Clinical Study Using Biologics to Improve Multi OIT Outcomes (COMBINE)

Informed Consent Form

NCT03679676

March 11, 2025

IRB Use Only
Approval Date: March 11, 2025
Expiration Date: July 9, 2025

Please check all that apply:

☐ I am an adult participant in this study.

Write your name here:

_____

☐ I am the parent or guardian granting permission for a child in this study (the use of "you" refers to "your child" or "your ward.")

Write child's name here:

_____

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Are you participating in any other research studies? _____ Yes _____No

Brief Summary

Study Goals:

1) To see if taking two medicines (an injection and oral immunotherapy) can help you not react to your food allergies.

2) After taking these two medicines, to see how many people can pass food challenges to peanut and one or two other foods after 32 weeks of this treatment.

Study Duration and Procedures

- The study will last about 10 months and you will visit the clinic about 30 times.

- Clinic visits include: doctor's exam, blood tests, breathing tests, skin prick test, and eating peanut and other allergic foods. We may do other things at these visits.

Potential Risks and Benefits

During this study you could experience:

Skin problems	Stomach problems	Breathing problems
-itchy rash, hives, face swelling, facial redness or rash	nausea, throwing up, cramping or belly pain, diarrhea	cough, stuffy nose, runny nose, sneezing, wheezing and shortness of breath

A major risk would be trouble breathing or anaphylaxis (severe allergic reaction). This is rare but could happen.

- We can't promise that you will receive any benefits from this study. We can't know for sure if this study will help you at all. The medicines we are studying do not cure allergies. The medicines may help your allergies by making you less sensitive to peanut and the other food allergens. The medicines may improve your immune protection to the allergic foods over time.

- The things we learn from this study may help us understand food allergies and help us create new treatments and preventions.

- The alternative to doing this study is to just avoid all of the foods you are allergic to. This is the standard treatment for people with food allergies.

- If you want to be in this study but change your mind later, you are free to withdraw your consent (leave the study). You can leave the study at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

PURPOSE OF RESEARCH

You are invited to take part in a study to test the safety and effectiveness of food Oral Immuno-Therapy (OIT) with two medicines called omalizumab (Xolair) and dupilumab (Dupixent) to help food allergic children and adults safely eat the foods they are allergic to. In this study the food allergies we study must include peanut and at least one of the following: milk, egg, almond, cashew, hazelnut, walnut, fish, shellfish, sesame seeds, soy, and/or wheat.

Investigational/study drugs

The goal of OIT is to make you less sensitive to the foods you are allergic to. That way there is less risk of having an allergic reaction if you accidentally eat those foods. However, OIT does not work for everyone and many patients in OIT trials have side effects that make it difficult to keep taking the OIT.

Dupilumab and omalizumab are a type of drug called an "antibody." An antibody is a special kind of protein that your immune (defense) system normally makes to fight infections. Scientists can now make antibodies in the laboratory and produce them to treat many different diseases. Dupilumab has been shown to block the action of some proteins that might cause allergic diseases such as atopic dermatitis (eczema), asthma, and peanut allergy. Omalizumab blocks the action of IgE which is part of the allergic reaction cascade.

Omalizumab is approved by the Food and Drug Administration (FDA) and European Commission for use in patients 6 years and older who have moderate to severe asthma. It also approved for treatment of chronic rhinosinusitis with nasal polyps in patients 18 years and older, chronic urticaria (hives) with no known cause in patients 12 years and older. As of February 2024, the FDA has approved omalizumab for food allergy in adults and children 1 year and older in reducing allergic reactions, including anaphylaxis that may occur with accidental exposure to one or more foods.

Omalizumab does not prevent food allergies, but it is to be used along with avoiding the foods. Omalizumab is not to be used for emergency treatment of allergic reactions, including anaphylaxis.

Dupilumab is considered "experimental" because we are using it to treat food allergies. The FDA has approved dupilumab for patients 6 years and older with moderate to severe asthma, patients 6 months and older with atopic dermatitis (eczema), patients 12 years and older with chronic rhinosinusitis with nasal polyps, patients 1 year and older with eosinophilic esophagitis (EoE), adults with prurigo nodularis (chronic skin disorder with itchy bumps), and adults with uncontrolled chronic obstructive pulmonary disease (COPD). Dupilumab is not been approved for treatment of food allergies.

We think you could be in this study because you are allergic to peanuts and some other foods.

If you don't want to do this study any longer, please tell Dr. Sayantani Sindher (the study doctor). Her phone number is (650) 521-7237.

This research study enrolled 108 participants ages 4 to 55 with multiple food allergies (including peanut). Enrollment took place at 3 sites in the US. Stanford University enrolled 60 research study participants.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take about 10 months:
-Screening period of up to a year
-Active treatment period of 32 weeks
-Off treatment phase of 12 weeks.

PROCEDURES

If you choose to be in the study, Dr. Sayantani Sindher (the study director) and her team will explain the study to you and ask you to read this consent form. The study team will answer any questions you have about the study and what you are being asked to do. If you decide to enroll in the study you will be asked to sign this consent form. A copy of this form will be given to you.

People in the study will be put in to one of three study groups at random (like flipping a coin):

Group A (50 people) will get omalizumab for 8 weeks and then 24 weeks of the placebo (inactive) medicine.
Group B (50 people) will get omalizumab for 8 weeks, and then 24 weeks of dupilumab.
Group C (10 people) will get the placebo medicine for 8 weeks and then 24 weeks of with dupilumab.

All groups will get multi-food oral immunotherapy (OIT). At week 8, everyone does an Initial Dose Escalation Day (IDED) for all foods chosen, up to 3 foods (peanut included). Participants who tolerate the 1,000 mg dose per food will continue on 1,000 mg of each food allergen at home (maintenance/updosing) until week 32.

At the conclusion of the maintenance/updosing phase (Week 32), participants will undergo food challenges to their food allergens.

Participants will then continue in the study off of the food OIT for 12 weeks. At week 44 you will have a food challenge to see how much of those foods you can eat without having a reaction.

There will be about 30 visits to the clinic during the study. The study includes:

- Screening Visits (within 12 months of randomization visit) (up to 5)
- Randomization/study drug visits only (4 visits)
- Dose Escalation day visit
- Build up and maintenance visits with study drug (week 8 to 32, about 13 visits)
- Week 32 food challenge (up to 4 visits)
- Off treatment (week 32 to 44)
- End of study (week 44, up to 4 visits)

While you are in this study, you must be very careful to avoid the foods you are allergic to, except when Dr. Sindher and her team ask you to eat them during the study. You want to avoid an accidental allergic reaction.

Screening Phase (week-24-0)

If you choose to be in this study, you will first need to go through a screening process to see if you qualify for this study. The Screening/Baseline assessments may take place over several visits. We may ask to contact your primary provider or allergist to get a copy of any medical records about your food allergies.

At the screening visit, the following activities will take place:

- Consent and assent review and signature
- Review of your medical history, including all food allergies
- Physical exam
- Vital signs (heart rate, breathing rate, temperature, and blood pressure)
- Review the medicines you take
- Blood draw for allergy tests, clinical and research tests. Total amount will be about 70mls, or about 5 US tablespoons.
- Blood draw for pregnancy test for females of childbearing potential (about 1 teaspoon)

- As part of this study, pregnancy testing will be performed. The results of pregnancy tests for those under 18 are confidential according to California Minor Consent Laws. If you are a parent whose child is participating in this study, results will be given to your child by one of the study nurses or doctors in private. Every effort will be made to maintain confidentiality regarding positive pregnancy test results. Although we will not typically tell parent(s) or guardian(s) without your child's permission, under certain circumstances, we might be compelled to reveal this information. For example, if your child's life or someone else's life is at risk or if abuse is suspected, it may be necessary to inform you as parent(s) or guardian(s) of a positive pregnancy test. If we believe it's necessary to tell a parent or guardian of a positive pregnancy test without your child's permission, we will meet with your child first in private to discuss our concerns before divulging any information regarding pregnancy. During research, if your child has a positive pregnancy test, we may withdraw your child from the study. This means that even if we do not reveal the results, you may suspect that your child is pregnant despite our best efforts to maintain confidentiality. If your child becomes pregnant or if there is any chance that your child is pregnant (late menstrual period), please contact the study personnel immediately so that we may provide medical assistance and counseling.

- Collection of a stool and saliva sample (optional)
- Collection of urine, skin swabs, and cheek swabs (optional)
- Skin prick test to check food allergies. We will use a small needle that pricks the skin allowing a small amount of food extract to enter just below the skin. The size of the hive that develops will be measured. You may be asked to stop taking antihistamines such as Benadryl, Zyrtec, or Claritin, before the visit in order to undergo this skin prick test.
- Perform a breathing test called spirometry (a test that uses a hand-held instrument connected to a computer to measure how deep a breath you can take and how fast you can blow air out through your mouth); Or a Peak Flow Meter may be used (which uses a small tube with a mouthpiece that measures how fast you can blow air out through your mouth)
- Answer questionnaires
- Give you training on the following:
  - How to properly store and take your food OIT.
  - How to recognize allergic reactions and/or other side effects
  - What actions you must take should you have an allergic reaction

- How and when to use the epinephrine-containing autoinjector. You and/or your families will be required to have an epinephrine autoinjector with you at all times. If you do not have the auto injector, you will be given a prescription for an epinephrine-containing autoinjector at the beginning of the study.

- Perform a food challenge called Double-Blind Placebo-Controlled Food Challenge (DBPCFC). A placebo is a substance that is similar to the test substance in appearance, smell, and taste. The food will be given in a "double-blind" fashion mixed with food or juice under observation in the research center. "Double-blind" means that the study team (except the nutritionists) and you do not know if you are given the food you are allergic to, or a placebo. It is important for the study team not to know if you are getting the food or the placebo, so they are not influenced by their opinions about how you should react.

If you have a positive blood test, or skin prick test to peanut and up to 2 other foods (almond, cashew, hazelnut, soy, sesame seed, wheat, fish, shellfish, egg, walnut, and milk), you will have multiple DBPCFCs for up to 3 food allergens plus placebo that will be done on different days.

The screening DBPCFC will consist of 6 doses given every 15-30 minutes in increasing amounts for a total of less than or equal to 444 mg of food allergen protein or placebo. The doses will be 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, and 300 mg.

If the study team believes you are starting to react, they may wait longer between doses (one-hour maximum between doses). You will be asked to drink about 2 full glasses of water or more.

Before each challenge, you will have a physical. If you start to show any signs of an allergic reaction, or tell us that you are feeling unwell, the food challenge will be stopped, and you will be treated. You will be watched for at least two hours after your last dose, and sent home only when a study doctor says you are okay to leave. All food challenges happen with a doctor watching.

You must react at or before the 300 mg (444 mg cumulative) dose of food allergen protein to be allowed to join the study. If you don't react to the food allergen when you eat it during the food challenge, you will not be able to join the study.

The visit will take about 6-8 hours.

If your health or your test results change, or if the study doctor thinks it is a good idea, we may repeat any of the above procedures within the 24 weeks before you start the study treatment.

Randomization and Omalizumab/Placebo Treatment (Week 0 – 8)

If you qualify and react to the DBPCFCs at the screening phase, you will be randomly assigned to one of three cohorts (all cohorts receive an antibody drug):

- Cohort A (50 participants) will be treated with omalizumab for 8 weeks then placebo.
- Cohort B (50 participants) will be treated with omalizumab for 8 weeks then dupilumab.
- Cohort C (10 participants) will be treated with placebo for 8 weeks then dupilumab.

For the first 8 weeks, you will receive subcutaneous (under the skin) injections every 2 or 4 weeks of either omalizumab or placebo. Participants in Cohorts A and B (omalizumab) will receive omalizumab injections every 2 weeks or 4 weeks. Participants in Cohorts C will receive a placebo injection every 2 or 4 weeks.

Because of the risk of reactions, patients will be observed closely at the clinic for two hours after the first 3 omalizumab administrations, and 30 minutes for visits after that.

At each visit you will also have:

- Physical assessment
- Review the medications you are currently taking
- Review any reaction symptoms or health problems you have had since your last clinic visit
- Review of the diary: you will get a diary and we will teach you how to use it at the first randomization visit

Each visit will last about 2h.

Initial Dose Escalation Day (Week 8)

At week 8, all participants will undergo an Initial Dose Escalation Day (IDED) for all foods chosen (up to 3 food allergens including peanut), starting at a dose of 1 mg protein of each food allergen and escalating to 10 mg, 50 mg, 100 mg, 210 mg, 420 mg, and 1,000 mg.

At this visit you will have:

- Physical exam

- Review the medications you are currently taking
- Review any reaction symptoms or health problems you have had since your last clinic visit
- Blood draw (about 70mls, or 5 tablespoons)
- Perform a lung function test called spirometry or a peak flow meter reading test
- Review your diary
- Answer questionnaires
- Omalizumab or placebo injection

You will be instructed to keep a daily diary to document that you have taken your daily dose of food allergen and any symptoms that occur at home.

This visit will last about 4h-8h.

If you tolerate the 1,000 mg dose of each food allergen, you will be sent home and continue on that dose until week 32.

However, if you fail to reach the 1,000 mg dose, you will receive the highest tolerated dose on IDED as your home dose. If you cannot take your first home dose the day after your IDED visit, you will have to come in to take your dose in clinic.
You will then return to the clinic every two weeks for updosing to the next step. You should withhold your daily home dose and any prophylactic antihistamines on the clinic updosing day but should take all other prescribed medications. These attempts will continue until week 30 or until you reach 1,000 mg of each FA.
If you do not tolerate 1 mg of each food allergen at your IDED, you will be deemed a treatment failure. You will be discontinued and asked to come for safety and blood draw visits, and will be referred for clinical care.

Placebo/Dupilumab and OIT (Week 10 – 32)
Group A will receive placebo injections every 2 or 4 weeks over the next 24 weeks.
Group B will receive dupilumab every 2 or 4 weeks for 24 weeks.
Group C will receive dupilumab every 2 or 4 weeks for 24 weeks.

Again, you and the study team will not know what group you are in because this is a blinded trial.

You will begin your OIT at week 8 and take your home dose of 1,000 mg of each food allergen daily until week 32. The daily home dose should be taken as part of a meal, at the same time every day (within 24±2 hours of the previous day's dose), and it is very important to take the dose every day. Doses should be at least 12 hours apart. If you miss a dose and remember less than 12 hours from when you were supposed to take that dose, you may take the dose and resume the next dose on schedule. If you are within 12 hours of the next dose, do not take the missed dose, but wait and take the next scheduled dose at the usual time. Drink at least 2 extra glasses of water daily during OIT.

Vigorous exercise is not permitted for at least 2 hours after the dose of oral allergen immunotherapy. Also, if you exercise before your dose, there must be at least 1 hour between that vigorous exercise and taking a dose of oral allergen immunotherapy.

*Please note that allergic reactions are still possible when exercise takes place more than 2 hours after the dose.

You will come every two weeks for the following procedures:

- Physical assessment
- Review the medications you are currently taking
- Review any reaction symptoms or health problems you have had since your last clinic visit
- Perform a lung function test called spirometry or a peak flow meter reading test
- Review your diary
- Answer questionnaires
- Dupilumab or placebo injection
- Take an observed OIT dose

These visits will last about 2h.

If you did not reach the 1,000 mg dose at the Initial Dose Escalation Day at week 8, and you failed the subsequent updosing attempts and did not reach 1,000 mg of each food allergen by week 30 you will be discontinued, asked to return for safety and blood draw visits, and referred to a doctor for your allergy.

If you want to finish the study, or, if you have to finish the study early, you will be offered a list of potential allergist offices to visit for your follow up after the study.

First DBPCFC (food challenge) (Week 32)

At the end of the maintenance/updosing phase (week 32), you will do DBPCFCs for each food allergen in your OIT treatment that you've been on. These challenges will be on separate days. After the last dose of the food challenge, you will be watched for 2 hours in the clinic and then sent home.

At this visit, you will also have:

- Physical assessment
- Review the medications you are currently taking
- Review any reaction symptoms or health problems you have had since your last clinic visit
- Skin prick testing
- Blood tests (about 70mls, or 5 tablespoons)
- Stool and saliva sample collection (optional)
- Collection of urine, skin swabs, and cheek swabs (optional)

- Perform a lung function test called spirometry or a peak flow meter reading test
- Review your diary
- Answer questionnaires

Each visit will last about 4-8 hours.

If you pass all your food challenges with no or mild reactions to a cumulative dose of >/=1043 mg of the food allergens in your OIT at the end of this phase, you will be considered desensitized, meaning that you can eat those foods without have a reaction, as long as you keep eating them on a regular basis.

If you pass at least one food challenge, you will then come off treatment and will be tested at week 44 for the foods that you tolerated at the week 32 food challenge.

If you don't pass any of the food challenges, you will be discontinued, and asked to return for a safety and blood draw visit at week 44. You will be referred for clinical care for your allergy.

If you want to finish the study, or if you have to stop the study early, you will be offered a list of potential allergist offices to visit for your follow up after the study.

Off Treatment Phase (Week 32 to Week 44)

The off-treatment phase lasts for 12 weeks, from week 32 to week 44. During this time, you will stop taking your daily home dose of OIT. This phase is designed to see if you can still eat those foods after being off of them for 12 weeks, without a reaction.
At week 44, after 12 weeks of no treatment, you will undergo DBPCFCs on separate days only to those foods that you tolerated at week 32**.**

At this visit, you will also have:

- Physical exam
- Review the medications you are currently taking
- Review any reaction symptoms or health problems you have had since your last clinic visit
- Blood draw for allergy, clinical, and research tests (about 7 ½ teaspoons)
- Collect stool and saliva sample (optional)
- Collection of urine, skin swabs, and cheek swabs (optional)
- Perform a skin prick test to check your sensitivity to the food allergen
- Perform a lung function test called spirometry or a peak flow meter reading test
- Review your diary
- Answer questionnaires
- Provide Epi injector training

This visit will last about 4-8 hours.

If you pass your food challenges with no or just mild reactions to a cumulative >/=1043 mg of each food allergen in your OIT at the end of this phase, you will be considered able to eat those foods without a reaction.

If you want to finish the study, or have to stop the study early, then you will be offered a list of allergist offices to visit for your follow up after 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).
At the end of study visit, you will be offered a list of potential allergist offices to visit for your follow up after the study.

Unscheduled Visits

If your allergies get worse, if you have a new severe allergic reaction, or if other concerns come up between your regular visits, you should contact the study

team. You may be asked to come into the clinic for an "unscheduled" visit. Unscheduled visits may include physical assessment, blood draw and/or skin prick test.

Participants in the study have the option to go through extra food challenges to see if one of the foods in their OIT (like walnut) can cause a cross reaction to a similar food (like pecan). The specific cross 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.

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)*	*Every 2-4 wks(Weeks 10 - 32)*	*Week 32*	Week 44 *End of Study*
Visit Window	*±12*	*±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 differential	X		X			X	X
Blood for mechanistic studies	X	X	X			X	X
Serum pregnancy test	X						
Lung Function	X		X	X	X	X	X
Diaries		X	X	X	X	X	X
Inject Epi training	X						X
Omalizumab or Dupilumab Injection[1]		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 2-4 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)

Participant ID:

STUDY

Throughout the study

- You will keep a diary during the study to record that you have taken your dose, and to record any symptoms that happen at home.
- You will be asked to not eat or drink any of the foods you are allergic to during the study. We will check to make sure by asking every visit and by reading your study diary.
- If you miss any of your food powder doses, please let the study team know and ask what you should do about your next dose.
- You will be asked to bring all the doses that you did not take back to the clinic at every clinic visit.

Women of Childbearing Potential

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to potential dangers.

If you are pregnant or currently breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study.

You must agree to remain abstinent (refrain from heterosexual intercourse) or use acceptable birth control methods (barrier methods or oral, injected, or implanted hormonal methods) during the treatment period and for 60 days after the last dose of study drug.

Future Use of Private Information and/or Specimens

Research using private information and/or specimens is an important way to try to understand human disease. You are being given this information because the investigators want to save private information and/or specimens for future research.

Your specimens will be stored for an indefinite period of time under a unique numbered identifier in the Parker Center Lab for Allergy and Asthma Research. Your specimens will be sent outside of Stanford University for analysis. These research studies are very important to understand the changes in the immune system that may occur as you become less sensitive to your allergens. These results may help us to design better treatments in the future for multi food

allergic patients. By signing this consent form, you agree to have your specimens stored and used for future research.

This research study does not include whole genome sequencing.

Identifiers might be removed from identifiable private information and/or identifiable specimens and, after such removal, the information and/or specimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

The results of the study of your specimens will be used for research purposes only and you will not be told the results of the tests.

Any of your specimens which are used in research may result in new products, tests or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, Stanford University and/or others. However, donors of specimens do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests or discoveries.

Genetic Testing and Future Research

As part of the analysis on your specimens, the investigators will do genetic testing. Genetic research is research that studies genes, including gene characteristics and gene versions that are transmitted by parents to children. Genetic research may include looking at information, such as personal appearance and biochemistry, gene sequences, genetic landmarks, individual and family medical histories, reactions to medications and responses to treatment. Genetic research raises certain questions about informing you of any results. Possible risks of knowing results include: anxiety; other psychological distress; and the possibility of insurance and job discrimination. A possible risk of not knowing includes being unaware of the need for treatment. These risks can change depending on the results of the research and whether there is a treatment or cure for a particular disease.

Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.

The results of the study of your specimens from this project will be used for research purposes only, and you will not be told the results of the tests.

Genetic Information

Information from analyses of your coded specimens and your coded medical information will be put into one of the National Institutes of Health (NIH) databases along with information from the other research participants and will be used for future research. These databases will be accessible by the Internet. Only anonymous information from the analyses will be put in a completely public database, available to anyone on the Internet.

No traditionally-used identifying information about you, such as your name, address, telephone number, or social security number, will be put into the public database. While the public database will not contain information that is traditionally used to identify you, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to identify you (or your blood relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.

However, your privacy is very important to us and we will use safety measures to protect it. Despite all of the safety measures that we will use, we cannot guarantee that your identity will never become known.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Take the study drug as instructed.
- Call the 24/7 on call number if you missed any doses or have any allergic reactions.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.

- Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Keep the study drug in a safe place, away from children and for your use only.
- Keep your diaries as instructed.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Dr. Sindher at (650) 521-7237.

If you withdraw from the study, or the study medication is stopped for any reason,

- You will be asked to return to clinic for an end of study visit.
- You must return all study-related supplies, including unused study drug.

The Protocol Director may also withdraw you from the study and the study medication may be stopped, without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

Food challenge and OIT risks
Food challenge and OIT may cause an itchy rash, hives, nausea, abdominal pain or discomfort, vomiting, diarrhea, lips, mouth or facial swelling, cough, stuffy, runny nose, sneezing, wheezing, throat tightness and shortness of breath.

The most serious risks are severe breathing difficulties, and rarely, anaphylactic shock (a severe allergic reaction including many of the above symptoms plus a sudden drop in blood pressure and loss of consciousness). This type of allergic reaction would require immediate medical treatment and could result in permanent disability or death. Medications, trained and experienced personnel, and equipment will be immediately available to treat these types of allergic reactions. You will also be provided a prescription for an Epinephrine autoinjector to have with you at all times and to use in case of an allergic reaction.

The other major concern besides anaphylaxis is eosinophilic esophagitis (EoE). EoE is a condition where a type of white blood cell (eosinophil) builds up in the tube that connects your mouth to your stomach (esophagus). This can cause stomach/chest pain, vomiting, regurgitation, and/or difficulty swallowing. It is possible that EoE may be reversed after stopping the dosing with OIT, but this is not certain.

The food powders used in this study are like ones you can purchase. We have tested these powders to minimize the risk of contamination. These powders like all foods can grow mold. Mold in foods has the possibility of making you sick. If you see mold in your doses, please do not eat and alert your study team.

There is a risk that those who take part in the study may not carefully avoid accidental food allergen ingestion during their participation in the trial because they believe they are "protected." It is very important that you continue to practice your usual vigilance against accidental food ingestion of allergen-containing foods while you are in this study. If you miss your daily OIT doses, this can result in an allergic reaction. Please contact your study team if this applies to you. It is also very important to always continue to carry the epinephrine auto injector.

Omalizumab Risks

The bad side effects of omalizumab that have been observed during drug development were very similar to placebo with the most commonly reported side effect being mild reactions at the site where the omalizumab was given/injected (injection site reactions). The overall frequency of injection site reactions was similar in omalizumab-treated patients and placebo patients. Other than injection site reactions, the most commonly reported side effects were inflammation of the nose and throat, upper respiratory tract infection and headache.

In clinical studies with adult and adolescent patients 12 years of age and older, the most commonly reported bad reactions were injection site reactions, including injection site pain, swelling, redness, itching and headaches.

In clinical studies with patients 6 to 12 years of age, the most commonly reported bad reactions were headache, fever and upper abdominal pain. Most of these reactions were mild or moderate in severity.

Of the bad reactions of special interest, anaphylactic reactions (wheezing, shortness of breath, cough, chest tightness, or trouble breathing, flushing, itching, hives or feeling warm, swelling of the throat or tongue, throat tightness, hoarse voice or trouble swallowing, low blood pressure, dizziness, fainting, rapid or weak heartbeat, anxiety) were observed but were rare and typically occurred within 2 hours of the first injection. Anaphylaxis is a life-threatening condition and can lead to death. There were no reported cases of anaphylaxis with a fatal outcome in any of the clinical studies.

Cases of cancer were observed in some people who received omalizumab. Although more cases of malignancy (cancers) were observed in the omalizumab treatment group compared with the placebo group.

Some people who received omalizumab have had heart and circulation problems such as chest pain, heart attack, blood clots in the lungs or legs, or temporary symptoms of weakness on one side of the body, slurred speech, or altered vision. It is not known whether this is caused by omalizumab.

Dupilumab risks

In clinical studies of dupilumab in children and adults, side effects reported more often in patients treated with dupilumab compared to those receiving placebo, and which were possibly related to dupilumab, are listed in the table below:

Most Common (more than 10% of patients)	**Common** (1 to 10% of patients)	**Rare** (less than 1% of patients)
Conjunctivitis: 'Pink eye' due to allergy, infection or other cause	Headache	Serum sickness like reaction,: A type of reaction in which patients may develop symptoms including fever, skin rash, joint swelling, joint pain, muscle pain, headache, nausea, diarrhea, swollen glands and blurred vision
Injection site reaction: Complaints of pain, itching, swelling, redness, etc. at the site of study drug injection	Oral Herpes: 'Cold sores'(also known as 'fever blisters') on the mouth and lips or other viral infections (Hand-foot-and-mouth disease*) in 6 mo-5 years old)	Blood clots or stroke that could include death, non-fatal heart attack, and non-fatal stroke.
Antibody development: Antibodies form that recognize dupilumab but do not necessarily block it's action	Eosinophilia: Increase in a certain kind of white blood cells called eosinophils detected in a blood test	Cholecystitis: Redness and swelling (inflammation) of the gallbladder
Upper respiratory tract infection: including infections of the lungs and sinuses	Inflammation (swelling and redness) of the eyelid	
	Itching in eye	
	Dry eye: Dryness of the eyes	
	Keratitis: Swelling and redness of the cornea (the outer layer of the eyeball)	
	Arthralgia: Joint pain	
	Warts*	

Most Common (more than 10% of patients)	**Common** (1 to 10% of patients)	**Rare** (less than 1% of patients)
Viral Infection	Myalgia: Musculoskeletal chest pain	
	Dizziness: Altered sense of balance, possibly described as lightheaded, feeling faint, or as if head is spinning.	
	Diarrhea: Loose, watery stools, that occur more frequently than usual.	
	Neutralizing antibody development: Antibodies form that block the action of dupilumab	
	Urinary Tract Infection: Infection in any part of the urinary system, in any part of the kidneys, ureters, bladder, and urethra	
	Toothache: Pain or soreness in or around the teeth	
	Back Pain	
	Gastritis: Inflammation of the stomach which may cause upper belly pain, nausea, and/or vomiting	
	Rhinitis: Inflammation (irritation and swelling) of the mucous membrane in the nose	
	Nasopharyngitis: Viral infection of the nose and throat	

* *Only observed in the 6-month to 5 year old population*

Most Common (more than 10% of patients)	**Common** (1 to 10% of patients)	**Rare** (less than 1% of patients)
	Injection site reaction: Complaints of pain, itching, swelling, redness, etc. at the site of study drug injection	
	Conjunctivitis: 'Pink eye' due to allergy, infection or other cause	
	Antibody development: Antibodies form that recognize dupilumab but do not necessarily block its action	

Facial rash or redness has been identified during the post-approval use of Dupilumab.

There is a higher risk of pink eye, inflammation of the eyelid or outer layer of eyeball, in patients treated with dupilumab who have atopic dermatitis (eczema),

prurigo nodularis (chronic skin disorder with itchy bumps), chronic rhinosinusitis with nasal polyps, and COPD.

There is a higher risk of herpes sores in patients treated with dupilumab for atopic dermatitis (eczema), EoE, and Prurigo Nodularis.

There is a higher risk of arthralgia (joint pain), in patients treated with dupilumab for chronic rhinosinusitis with nasal polyps, COPD and EoE.

You should let your study doctor know about any new or worsening eye symptoms, sores or joint symptoms.

In studies of people using dupilumab to treat chronic inflammation of the nose and sinuses: common side effects were injection site reactions, eye infections, joint pain, stomach pain, trouble sleeping, and toothache.

A severe allergic reaction requires immediate medical treatment and could result in permanent disability or death if not treated promptly. If you believe you are having a severe allergic reaction, you should immediately seek emergency medical treatment and alert the study doctor and study staff as soon as possible.

Another kind of hypersensitivity reaction called 'serum sickness' sometimes occurs days to weeks after study drug injection and may cause complaints of fever, skin rash, swelling and pain in joints, muscle pain, swollen glands, headache, nausea, diarrhea and blurred vision.

We do not know if Dupilumab (one of the drugs in this study) impacts the safety or effectiveness of live vaccines like the ones given at your regular pediatric well check visits. Because we don't know, you will not be able to start the injection phase of this trial until you have completed the vaccination series with DTaP, MMR, Varicella or IPV. The Pfizer, Moderna, and Novavax COVID-19 vaccines are not live vaccines.

If you also have asthma, please do not adjust or stop your asthma medicines without consulting with your study doctor.

Procedure risks and discomforts

Skin Prick Testing

The risk involved with allergy skin testing includes discomfort from the needle prick, along with itching and swelling at the skin test site in positive responses.

Less common side effects include severe allergic reactions. You may be given topical steroid creams for application to the affected areas if needed.

Blood Drawing
Risks with blood draws include fainting, local pain, stinging, bleeding, or bruising at the site where the needle is inserted into the vein. On rare occasions infection at the needle stick site may occur.

Lung Function Testing
The risk of a lung function test is the discomfort of exhaling forcefully. This may be associated with mild shortness of breath, slight dizziness, temporary cough and/or chest discomfort. Most patients do not have any symptoms.

POTENTIAL BENEFITS

We cannot and do not guarantee or promise that you will receive any benefits from this study. This study may make you less sensitive to your allergic foods, and it may improve your immune responses to the allergic foods. What we learn from this study may help us understand food allergies and help to design better treatments for allergies.

ALTERNATIVES

You can continue to avoid the food, with or without the use of Xolair® (omalizumab) given by injection subcutaneously (under the skin). Xolair®(omalizumab) is approved for the reduction of allergic reactions including anaphylaxis, that may occur with accidental exposure to one or more foods in adults and pediatric patients aged 1 year and older. Xolair® is to be used along with avoiding the food.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law. However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain data or information on the safety and effectiveness of Oral ImmunoTherapy (OIT) with omalizumab and dupilumab; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

CERTIFICATE OF CONFIDENTIALITY

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the NIH which is

funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of child abuse and neglect, or harm to self or others.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document such as your information related to this study.

Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The purpose of this study is to study the immune response in food allergic participants undergoing oral immunotherapy (OIT) with omalizumab and/or dupilumab. The study doctor, Dr. Sindher, will use your personal health information to complete this research. Regulatory authorities such as the FDA and the IRB may also review or copy your information to make sure that the study is done properly or for other purposes required by law. The results of this study may be published in a medical journal and shown at medical meetings. You will not be identified (by name or any other means) in any of these publications.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study including receiving any research-related treatment.
Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health

information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to: Dr. Sindher, Sean N. Parker Center for Allergy and Asthma Research, 750 Welch Rd, Suite 114, Palo Alto, CA 94304.

What Personal Information Will Be Obtained, Used or Disclosed?

Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, your demographic information (including date of birth, gender, race/ethnicity, and medical record number), medical history, history of allergies, physical examinations, lab test results, and information derived from analysis of your samples.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director Dr. Sindher
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services

- The National Institutes of health (NIH)
- Food Allergy Research & Education (FARE)
- The Food and Drug Administration
- Research collaborators outside of Stanford
- Medical and research records from this study will be reviewed by the United States agency funding this study (the National Institute of Allergy and Infectious Diseases), including its, representatives, agents, employees, contractors, and other persons assisting in conducting, monitoring or analyzing the study. In addition, the U.S. Food and Drug Administration (FDA), or other health authorities, and pharmaceutical or device sponsor(s) and their commercial partners may review your medical and research records for regulatory purposes.

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will end on December 31, 2100 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

_____ _____
Signature of Legally Authorized Representative (LAR) Date
(e.g., parent, guardian or conservator)

_____
Print Name of LAR

_____
LAR's Authority to Act for Participant
(e.g., parent, guardian or conservator)

FINANCIAL CONSIDERATIONS

Payment/Reimbursement
You will be reimbursed $25.00 for each completed in-person visit during the study. Reimbursements will be issued periodically throughout the study. Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa. You may need to provide your social security number to receive payment.

Costs
There is no cost to you for participating in this study, other than basic expenses like transportation and the personal time it will take to come to all of the study visits.

Sponsor
The National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) and Food Allergy Research & Education (FARE) are providing financial support and/or material for this study.

Consultative or Financial Relationships
Dr. R. Sharon Chinthrajah is a paid consultant to Genentech and Novartis, the companies that are the makers of omalizumab (Xolair).

Dr. Sayantani Sindher is a paid consultant to Genentech, the company that is a maker of omalizumab (Xolair).

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these

costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Dr. Sindher at (650) 521-7237. You should also contact her at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, 1705 El Camino Real, Palo Alto, CA 94306.

Appointment Contact: If you need to change your appointment, please contact snpcenterallergy.scheduler@stanford.edu

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;

- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you?
____ Yes ____ No

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant or Legally Authorized Representative Date
(e.g., parent, guardian or conservator)

_____
Print Name of LAR

_____
LAR's Authority to Act for Participant
(e.g., parent, guardian or conservator)

_____ _____
(If available) Signature of Other Parent or Guardian Date

_____
Print Name of Other Parent or Guardian

_____
Authority to Act for Participant

The panel determined that this study falls under 21 CFR 50.53 and therefore two parent signatures are required.

The permission of the second parent was not obtained because:

[ ] This parent is deceased
[ ] This parent is unknown
[ ] This parent is incompetent
[ ] This parent is not reasonably available*
[ ] One parent has legal responsibility for the care and custody of the child

*Not reasonably available
Means the other parent is not contactable by phone, mail, email or fax or the other parent's whereabouts are unknown.
Does not mean the other parent is at work, at home, lives in another city, state or country, but is contactable by phone, mail, email or fax
Examples of not reasonably available:
The other parent is on active military duty and is not contactable by phone, mail, email or fax.
The other parent is incarcerated and is not contactable by phone, mail, email or fax.
The whereabouts of the other parent are unknown only one parent has legal responsibility for the care and custody of the child. Not reasonably available means that the other parent is not present during the consenting process, or will not be available prior to the start of research procedures.

_____ _____
Signature of Person Obtaining Consent Date

_____
Print Name of Person Obtaining Consent