)	Binary variable 1: participant's ratio between week 32 and baseline CTD is equal to greater than 10 for three allergens 0: indicates that the ratio between week 32 and baseline CTD is less than 10 for three allergens	Source:REDCap Study arm CTD		**This variable is only measured among those who have allergies to peanut and at least two other allergens**. If the patient failed the second allergen test (FC_W32_O2= 0), their value for this variable will also be 0. Participants with two allergies will have a null value, not a missing value.

Time to Failure for Peanut (Subset Analysis)

We will display time to fail curves for peanut cumulative tolerated dose (mg) for each of the three arms. We will subset the arms by their Week 32 Peanut DBPCFC results. For each arm, we will subset the arm into three subgroups:
Subgroup A: Participants who's Peanut CTD at Week 32 is ≥ 1043 mg and < 2043
Subgroup B: Participants who's Peanut CTD at Week 32 is ≥ 2043 mg and < 4043
Subgroup C: Participants who's Peanut CTD at Week 32 is ≥ 4043 mg

This will help us understand the relationship between how well participants did at Week 32 and how much peanut protein they were able to tolerate at Week 44.

Week and cumulative tolerated dose will be considered jointly. We will show all three arms for transparency. **We will calculate the hazard ratio and the 95% confidence interval for the comparison between arm A and B.**



Allergen-Specific IgE analysis

As part of the main analysis, we do a difference of differences analysis for peanut-specific IgE, walnut-specific IgE, and cashew specific IgE. If interested, we will also look at other allergen -specific IgE. These analyses, however, will not be a part of the larger significance testing procedures. Results found at this stage should be interpreted with caution and not be used to infer clinical treatments.

7. Appendix

Study Population (Exclusion/ Inclusion Criteria)

2.1 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.

2.2 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.

8. References

Papers with adverse event table (to use as examples):

https://pubmed.ncbi.nlm.nih.gov/31193674/

https://pubmed.ncbi.nlm.nih.gov/29242014/

Paper with survival analysis (to use as example):

https://pubmed.ncbi.nlm.nih.gov/31522849/

Fishers – Freeman – Halton Test

Freeman, G.H. and Halton, J.H., "Note on exact treatment of contingency, goodness of fit and other problems of significance," *Biometrika,* 38:141-149, 1951.

Time to Event Analysis for Allergy Tests:

https://pubmed.ncbi.nlm.nih.gov/33959986/