1. PARTICIPANT INFORMATION SHEET AND CONSENT FORM - UK

NAME OF STUDY:	A Randomized, Double-blind, Single-centre, Placebo-controlled Study of Antigen-specific Sublingual immunotherapy plus Dupilumab for Induction of Tolerance in Adults with Seasonal Allergic Rhinitis
SHORT TITLE:	Grass Immunotherapy plus Dupilumab for Tolerance Evaluation
STUDY NUMBER:	ITN084AD
STUDY SPONSOR:	National Institute of Allergy and Infectious Diseases (NIAID), Division of Allergy, Immunology and Transplantation (DAIT) [redacted]
STUDY DOCTOR (INVESTIGATOR):	Professor Stephen Durham, Head of the Section of Allergy and Clinical Immunology Imperial College London National Heart & Lung Institute [redacted]
ETHICS COMMITTEE (EC)	NRES Committee North West – Greater Manchester South

2. INVITATION

We would like to invite you to take part in our research study. Before you give your consent, it is important that you read this information. Joining the study is entirely up to you, before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you, to help you decide whether you would like to take part and answer any questions you may have. Please feel free to talk to others about the study if you wish.

Do ask if anything is unclear. You are under no obligation to take part in this study.

3. INTRODUCTION/BACKGROUND

About 45 million people in Europe have allergic rhinitis (commonly called hay fever), which is an allergic irritation of the nasal passages that is caused by inhaled airborne pollens. Typical symptoms during the pollen season include sneezing, runny nose, nasal congestion, itching and tearing of the eyes. During the peak pollen season there may also be associated cough, wheezing and chest tightness. For many sufferers, hay fever may impair quality of life with reduced sleep quality, interference with daily activities and impairment of school or work performance.

The standard treatment for hay fever consists of treating the symptoms with nasal sprays and antihistamine tablets. However, a survey performed in a UK general practice revealed that only 40% of patients with hay fever reported good symptom control with this standard treatment. For those patients whose symptoms are not well-controlled by treatment with antihistamines and/or nasal sprays, sublingual immunotherapy (SLIT) has become available. This treatment involves using a grass allergen

tablet, (Grazax®). The researchers believe the combining Grazax® with an injected drug called Dupixent® (dupilumab) will result in greater benefits from Grazax®, fewer side effects and enable a shorter course of treatment in order to induce long-term benefits.

Grazax® is a fast-dissolving tablet that is placed under the tongue on a daily basis and is effective in helping relieve many patients of their hay fever symptoms during the pollen season. It is approved for use in the UK. Although Grazax® has been shown to be effective within 2-4 months, it is recommended to take the tablet daily continuously for 3 years since this has been shown to relieve symptoms long-term including for at least 2 years after stopping the treatment. Whereas GRAZAX® is effective in patients with moderate-severe hay fever, a proportion get local irritation with itching and swelling in the mouth that lasts for several minutes after taking the tablets, although these symptoms generally resolve within 2 weeks. Grazax® contains fish-derived gelatin and this may possibly be relevant for vegetarian/vegans.

Dupilumab (Dupixent®) is a treatment that is given by injection under the skin every two weeks and has been shown to be effective in patients with atopic dermatitis (allergic eczema) and in allergic asthma. The benefits of Dupixent wear off within weeks of stopping the injections and the treatment has not been tested in allergic rhinitis. Both Dupixent and Grazax® reduce allergic inflammation although by distinct mechanisms. The investigators believe that giving both together will result in a shorter course of treatment in order to induce long-term benefits.

4. PURPOSE OF THE STUDY

The purpose of this study is to determine whether a two year course of Dupixent® when given with Grazax® will result in prolonged clinical benefit for at least one year after both drugs have been discontinued. It is also possible that the combination may result in better symptom control and fewer local side effects.

5. WHAT IS THE DRUG THAT IS BEING TESTED?

The researchers are interested in combining Grazax® with dupilumab (Dupixent®). Dupixent® is a drug that is given by an injection every two weeks. Grazax® is a fast dissolving pill that is placed under the tongue and taken daily.

6. WHY HAVE I BEEN CHOSEN?

We are asking you to be in this research study because you have allergic rhinitis (hay fever). By measuring your body's reaction to grass pollen allergens during the study, we will be able to determine if combining Grazax® with Dupixent® will help treat allergic rhinitis (hay fever).

7. YOUR PARTICIPATION IS VOLUNTARY

You are under no obligation to take part in this study. Your refusal will not influence your NHS treatment in any way. Please carefully read this information sheet before you decide whether you will take part in this research. Please ask the study doctor or staff to explain anything that is not clear to you. You may discuss your decision with your family and friends and your health care team. **Before any study procedures are done, you should read this information and sign the attached consent form.**

Please remember:

- We will explain this research study to you. You may ask questions.
- You can change your mind at any time even after signing the consent.
- By signing this consent document, you agree to participate in this research study.
- We will give you a copy of the signed consent for your records.
- If you decide not to be in this study, you will still be able to receive medical care and any benefits for which you are already entitled.

8. STUDY COMPONENTS

About 240 adults will be screened and 108 of them will be enrolled in the study. Screening for the study is to check if you are suitable for the study and it is right for you. If you are enrolled in the study, your

participation will be for about 3 and a half years.

The following things will occur during the study:

Nasal Allergen Challenge. (1.5 hours) A Nasal Allergen Challenge "challenges" the lining of your nose and involves having a small amount of grass pollen extract sprayed into your nose. Wewill spray a small amount of a purified grass pollen extract into your nose. At 5, 15, 30, and 60 minutes after the spray, we will be measuring 3 things:

- How freely you can sniff through your nose using a special device called a "nasal inspiratory peak flow meter,"
- Your symptoms, and
- Nasal fluid collection to measure the amounts of certain proteins that we think may be important in causing hay fever and to observe the effects of the treatment on these proteins.

Nasal Fluid Collection. A small sponge will be placed into each nostril using sterile forceps for 2 minutes in order to collect nasal fluid. The sponges are then removed and the fluid later extracted and frozen.

Nasal Brushing. This involves inserting a small brush inside one nostril to brush the lining inside your nose which will be done about 8 hours after a nasal allergen challenge.

Allergy Skin Prick Testing. Skin testing involves putting drops of allergy extracts on the forearm and lightly pricking the skin with a sterile lancet through the allergy extracts. The results are apparent within 15 minutes.

Allergy intradermal skin testing. This involves injecting a tiny amount of grass allergen solution just into the skin of the forearm. The results are read after 15 minutes and again after 8 hours, at the same time that you attend for nasal brushing.

Lung Function Tests. This simple test involves breathing through a tube into a machineto measure how well your lungs are working. The test is repeated 2-3 times and takes a few minutes to complete.

Questionnaires. At certain times during the study, you will be asked to complete some questionnaires by providing information about your allergy symptoms that you have experienced and about any allergy medications you may have taken. We may ask you to complete some of these questionnaires at the visit and other times you may be asked to use a mobile app.

Mobile Health App. The research staff will assist you in downloading a mobile health app, called MyOwnMed, onto your mobile device or electronic tablet. This health app will allow you and the study staff to actively communicate while you are in the study. A member of the study team will train you on how to use the app. You will be asked questions periodically throughout the study about changes in your health and medications that you are taking during the study. You may also receive text reminders about appointments and when to take your study medication. There may be instances where your responses may trigger study staff to contact you to find out more information. For participants who do not have a mobile device or do not wish to use it, instructions will be provided to access the system via a web application. Participants may also be provided paper versions of questionnaires to complete if they do not have internet or mobile access. Site personnel then will enter questionnaire responses into the system.

Blood Samples. A small needle will be inserted into a vein in your arm and blood will be collected during screening and at intervals during the study. We shall ask to take blood at several time points during the study. The volume of blood collected for research and safety assessments can be seen in the schedules of events in Section 9.

Rescue Medications. During the pollen season, you will be provided with medications to alleviate your symptoms in

the nose and eyes. This "rescue medication" set will include antihistamines,nasal sprays and eye drops; all of them are similar to the ones that you have likely taken before to treat your hay fever.

Research Tests. Blood samples are collected during the study. These samples are used for research tests and for safety. Research tests help us learn more about your disease, theimmune system (the body's natural defense system against illness), and response to drugs or treatment. The results of the research tests will not be shared with you. These research samples will not identify you. Research tests may include genetic tests. Genetic tests study an individual's inherited characteristics, found in DNA, which is present in each of the cells of your body. DNA contains information needed to construct and operate a human body.

Randomisation. If you join the study, you will be randomly assigned to receive one of the three groups of treatment described below.

Grazax® plus Dupixent®
Grazax® plus Dupixent® placebo
Grazax® placebo plus Dupixent® placebo

Randomly assigned, means that you will be assigned by chance, like flipping a coin or pulling numbers out of a hat. This means that you will have an equal chance of receiving any one of the three groups of treatment. Neither you nor the study doctor can choose which group you will be assigned to. A placebo is something that looks like an actual medication but does not have the active ingredient. Whichever group you are randomly assigned to, you will receive both a tablet under the tongue every day (Grazax® or Grazax® placebo) and injections every two weeks (Dupixent® or Dupixent® placebo) for the first two years of the study.

Pregnancy test. Women will have a pregnancy test before receiving Dupixent®/placebo. You will not be able to receive this medication if you becomepregnant.

Grazax®/Grazax® placebo tablet administration. Your first Grazax®/Grazax® placebo tabletwill be taken during a clinic visit. You will then be given enough Grazax for 3 months to take home. You will dissolve one tablet under your tongue every day for two years.

Dupixent®/ Dupixent® placebo injection. An injection under the skin every 2 weeks, either during your visits to the clinic or at home over two years.

Vital Signs. Your heart rate and blood pressure will be measured.

9. STUDY VISITS

The study visits and procedures at each visit are listed below. If any procedures cannot be performed or if any samples are missing, insufficient or damaged, you may be invited to return for an unscheduled visit to repeat procedures or sample collections, or we may repeat them on a subsequent scheduled visit. You are not required to repeat procedures or blood draws if you do not want to.

Broadly, the visits for the study comprise:

1. Up to 4 Screening and Baseline visits – to check if you are suitable and collect information about you before starting any treatments, as well as to provide rescue medications for your hay fever in the summer
2. Treatment and Observation visits – these will be short visits every 2 to 4 weeks for 2 years where you will be given treatment and a chance to report on any issues; then phone calls every 4 weeks in the third, follow up year to check in with you.
3. Allergy Assessment visits – these are longer visits, less frequent throughout the 3 years, to assess in detail the impact of the treatments and provide you with rescue medications if needed.

Screening and Baseline Visits (up to 4 visits total)

Screening Visit - This visit will determine if you are eligible for the study, and will take approximately 3 to 4

hours.

- Your medical and allergy history
- A physical examination (skin, nose and chest)
- Assessment of vital signs
- Lung Function Tests
- Recording of any health updates and your current medications
- Allergy skin prick test
- For women, a urine pregnancy test
- Blood samples (approx. 2 ml, 1½ tablespoons)For general clinical safety assessments

Rescue Medication and Baseline In-season Assessments Visit(s) – April-July - You will have 1 or 2 visits between screening and baseline where you will be provided with medication to treat the symptoms of your hay fever before the start of the pollen season and have your allergy assessed.
Visits where you receive rescue medication will take approximately 1 hour.

- Check for any updates to your medications or health
- Dispense rescue medications for your hay fever
- Provide you with a questionnaire to record weekly your hay fever symptoms and rescue medications used
- At one visit only you will be asked to provide nasal fluid / brushing and blood samples (approx. 200ml, 13 tbsp.) for safety and research use.

Baseline Out of Season Visit – September-December - This visit will collect information and research samples before you start the study treatment, and will be split into 2 parts: 2 hours in the morning and 1 hour in the evening, approximately 6 hours later.

- Assessment of vital signs
- Check for any updates to your medications or health
- Provide you with a short questionnaire to record hay fever symptoms during the grass pollen season
- An allergy intradermal (skin) test
- A urine pregnancy test for women
- Blood samples (approx. 50ml, , 3.5tbsp)
  - for safety
  - for research tests
  - To undertake a more accurate pregnancy test for women, results required before starting treatment
- Nasal Allergen Challenge
  - nasal fluid and nasal brushings
  - 2 written evaluations

The Schedule of Events below shows the above information in table form.

Schedule of Events – Screening and Baseline Visits

	2020 - 2021			
	Screening	**Rescue Medication Dispensing visit**	**Baseline In Season Assessments**	**Baseline NAC**
Visit	**-4**	**-3**	**-2**	**-1**
General Assessments				
Informed consent	X			
Demographics	X			
Medical history	X			
Allergy history	X			
Directed physical exam	X			
Rhinoconjunctivitis Severity Screening Evaluation (ARIA severity score)	X			
Vital signs	X			X
Pulmonary Function Testing	X			
Record any adverse events	X	X	X	X
Record other medications	X	X	X	X
Local Labs				
Serum pregnancy test				X
Urine pregnancy test	X			X
Hematology	X			X
Comprehensive chemistry	X			X
Total IgE and Specific IgE to grass and birch pollen	X			
Study Medications				
Dispense Rescue medications		X	X	
Clinical Assessments				
Nasal allergen challenge				X
Visual Analogue Scale				X
Total nasal symptom score				X
Peak nasal inspiratory flow				X
Peak Expiratory Flow				X
Skin prick test – multiple allergens	X			
Intradermal test - *Phleum pratense*				X
Rhinitis Assessments				
Weekly (in season) CSMS			X	

	2020 - 2021			
	Screening	**Rescue Medication Dispensing visit**	**Baseline In Season Assessments**	**Baseline NAC**
Visit	**-4**	**-3**	**-2**	**-1**
Weekly (in season) Mini RQLQ			X	
Modified Rhinitis Symptom Utility Index			X	
Global Evaluation No. 1				X
Mechanistic Assessments				
Research Blood Collection			200ml/13tbsp	30ml/2tbsp
Nasal fluid collection and nasal brushings			X	X

Randomisation, Treatment and Observation Visits – Treatment every 2 weeks for 2 years, in clinic or at home, and up to 12 phone calls in the follow up year (year 3)

Randomisation/first Dupixent® or Dupixent® placebo injection visit. At this visit you will be randomised into one of the three treatment groups. This visit will take approximately 4 hours.

- Randomisation
- Vital signs
- Physical exam
- Check for any updates to your medications or health
- Allergy skin prick testing
- Nasal fluid and brushings collection
- A urine pregnancy test for women (This must be negative before you receive the Dupixent® or Dupixent ® placebo)
- Blood samples (approx. 200ml, , 13tbsp) for research tests
- First injection of Dupixent® or Dupixent® placebo
- Training for self-administration of Dupixent® / Dupixent® placebo
- Provide you with a short questionnaire to record current allergy symptoms

First Grazax or Grazax placebo dose visit. This visit will take place the day after the first dose of Dupixent® or Dupixent® placebo. The visit will take approximately 1-1.5 hours.

- Vital signs
- Check for any updates to your medications Nasal fluid collection
- or health
- Take your first dose of Grazax® or Grazax® placebo.
    - Thereafter, you will take a Grazax® or Grazax® placebo tablet under the tongue every day for two years at home.
- Take home 3 months' supply of Grazax® or Grazax® placebo

Treatments (Visits 26-51) – For two years, you will have your Dupixent® or Dupixent® placebo injection every two weeks. Once you are happy to self-administer the injection, we expect alternating injections to be administered at home. The clinic visits will take approximately half to one hour.
At the time of each injection, you will have the following procedures:

- Check for any updates to your medications or health
- Administer an injection of Dupixent® or Dupixent® placebo (taking your dose of Grazax® or Grazax® placebo tablet at least six hours apart from Dupixent injection)
- For the times when you have the injection at home, you will have access to video or telephone support, and the nurse will call in any case to check your progress and collect any additional information.

In addition to these procedures, when you attend an in-person visit once every 4 weeks you will:

- Provide urine for a pregnancy test if you are female
- Take home 3 months' supply of Grazax® or Grazax® placebo (every 3 months)
- Return your used Grazax® or Grazax® placebo tablet strips in order to record your total Grazax usage during the trial.

Observation/off-treatment period telephone visits during year 3 (12 phone calls). After you have completed 2 years of treatment, you will have monthly telephone calls for one year. These phone calls will take approximately 30 minutes.

- Check for any updates to your medications or health, including pregnancy status for women

The Schedule of Events below shows the above information in table form.

Schedule of Events – Randomisation, Treatment, and Observation Visits

	DOSING YEARS 1 & 2 (53 visits total)			OBSERVATION YEAR 3 (12 visits total)
Week	**0**	**0**	**2-104**	**108-152**
Visit Type	**Randomisation/first Dupixent® or Dupixent® placebo injection**	**First Grazax or Grazax placebo dose (1 visit)**	**Treatment visits (every 2 weeks)**	**Observation/off-treatment period telephone visits during year 3**
Visit number	**0**	**1**	**2-53**	**54-65**
General Assessments				
Directed physical exam	X			
Vital signs	X	X		
Record any Adverse events	X	X	X	X
Record other medications	X	X	X	X
Randomisation	X			
Pregnancy questionnaire				X
Study Medications				
Dupixent®/Dupixent ® placebo	X		X	
Daily Grazax®/Grazax® Placebo		X	X	
Rhinitis Assessments				
Modified Rhinitis Symptom Utility Index	X			
Local Laboratory Assessments				
Monthly urine pregnancy test	X		X	
Mechanistic Assessments				
Research blood collection	200 ml/13 tbsp.			
Allergy skin prick test	X			
Nasal fluidcollection and nasal brushings	X			

Allergy Assessment Visits in and outside the pollen season (5 visits each year)
Once you have started on your treatment, you will have evaluations during the pollen season and outside the pollen season each year. Most of these visits can be combined with your pre-arranged treatment visits.

Spring Out-of-pollen season visit (between February and March)

- Check for any updates to your medications or health
- Provide you with a short questionnaire about any allergy symptoms
- At the start of years 2 and 3, your follow up physical exams will be conducted at this time
- Blood samples
    - for research (approx. 10ml, 0.7 tbsp.)

Pre-pollen season visit (between April and May)

- Check for any updates to your medications or health
- Dispense rescue medications

In-pollen season visit (between June and July)
During the pollen season, you will have one clinic visit which will take approximately 2 hours.

- Check for any updates to your medications or health
- Nasal fluid collection and nasal brushings
- Dispense rescue medications
- Blood samples
    - for safety (approx. 5ml, 1 teaspoon)
    - for research (approx. 185ml, 12.5 tbsp.)
- You will receive a questionnaire to record weekly your hay fever symptoms and rescue medications used during this period

Autumn Out-of-pollen season visit 1 (between September and December). This annual visit will take approximately 2-3 hours in the morning, and you will return to the clinic for 1 hour in the evening (6 hours later).

- Vital signs
- Lung function tests
- Check for any updates to your medications or health
- Nasal Allergen Challenge
    - nasal fluid collection
    - nasal brushings
    - written evaluations
- Intradermal skin test
- Provide you with a short questionnaire to record hay fever symptoms during the grass pollen season
- Blood samples
    - For research (approx. 35ml, 2.5 tbsp.)

Autumn Out-of-pollen season visit 2 (between October and January). This annual visit will take approximately 1 – 2 hours.

- Check for any updates to your medications or health
- Complete a questionnaire related to your allergies
- Blood samples
- Allergy skin prick test
- Nasal fluid collection and nasal brushings
- At the end of the final observational year, a physical exam will be conducted at this visit
- Blood samples

- For research (approx. 185ml, 12.5 tbsp.)
- For safety (approx. 5ml, 1 tsp)

The Schedule of Events below shows the above information in table form.

Schedule of Events – Allergy Assessment Visits In and Outside the Pollen Season

	2022					2023					2024				
	Out of Season	Pre-season	In season	Out of season		Pre-season	In season	Out of season			Pre-Season	In season	Out of season		
Month	Feb-Mar	Apr-May	Jun-Jul	Sep-Dec	Oct-Jan	Feb-Mar	Apr-May	Jun-Jul	Sep-Dec	Oct-Jan	Feb-Mar	Apr-May	Jun-Jul	Sep-Dec	Oct-Jan
Visit	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15
General Assessments															
Directed physical exam						X					X				X
Vital signs				X					X					X	
Pulmonary function testing				X					X					X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Medications															
Dispense Rescue Medications		X	X				X	X				X	X		
Clinical Assessments															
Nasal allergen challenge				X					X					X	
Visual Analogue Scale	X			X	X	X			X	X	X			X	X
Total nasal symptom score				X					X					X	
Peak Expiratory Flow				X					X					X	
Peak nasal inspiratory flow				X					X					X	

Skin prick test endpoint titration - *Phleum pratense*					X					X					X
Intradermal test- *Phleum pratense*				X					X					X	
Local Laboratory Assessments															
Hematology			X		X			X		X			X		X
Comprehensive chemistry															X
Urine pregnancy test														X	
Rhinitis Assessments															
Weekly (in season) CSMS			X					X					X		
Weekly (in season) Mini RQLQ			X					X					X		
Modified Rhinitis Symptom Utility Index			X		X			X		X			X		X
Global Evaluation No. 1				X					X					X	
Global Evaluation No. 2				X					X					X	
Mechanistic Assessments															
Research Blood Collection	10ml/ .7tbsp		185ml/ 12.5tbsp	35ml/ 2.5tbsp	185ml/ 12.5tbsp	10ml/ .7tbsp		185ml/ 12.5tbsp	35ml/ 2.5tbsp	185ml/ 12.5tbsp	10ml/ .7tbsp		185ml/ 12.5tbsp	35ml/ 2.5tbsp	185ml/ 12.5tbsp
Nasal fluid collection and/ nasal brushings	X		X	X	X	X		X	X	X	X		X	X	X

WHAT WILL HAPPEN AT THE END OF THE STUDY?
Prof Durham and team will discuss future treatment options for your continued hay fever care when you are no longer in this study. A summary of the results of the trial will be made available to you.

If you are one of the participants who receive double-placebo during the treatment phase, Prof. Durham and the Royal Brompton Hospital can offer you sublingual immunotherapy with the active Grazax® after you complete this trial. This treatment with the active Grazax® will be optional, and will not be part of this trial.

10. RISKS and/or DISCOMFORTS

There are risks involved in participating in this study. These risks are related to the study medications and the study procedures. During your participation in the study, you or your family members should tell the study doctor if you have any unusual health problems, injuries or side effects, even if you do not think these problems are caused by the study tests and procedures or by the study drugs. If you have any questions or concerns about these risks, please talk to the study doctor.

STUDY MEDICATIONS:
Grazax® Standardised Grass Allergy Tablet (under the tongue tablet). Very commonly reported side effects (occurring in up to 70% of patients treated with Grazax®) are local allergic reactions in the mouth.

These may include, lip swelling, swollen tongue and mild discomfort, itching and swelling of the lining of the mouth. Common abdominal symptoms include stomach irritation, acid reflux, vomiting and diarrhoea. Other common side effects of Grazax® include: headache, fatigue, watery eyes, sneezing, nasal congestion, itchy ears, mild asthma (wheezing, cough), itchy nose, and runny nose. All of these side effects are mostly mild to moderate in severity and occur right after placing the tablet under the tongue. These symptoms may last from minutes to hours after each intake of Grazax® and tend to go away on their own within 1 to 2 weeks. These side effects are usually well tolerated and do not require treatment. However, anti-allergic medication is always available.

There is a very small possibility that you will have a more serious allergic reaction to the tablets. The onset of a severe allergic reaction may include flushing, intensive itching in palms of hand and soles of the feet, and other areas of the body (like a nettle rash). If you experience a sense of heat, general discomfort and agitation/anxiety may also occur. In case of severe reactions, facial/mouth swelling difficulty in swallowing, difficulty in breathing, changes in voice, a drop in blood pressure or feeling of fullness in the throat a physician should be contacted immediately. In such cases, treatment should be discontinued permanently or until otherwise advised by the physician. Very rarely, cases of anaphylactic reactions (severe allergic reactions that include acute breathing difficulty and/or low blood pressure and associated faintness or loss of consciousness) have been reported. As a result, medical supervision for the first dose of the treatment is an important precaution.

To help reduce risks to a minimum, the first dose will always be taken while being observed by medical staff. There is also a 24-hour telephone contact line (+447542126521) for advice concerning any suspected side effect at any time. The usual medication information sheet for Grazax® is available on request through your study doctor.

Dupilumab (Dupixent®) injection. Dupixent® is approved in the UK for treatment of severe eczema. Dupixent® is generally safe and well tolerated.

Very common side effects (that may affect more than 1 in 10 people) include injection site reactions: local redness, itching and swelling at sites of Dupixent® injection. Other side effects may include conjunctivitis (eye redness, itching, dryness), blepharitis (eyelid redness and swelling), eye infections, and cold sores on the lips and skin.

It is important that you do not receive any live attenuated vaccines during your participation in this trial as their effectiveness and safety have not been established with Dupixent. Live attenuate-vaccines include BCG

(the anti-tuberculosis vaccine), MMR (Measles, Mumps, Rubella), Chickenpox, Yellow fever and the intranasal Flu vaccine. You may receive the annual intramuscular Flu vaccine (the 'Flu jab') as needed, since this is a killed virus vaccine. If you need a live attenuated vaccine, you should seek advice from the study doctor and your general practitioner.

Very rarely (less than 1 in 1000 treated patients) anaphylaxis (a severe allergic reaction that include acute breathing difficulty and /or low pressure and associated faintness or loss of consciousness) has been reported following Dupixent® injections.

STUDY PROCEDURES:

Allergen Intradermal and Skin Prick Tests. These tests are routinely performed in clinic. You may experience mild to moderate itchiness and discomfort at the sites of the intradermal and surface skin pricks with allergens and the positive control, which is histamine. The symptoms are usually not bothersome and treatment with topical or oral antihistamines is available if needed. In view of the extremely remote risk of a more serious reaction, a physician is always present and drugs and equipment for treatment of anaphylactic reactions are available.

Blood Samples. You will feel the sting of the needle as it enters your arm. There is a small risk of bruising and swelling at the site where the needle is inserted. Some people feel faint when they have their blood taken. You will be seated when you have your blood sample taken. True faints ('vaso- vagal' faints) are rare and resolve on lying down.

Lung Function Tests. Very rarely patients may feel slightly dizzy afterwards but this rapidly resolves without treatment. In patients with asthma the test may rarely lead to coughing or an asthma attack.

Nasal Allergen Challenge. You will experience typical hay fever symptoms including nasal itching, nasal blockage, sneezing, nasal watery discharge, itchy eyes, watery eyes, and redness of the lining of the eye. Nose and/or eye symptoms are prominent within minutes and fade rapidly, whereas mild nasal congestion may last 8 to 10 hours. There is a small risk of causing mild asthma symptoms. You will perform a breathing test before and after the nasal challenge and treatment with inhaled bronchodilators and steroids will be immediately available. As discussed above, for any intervention using the allergen to which you are allergic, there is that small risk of developing a severe allergic reaction, although this has never been observed in studies of several hundred participants over the past 20 years in our department.

Nasal Brushing. A small soft brush is inserted into the nose, rotated twice, and withdrawn. Risks include local pain with eye tearing, and rarely slight local bleeding that resolves with finger pressure. The symptoms are generally mild and resolve within minutes.

Nasal Lavage. Nasal lavage with salty water (SinuRinse®) will be used before the nasal challenge. SinuRinse® is widely available and no adverse effects are expected.

Unknown Risks: The treatment and procedures in this research study may have risks that are not yet known. These unknown risks may affect your willingness to participate in this study now or at some point in the future.

11.POTENTIAL BENEFITS

Taking part in this trial may or may not be of benefit to you. However, your participation in the study may benefit society by helping us learn more about better ways to treat allergies in the future.

During the pollen season, you will be provided with anti-allergic medications to alleviate your symptoms in the nose and eyes. This "rescue medication" set will include antihistamine tablets, nasal corticosteroid sprays and eye drops; these are likely similar to the ones you have taken before and do not cause drowsiness. If you do not respond adequately to these medications you will be able to consult with the study doctor who additionally may prescribe a short 5 day course of prednisolone (steroid) tablets to alleviate your symptoms during the peak pollen season.

Two out of three participants in the study will be randomised to a group that will receive either the combination of Dupixent® + Grazax® or Grazax® alone (i.e. Grazax® + Dupixent® placebo) for two years. These participants will likely benefit from Grazax® which is an approved treatment that has been shown to relieve hay fever symptoms. The effect of Dupixent® on hay fever symptoms is unknown since it has not previously been tested in hay fever. One out of three participants will receive Grazax® placebo + Dupixent® placebo during the 2 years treatment phase. They will also be supplied with the above rescue medications during the pollen season to provide some relief from their symptoms.

Once this study has finished (i.e. at the end of year 3, one year following discontinuation of study medication) and we have unblinded the study treatment groups, those participants who received double-placebo will have the option to receive 2 years treatment with Grazax® free of charge. This option will not be compulsory and is independent of this study.

12.ALTERNATIVES TO PARTICIPATION

Before you decide to take part in this study, Prof. Durham or his study doctors will talk with you about these and other options you may have, which may include just staying on the standard treatment for your hay fever.

13.NEW FINDINGS

Prof. Durham or his study doctors will tell you about any new information that may affect your willingness to continue in this study.

14.VOLUNTARY WITHDRAWAL FROM STUDY

You may decide not to take part or to leave the study at any time. If you decide to leave the study, there is no penalty or loss of benefits in your routine medical care or any other benefit(s) that you would otherwise be entitled to receive.

If you or the study doctor decides that you should stop taking the study medication, we would like to have you continue with the study visits and procedures, to follow your progress after coming off the study medicine. This will also be very helpful for comparison to those participants who continue on the study medication for the duration of the study.

15. REASONS WHY YOU MAY BE TAKEN OFF STUDY WITHOUT YOUR CONSENT

You may be removed from the study without your consent at any time. Reasons why you may be removed from the study include, but are not limited to, the following:

- Prof. Durham decides that it is best for you not to continue.
- You are unable to complete study treatments or tests.
- The Institution, the Sponsor, the MHRA, or other Health Authorities stop the study.
- You meet one of the pre-defined stopping rules as written in the study protocol. If you are removed from the study, Prof. Durham will notify you about treatment or procedures for your continued care.

16.PREGNANCIES, BREASTFEEDING AND BIRTH CONTROL

You cannot participate in this study if:

- You are pregnant
    - You are planning to become pregnant while in the study or
    - You are breastfeeding

Grazax® (the grass allergen tablets used in this trial) is not recommended to be started during pregnancy. Although it is usual practice that once established on Grazax®, the treatment may be continued during pregnancy, in this study there are additional procedures such as nasal challenges and repeated blood samples that are not advisable during pregnancy such that pregnant women are excluded.

The effects of Dupixent® in pregnant women are not known, so it is not recommended for pregnant women. You should not breast-feed while taking Dupixent®.

Therefore, if you join this study, you must agree to use birth control during the entire length of the study. You and the study team will talk about different methods of birth control. Women will be given a pregnancy test before and during the study.

If you become pregnant while in this study, or if you think that you have become pregnant, you must contact Prof. Durham or the study team right away.

17. EXPENSES AND PAYMENTS (REIMBURSEMENT)

Taking part in this trial will not cost you anything. You will be reimbursed reasonable travel expenses. You will receive no payment for your participation in this research study, however, you will receive an additional £20 compensation for time and inconvenience for each of the visits involving the collection of in-pollen-season and out-of-pollen-season research blood tests (12 visits) and an additional £40 for your participation on the day of the yearly nasal challenges (4 visits).

18. WHO IS FUNDING THIS RESEARCH?

The Immune Tolerance Network, which is a group of researchers based in the United States that works on many conditions including allergies, is conducting the study and the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) located in the United States is funding the study. All study visits will be completed at Royal Brompton Hospital, London.

19. WHAT IF THERE IS A PROBLEM?

In the event that you are harmed during the research, you may have grounds for legal action for compensation where the injury probably resulted from:

- A drug being tested or administered as part of the trial protocol
- Any test or procedure you received as part of the trial

Any payment would be without legal commitment. (Please ask if you wish more information on this).

In case of injury resulting from this study, you will not lose any legal rights by signing this form.

Copies of these guidelines are available from your study doctor, Prof. Stephen Durham, on request.

If you have a concern about any aspect of this study, you should ask to speak with the study team who will do their best to answer your questions [INSERT CONTACT DETAILS].

For further support, assistance, advice, or to lodge a complaint the Royal Brompton Hospital offers the Patient Advice and Liaison Service (PALS). They can help you if you are having difficulties, or have any complaints (or compliments!). You may contact: [redacted]

RESEARCH-RELATED INJURY

It is important that you tell your study doctor if you feel that you have been injured as a result of taking part in this study. You can tell the doctor in person or call

Prof. Stephen Durham on [INSERT CONTACT DETAILS HERE] or the Study Manager [INSERT CONTACT DETAILS HERE], at the Royal Brompton & Harefield NHS Foundation Trust. If you are hurt or get sick from something that was done as part of this study, doctors at the clinic or hospital can arrange for emergency medical care.

20. HOW WILL YOUR CONFIDENTIALITY BE RESPECTED AND THE PRIVACY OF YOUR PERSONAL INFORMATION BE MAINTAINED?

The study site will record basic personal details about you, including your name, contact details, gender,

height, weight and racial origin (to be used only for clinical purposes), as well as information on your medical history and clinical data collected about your participation in the study. The following people will also have access to your medical and research records:

- The Sponsor, which is the United States agency funding this study (DAIT, NIAID which is a part of The National Institutes of Health), including its representatives, agents, employees, contractors, and other persons assisting in conducting, monitoring or analysing the study;
- National and international regulatory authorities involved in keeping research safe for participants.

To ensure privacy, your name and other directly identifying information will not be attached to records or samples released to the Sponsor and its service providers for research purposes. Instead, you will only be identified by a code. Only the study doctor and authorised personnel will be able to connect this code to your name, by a list that will be kept securely by the study site for 15 years. *Your date of birth and initials may also be recorded to help identify your study record.* Your coded data will be forwarded to DAIT, NIAID and its service providers for activities related to the study e.g. laboratory analysis. Your coded data will also be viewed and analysed at Imperial College London. A list of companies to whom your coded information is transferred is available from the DAIT, NIAID via your study doctor.

Under the Data Protection Act, DAIT, NIAID makes important decisions on how your information collected for the research project are used and disclosed and is responsible as controller for ensuring that the rules of this law are followed. DAIT, NIAID has appointed PPD Global Limited as its representative to fulfil its obligations under this law. The study site will have similar responsibility in respect to the handling of data in your medical files at the site.

To the extent there is no conflict with the purpose of the study, you have the right to access, through your study doctor, all the information collected about you and, if applicable, ask for corrections. You may have the additional rights to object to how your information is being handled, request deletion of your data, restrict aspects of the processing of your information, or ask for a copy of your data to be provided to you, or a third party, in a digital format. Note however, in order to protect the scientific integrity of the study, the treatment you receive in this study needs to remain unknown (= blinded) until the study data is analysed.

You also have the right to complain about how your information is handled to a supervisory authority that is responsible for enforcing data protection law. In the UK, this is the Office of the Information Commissioner.

If you should withdraw from the study, data collected prior to your withdrawal may still be processed along with other data collected as part of the study. Normally no new information will be collected for the study database unless you specifically consent to that. However, the law does require that any effects that you may suffer are documented. You have the right to require that any previously retained samples are destroyed.

If you have any questions, comments or complaints about how your information is handled in this study, or wish to obtain a copy of the Standard Data Protection Clauses, you should firstly contact your study doctor who will be able to direct your query where appropriate to staff responsible for data protection at the NIAID, DAIT, or site, including the site Data Protection Officer.

21. ETHICS APPROVAL

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the NRES Committee North West - Greater Manchester South.

22. INVOLVEMENT OF THE GENERAL PRACTITIONER/FAMILY DOCTOR (GP)

With your consent, we will inform your GP about your participation in this study.

23. ANY QUESTIONS?

If you ever have questions about this study you should contact [redacted] or the Study Manager [redacted]

24. FUTURE USE OF YOUR DATA/BIOLOGIC MATERIALS

Your blood and nasal samples will be stored and analysed in the laboratories at Imperial College (London) and at the Immune Tolerance Network (Bethesda, MD, USA). The response of certain cells within the samples, including numbers of different cell types, mediators released and genes switched on or off, will be studied. With your consent, the following organisations shall store any leftover samples and information:

BioStorage Technologies, Inc.
USA

RUDCR Infinite Biologics
USA

Imperial College London
UK

Your samples and data may be stored for a minimum period of 10 years. Remaining samples are stored when all other study required tests are completed. The purpose is to make these samples and information available for future research which is not yet planned. These tests may or may not be related to the study of hay fever.

There is no benefit to you from the storage of samples and information. However, the use of your samples and information may help researchers learn more about your disease or the genetics related to a specific condition. The purpose of storage and sharing data is to make information available for use in health research and to share what is stored with other researchers. Collecting, storing, sharing information and making it available for other studies may help people in the future. Your samples/data may be shared with other researchers; this data would be coded so that other investigators would not have access to your personal information. Coded information put into databases together with other stored information from many studies conducted in different places allow researchers to study the combined information and learn even more about health and many different diseases.

The results of tests done on your stored samples will not be given to you or your doctor. Samples will not be analysed or tested for serious infection, such as HIV or Hepatitis B, nor for any inherited genetic conditions. The results will not be put in your records and will not change your medical care. They will not identify you and will not affect your routine medical care.

There may be unknown risks associated with the storage of samples and information. For example, if the future research involves genetic testing it is possible that it could be traced back to you because your genes are specific to you. We will make every attempt to protect your confidentiality and to make sure that your personal identity does not become known.

Your stored research samples will never be sold. However, the information obtained from the research performed on your samples may in the future lead to the development of commercial products. You will not receive any money from research using your stored samples and information.

You can change your mind at any time and ask to have your samples destroyed. This request should be made in writing to the study doctor. If you make this request, all remaining stored samples will be destroyed. However, the results of any previous tests using your stored samples will be used. Your decision regarding the storage of samples or the information resulting from the analysis of your samples

will not affect your ability to participate in this study. The future use of your samples and information may contribute to learning more about disease or help to study the genetics related to a specific condition.

Royal Brompton & Harefield NHS
NHS Foundation Trust

CONSENT FORM

Principal Investigator: Professor Stephen Durham **Participant Initials: Participant Number:**

Short Title: Grass Immunotherapy plus Dupilumab for Tolerance Evaluation

Statement of Consent	If you agree, please initial in the boxes below
1. I confirm that I have either read or had the participant information sheet (version __dated_____) explained to me. I have had the opportunity to consider the information and ask questions and I am satisfied with the explanations provided.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care or legal rights being affected.	☐
3. I agree for my information and samples to be collected, used and shared as described below: a. The authorised representatives of the United States sponsor, DAIT, NIAID and regulatory authorities' inspectors will have direct access to my medical records. b. Study data, including my coded medical information, will be retained and later used for further research, unless you object. c. My anonymised data/samples collected during the study will be sent for research outside the European Union/United Kingdom.	☐
4. I agree to my GP being informed of my participation in the study as described in this information sheet.	☐
5. I understand that I will receive a copy of this signed and dated information sheet and consent form.	☐
6. I voluntarily agree to take part in this study.	☐

Research Participant's Name *(Typed or printed)*	Research Participant's Signature	Date

Signature of person explaining and obtaining the consent:

Name and Title	Signature	Date

NOTE: This consent form with the original signatures MUST be retained on file by the principal investigator. A copy must be given to the research subject. A copy should be placed in the research subject's medical record, if applicable.

Royal Brompton & Harefield NHS
NHS Foundation Trust

CONSENT for storage of samples for Genetic and Non-genetic research

Principal Investigator: Professor Stephen Durham **Participant Initials: Participant Number:**

Short Title: Grass Immunotherapy plus Dupilumab for Tolerance Evaluation

Please indicate your response below:

	If you agree, please initial in the box below
1. I agree to the storage and sharing of biological samples (blood, nasal samples) and information resulting from the analysis of my samples **for ethically approved research, including research not currently planned**. All research has been or will be pre-approved by an ethics committee.	☐
2. I agree to the storage and sharing of biological samples (blood, nasal samples) for **genetic tests, including future tests not currently planned**. All tests have been or will be pre-approved by an ethics committee.	☐

Research Participant's Name *(Typed or printed)*	Research Participant's Signature	Date

Signature of person explaining and obtaining the consent:

Name and Title	Signature	Date

1 copy for patient; 1 copy for study file; 1 copy to be kept with hospital/clinic notes.