Immune Tolerance Network

National Institute of Allergy and Infectious Diseases

Protocol ITN084AD GRADUATE

Grass Pollen Sublingual Tablet Immunotherapy plus Dupilumab for Induction of Tolerance in Adults with Moderate to Severe Seasonal Allergic Rhinitis

Version 4.0 (December 14, 2021)

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INVESTIGATOR SIGNATURE PAGE

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Protocol: ITN084AD	**Version/Date:** V4.0 December 14, 2021
Site Principal Investigator: Stephen Durham, MD	
Title: Grass Pollen Sublingual Tablet Immunotherapy plus Dupilumab for Induction of Tolerance in Adults with Moderate to Severe Seasonal Allergic Rhinitis	
Study Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	
INSTRUCTIONS: *The site Principal Investigator should print, sign, and date at the indicated location below. A copy should be kept for your records and the original signature page sent. After signature, please return the original of this form by surface mail to:* [redacted]	

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the International Conference on Harmonization (ICH) document *Guidance for Industry: E6(R2) Good Clinical Practice: Consolidated Guidance*. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the National Research Ethics Committee (NREC) and NIAID.

By participating in this protocol, investigators and their designees also agree to:

i) Use Grazax® & Dupixent® and placebo for Grazax® & Dupixent® only in accordance with the Protocol and for no other purpose
ii) Not transfer Grazax® & Dupixent® or Placebo for Grazax® & Dupixent® to any parties other than the Distributor identified by the NIAID
iii) Not chemically modify, replicate, make derivatives of, or reverse engineer Grazax® & Dupixent® or placebo for Grazax® & Dupixent®

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Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PROTOCOL SYNOPSIS

Title	Grass Pollen Sublingual Tablet Immunotherapy plus Dupilumab for Induction of Tolerance in Adults with Moderate to Severe Seasonal Allergic Rhinitis
Short Title	**Gra**ss Pollen Immunotherapy plus **Du**pilumab for **T**olerance Induction.
Clinical Phase	Phase II
Number of Sites	1 site
CTA Sponsor/Eudra Number	DAIT NIAID, 2018-003456-20
Study Objectives	The primary objective is to compare the effect of the combination of SLIT and dupilumab versus double-placebo on the nasal allergen challenge (NAC) response to grass pollen at year 3, one year after completion of study treatment.
Study Design	This is a randomized, double blinded trial in adults (n=108) with moderate to severe seasonal allergic rhinitis with allergic sensitization to grass pollen. Participants will be recruited from October 2020 through May 2021. Eligible participants will be randomized to one of the following 3 groups in a 1:1:1 ratio. • Combination of SLIT and dupilumab (n=36) • SLIT plus dupilumab placebo (n=36) • SLIT placebo plus dupilumab placebo (n=36) Grazax® is a sublingual grass immunotherapy product approved for clinical use in the United Kingdom and will be used as SLIT in this study. It (and its matching placebo) will be self-administered daily by participants through week 104. Dupixent® is the brand name for dupilumab and is a monoclonal antibody against the IL-4 receptor. Dupilumab and its placebo will be administered every two weeks by subcutaneous injection through week 104. With appropriate training by study personnel, alternate doses of dupilumab (and other occasional doses as required) may be self-administered by participants at home. Dupilumab is approved for self-administration by patients. The treatment phase of 104 weeks will be followed by an observation phase of 52 weeks.

Primary Endpoint	NAC (TNSS Area-under-Curve [$AUC_{0\text{-}1hr}$]) at year 3, one year after completion of treatment. The primary comparison will be between the combination of SLIT and dupilumab arm and the double-placebo arms (clinical tolerance endpoint).
Secondary Endpoint(s)	<u>Clinical tolerance endpoints at year 3, one year after completion of study treatment.</u> The comparison will be between the combination of SLIT and dupilumab and the double-placebo arms. 1. Peak nasal inspiratory flow (Delta PNIF $AUC_{0\text{-}1hr}$) 2. Size of early and late intradermal skin test response 3. Size of the skin prick test endpoint titration response 4. Seasonal outcomes a. Weekly seasonal symptoms (Visual Analogue Scale [VAS] 0-10 cms) and combined symptom medication scores (CSMS) b. Weekly rhinitis quality of life scores (Juniper mini-Rhinoconjunctivitis Quality of Life Questionnaire [miniRQLQ]) measured in-season c. Modified Rhinitis Symptom Utility Index (MRSUI) measured in-season and out-of-season d. Global Evaluations No. 1 and No. 2 after the season <u>Clinical desensitization endpoints at year 1 and 2 whilst on study treatment.</u> The comparison will be between the combination of SLIT and dupilumab and the double-placebo arms. 5. TNSS $AUC_{0\text{-}1hr}$ 6. Delta PNIF $AUC_{0\text{-}1hr}$ 7. Size of early and late intradermal skin test response 8. Size of skin prick test endpoint titration response 9. Seasonal outcomes a. Weekly seasonal symptoms (VAS 0-10 cms) and CSMS b. Weekly rhinitis quality of life scores miniRQLQ measured in-season c. MRSUI measured in-season and out-of-season d. Global Evaluations No. 1 and No. 2 after the season <u>Safety Endpoints</u> 10. The number, severity, and relatedness of local and systemic AEs and SAEs reported during screening, at baseline, during years 1 and 2 whilst on study treatment, and during year 3 (one year after completion of study treatment). Each treatment arm will be summarized separately.

Exploratory Endpoints	Clinical tolerance endpoints at year 3, one year after completion of study treatment. All pairwise comparisons not included in primary and secondary endpoints above will be reported. 1. TNSS $AUC_{0\text{-}1hr}$ 2. Delta PNIF $AUC_{0\text{-}1hr}$ 3. Size of early and late intradermal skin test response 4. Size of skin prick test endpoint titration response 5. Seasonal outcomes a. Weekly seasonal symptoms VAS 0-10 cms and CSMS b. Weekly rhinitis quality of life scores miniRQLQ measured in-season c. MRSUI measured in-season and out-of-season d. Global Evaluations No. 1 and No. 2 after the season Clinical desensitization endpoints at year 1 and 2 whilst on study treatment. All pairwise comparisons not included in primary and secondary endpoints above will be reported. 6. TNSS $AUC_{0\text{-}1hr}$ 7. Delta PNIF AUC0-1hr 8. Size of early and late intradermal skin test response 9. Size of skin prick test endpoint titration response 10. Seasonal outcomes a. Weekly seasonal symptoms VAS 0-10 cms and CSMS b. Weekly rhinitis quality of life scores miniRQLQ measured in-season c. MRSUI measured in-season and out-of-season d. Global Evaluations No. 1 and No. 2 after the season Mechanistic endpoints at year 3, one year after study treatment (i.e., immune tolerance) and at year 1 and 2 whilst on study treatment (i.e., immune desensitization). All pairwise comparisons will be reported. 11. Mechanistic assessments of local immune responses in the nasal mucosa before and after the NAC. 12. Mechanistic assessments of peripheral blood leukocytes (including eosinophils, mast cells, and basophils) and mononuclear cell subsets after the NAC. 13. Mechanistic assessments of local immune responses and peripheral blood leukocytes (including eosinophils, mast cells, and basophils) and

	mononuclear cell subsets during natural allergen exposure In versus Out of the pollen season.
Accrual and power calculation	90 of the 108 enrolled participants will complete the study assuming approximately a 16.6% dropout rate. Sample size for this trial was determined by calculating the total enrollment necessary to provide at least 80% power to detect an expected difference in the mean TNSS $AUC_{0\text{-}1hr}$ at year 3 comparing the combination of SLIT and dupilumab arm to the double-placebo arm.
Study Duration	4.25 years, Oct 2020 - Jan 2025. • Recruitment/screening: 11 months • Dosing: 28 months • Follow-up: 12 months
Treatment Description	Participants will receive daily sublingual Grazax® 75,000 SQ units (containing 15 mcg major allergen *Phl p* 5) or placebo tablets once daily and Dupixent® 300mg or placebo subcutaneous injection every two weeks for 2 years.
Inclusion Criteria	Individuals who meet all of the following criteria are eligible for enrollment as study participants: 1. Participant must be able to understand and provide informed consent. 2. Adults age 18 to 65 years. 3. A clinical history of grass pollen-induced allergic rhinoconjunctivitis for at least 2 years with peak symptoms in May, June, or July. 4. A clinical history of moderate to severe rhinoconjunctivitis symptoms for at least 2 years interfering with usual daily activities or with sleep as defined according to the Allergic Rhinitis and its Impact on Asthma (ARIA) classification of rhinitis. 5. A clinical history of inadequately controlled rhinoconjunctivitis symptoms despite treatment with antihistamines and/or nasal corticosteroids during the grass pollen season for at least 2 years. 6. Positive skin prick test response at screening, defined as wheal diameter greater than or equal to 3 mm, to *Phleum pratense*. 7. Positive specific IgE at screening, defined as greater than or equal to IgE class 2 (0.7 kU/L) against *Phleum pratense*. 8. Removed in protocol version 3.0. 9. A woman of childbearing potential (WOCBP; for definition, see Appendix 6), regardless of birth control history is required to consistently use one of the following highly effective methods of contraception throughout the study: hormonal (e.g. oral, transdermal, intravaginal, implant, or injection); intrauterine device (IUD) or system

	(IUS); vasectomized partner; bilateral tubal occlusion; or sexual abstinence (for definitions see contraceptive guidance in Appendix 6).
Exclusion Criteria	Individuals who meet any of these criteria are not eligible for enrollment as study participants: 1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol. 2. Prebronchodilator forced expiratory volume (FEV_1) less than 70% of predicted value at either screening or baseline visit. 3. A clinical history of asthma requiring regular inhaled corticosteroids for > 4 weeks per year outside of the grass pollen season. 4. A clinical history of moderate to severe allergic rhinitis, as defined according to the ARIA classification of rhinitis, caused by either: a. an allergen to which the participant is regularly exposed OR b. tree pollen during tree pollen season treated with regular antihistamine or intranasal corticosteroids. 5. History of emergency visit or hospital admission for asthma in the previous 12 months. 6. History of chronic obstructive pulmonary disease. 7. History of recurrent acute sinusitis, defined as 2 episodes per year for the last 2 years, all of which required antibiotic treatment. 8. History of chronic sinusitis, defined as sinus symptoms lasting greater than 12 weeks that includes 2 or more major factors or 1 major factor and 2 minor factors. Major factors are defined as facial pain or pressure, nasal obstruction or blockage, nasal discharge or purulence or discolored postnasal discharge, purulence in nasal cavity, or impaired or loss of smell. Minor factors are defined as headache, fever, halitosis, fatigue, dental pain, cough, and ear pain, pressure, or fullness. 9. History of systemic disease affecting the immune system such as autoimmune diseases, immune complex disease or immunodeficiency. 10. Current symptoms of, or treatment for, upper respiratory tract infection, acute sinusitis, acute otitis media, or other relevant infectious process; serous otitis media is not an exclusion criterion. Participants may be re-evaluated for eligibility after symptoms resolve. 11. A past history of any malignant disease in the previous 5 years. 12. Any tobacco smoking within the last 6 months, or a history of greater than or equal to 10 pack years of cigarette use. Any vaping or electronic cigarette use within the last 6 months.

	13. Previous immunotherapy with grass pollen allergen within the previous 5 years. 14. Previous treatment by dupilumab. 15. Previous Grade 4 anaphylaxis (WAO grading criteria) due to any cause. 16. History of anti-IgE, anti-IL-5, anti-IL-5 receptor, anti-IL-4/IL-13 receptor, or other monoclonal antibody treatment. 17. Current use of tricyclic antidepressants or monoamine oxidase inhibitors. 18. Ongoing systemic immunosuppressive treatment. 19. History of intolerance to the study therapy, rescue medications, or their excipients. 20. A positive pregnancy test. 21. Currently lactating/breast feeding. 22. The use of any investigational drug within 30 days of the screening visit. 23. The presence of any medical condition that the investigator deems incompatible with participation in the trial. 24. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or may impact the quality or interpretation of the data obtained from the study. 25. Eosinophilic esophagitis or a diagnosis of any hypereosinophilic syndrome. 26. Administration of live attenuated vaccines within four weeks of dupilumab or dupilumab placebo injections, before the first injection and throughout the treatment period.
Study Stopping Rules	• Any death that is possibly related or related to one of the investigational products (dupilumab/dupilumab placebo or SLIT/SLIT placebo) or a study procedure. • Any grade 4 AE that is possibly related or related to one of the investigational products (dupilumab/dupilumab placebo or SLIT/SLIT placebo) or a study procedure. • Any grade 3 AE that is possibly related or related to one of the investigational products (dupilumab/dupilumab placebo or SLIT/SLIT placebo) or a study procedure in three or more participants.

GLOSSARY OF ABBREVIATIONS

AE	Adverse event
ARIA	Allergic Rhinitis and its Impact on Asthma
AUC	Area under the curve
BAT	Basophil activation tests
CSMS	Combined Symptom Medication Score
DAIT	Division of Allergy, Immunology, and Transplantation
DSMB	Data and Safety Monitoring Board
eCRF	Electronic case report form
EMA	European Medicines Agency
FAB	Fragment antigen binding
FDA	US Food and Drug Administration
FEV_1	Forced expiratory volume
GCP	Good clinical practice
HLA	Human leukocyte antigen
ICH	International Conference on Harmonization
ITN	Immune Tolerance Network
IUD	Intrauterine device
IUS	Intrauterine system
IMP	Investigational medicinal product
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MiniRQLQ	Mini Rhinoconjunctivitis Quality of Life Questionnaire
mITT	Modified intent to treat
MRSUI	Modified Rhinitis Symptom Utility Index
NAC	Nasal allergen challenge

NCI-CTCAE	National Cancer Institute *Common Terminology Criteria for Adverse Events* (version 5.0, November 27, 2017)
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NREC	National Research Ethics Committee
PP	Per protocol
SAE	Serious adverse event
SACCC	Statistical and Clinical Coordinating Center
SAR	Suspected adverse reaction
SLIT	Sublingual immunotherapy
SmPC	Summary of product characteristics
TNSS	Total nasal symptom score
VAS	Visual analogue scale
WOCBP	Women of child bearing potential

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND

Allergic rhinitis affects 15% of the US[1] and 23% of the European population[2] and has major impact on quality of life, sleep and work/school performance.[3,4] Whereas modern antihistamines and topical nasal corticosteroids are effective,[5] community surveys suggest that around 60% of allergic rhinitis sufferers fail to respond adequately to these measures.[1,6] When avoidance of allergens is not feasible and patients have inadequate response to anti-allergic medications or suffered bothersome side-effects, allergen immunotherapy presents a rational alternative next step in treatment.[7-9] While subcutaneous immunotherapy has been shown to be highly effective in seasonal allergic rhinitis,[8,10] it requires administration by skilled personnel in a specialist allergy clinic. The risk of systemic side effects, including anaphylaxis, necessitates immediate access to a physician and resuscitative measures for safe administration of subcutaneous immunotherapy. The procedure is time-consuming and requires at least 30 minutes observation following injections.

With these reservations, sublingual immunotherapy (SLIT) has emerged as an effective and safer alternative.[11-13] Meta-analyses involving indirect comparisons have shown that SLIT for both seasonal and perennial rhinitis is at least as effective as anti-allergic drugs.[14] Like subcutaneous immunotherapy[15], three years of continuous SLIT has been shown to modify the underlying course of the disease with long-term remission of symptoms for several years after stopping treatment.[16,17] Although there are few direct comparisons, indirect meta-analyses suggest that the sublingual route may be less effective than the subcutaneous route.[18,19] The GRASS trial showed that whereas both sublingual and subcutaneous grass pollen immunotherapy were effective, the efficacy of the subcutaneous route came on earlier than for sublingual treatment. Furthermore 2 years treatment via either route, in contrast to 3 years, was insufficient for long-term tolerance.[20] Current guidelines therefore emphasize the need for at least 3 years treatment.[19]

The mechanism of allergen immunotherapy involves downregulation of antigen-specific Th2 responses as a consequence of induction of regulatory T cells and/or immune deviation in favor of antigen-specific Th1 responses.[20,21] Downstream events include suppression of effector cells (eosinophils, basophils and innate lymphoid cells) in target organs and the production of IgE-blocking antibodies. Whereas the mechanism for both routes appears similar, one striking difference that has emerged is that whereas IgE-blocking antibodies after subcutaneous immunotherapy reside within the IgG4 compartment, after sublingual treatment, this blocking activity has been shown to reside predominantly within the IgA subclass with 5-10 fold greater increases in grass-pollen specific IgA1 and IgA2 being detected in serum and local nasal fluid after sublingual treatment when compared with the subcutaneous route. Mechanistic studies from the GRASS trial imply that vaccines containing both T cell and B cell epitopes may be necessary for long-term allergen tolerance.[20,21] This is supported by the recent failure of

vaccines containing T cell epitopes alone (Phase 3 trials of cat and house dust mite T cell peptide vaccines, Circassia press releases).[22,23]

1.2 RATIONALE FOR STUDY

In view of the need for 3 years continuous immunotherapy to achieve durable tolerance and the safety concerns associated with the subcutaneous route, there is a need for an alternative strategy. One approach is the use of sublingual tablet immunotherapy in combination with immune modifiers that by design amplify desirable immune responses whilst reducing the likelihood of IgE-crosslinking, thereby enhancing efficacy, reducing side effects, and potentially enabling a shorter tolerance-inducing treatment regimen.[24]

We propose that the combination of an anti-interleukin 4 receptor alpha (IL-4Rα) antibody (dupilumab) with SLIT would augment suppression of Th2 responses by immunotherapy and effectively inhibit allergic inflammation thereby providing a neutral environment conducive to induction of antigen-specific tolerance.

Grazax® *Phleum pratense* is a fast-dissolving freeze-dried tablet that is registered in UK, Europe since 2006 and since 2012 in USA for daily sublingual treatment of moderate-severe seasonal allergic rhinitis due to grass pollen that has not responded adequately to oral and/or intranasal antihistamines or intranasal cortiscosteroids.[13,14,16,25]

Dupixent® (dupilumab) is a fully-humanized anti-IL-4 receptor alpha (IL-4Rα) antibody.[26] Dupilumab has been extensively trialed in atopic eczema and is currently US Food and Drug Administration (FDA), European Medicines Agency (EMA), and Medicines and Healthcare products Regulatory Agency (MHRA) approved for treatment of severe atopic eczema inadequately controlled by emollients, topical corticosteroids and/or calcineurin antagonists.[27] Dupilumab is also FDA and EMA approved for the treatment of severe asthma, eosinophilic type. Dupilumab has not been studied in allergic rhinitis although it has been shown to be effective in improving asthma control and reducing exacerbations in severe asthma,[28] and in reducing nasal symptoms in patients with severe nasal polyposis.[29] The results of these studies have led to FDA and EMA approval of dupilumab in the treatment of chronic rhinosinusitis with nasal polyposis.[30]

SLIT suppresses allergic inflammation and induces immune deviation, up regulation of T regs and the induction of blocking antibodies, particularly of the IgA subclass.[21] Targeting IL-4R inhibits both IL-4 and IL-13 signaling. IL-4 drives Th2 T cell differentiation and reciprocally inhibits Th1 differentiation. IL-4 and IL-13 drive epsilon germ-line gene transcription, the first step in B cell switching in favor of IgE antibody.[26] Thus, dupilumab targets both T and B cell arms of the allergic response and inhibits downstream effector cells including mast cells, basophils and airway mucus secretion. It is anticipated that the combination of dupilumab with SLIT would neutralize allergic inflammation and be more effective than immunotherapy alone in inducing long-term antigen-specific tolerance.

Alternative combinations of immune modifiers with SLIT have not been explored. Possible candidates alternative to dupilumab include the anti-IgE monoclonal antibody omalizumab that [31,32] has been combined with subcutaneous immunotherapy where there was enhanced safety but no impact on efficacy. There are no long-term studies of omalizumab combined with allergen immunotherapy.[33,34] Anti-TSLP has been shown to be effective in reducing asthma exacerbations [35] and is currently being investigated in combination with subcutaneous cat immunotherapy in an Immune Tolerance Network (ITN)-sponsored trial (Clinical Trials.Gov Identifier: NCT02237196).[36] The strengths of using dupilumab over these alternatives in combination with sublingual treatment include its ability to downregulate both cellular and humoral allergic responses.

In GRADUATE, a shortened 2 year course of conventional SLIT (Grazax® *Phleum pratense*) will be combined with parallel treatment with subcutaneous dupilumab in a randomized, double-blind placebo-controlled 3 parallel arm trial in patients with moderate-severe seasonal allergic rhinitis. The aim in combining dupilumab with SLIT is to provide proof of concept towards developing an effective 'allergen plus' vaccine approach for patients with moderate-severe allergic rhinitis that will increase efficacy and potential for long-term tolerance whilst reducing the local allergen-mediated side effects of SLIT and enable a shorter, more effective regimen.

As stated in Section 3.2, the primary comparison will be between the combination of SLIT and dupilumab and the double-placebo arms. The GRASS study showed that two years of SLIT followed by 1 year off of therapy did not result in clinical tolerance.[20] The primary hypothesis (see Section 2.1) is that the combination of SLIT with dupilumab will result in clinical tolerance. Three years treatment with SLIT (Grazax® alone) has been shown to result in an approximate 30% reduction in seasonal symptom scores consistently during 3 years treatment and for 2 years after withdrawal.[16] This is favorable compared to the WAO definition of the minimal clinical important difference as 20% for active immunotherapy compared to placebo.[37] In GRASS, 2 years treatment gave an approximate 30% reduction in total nasal symptom score (TNSS) (area under the curve $[AUC]_{0\text{-}10\ hr}$) during 2 years desensitization whereas on withdrawal this reduction was insignificant at 7% compared to placebo treatment.[20] A reasonable added effect of the combination of SLIT and dupilumab for 2 years may therefore be to convert the effect size of SLIT vs. placebo at the tolerance endpoint (in GRASS, 7% at 3 years) to that observed with SLIT alone at the 2 year desensitization endpoint (i.e.,., approximately 30% for the combination of SLIT and dupilumab at 3 years). The results of this study could allow for accurate assessments of the sample size needed to show difference between the combination of SLIT and dupilumab and SLIT monotherapy. Such data do not exist at this time making comparison of the combination of SLIT and dupilumab with SLIT monotherapy in this study premature.

1.2.1 CLINICAL EFFICACY AND SAFETY FOR GRAZAX® (STANDARDIZED GRASS POLLEN ALLERGEN TABLET IMMUNOTHERAPY)

Grazax® (grass pollen tablet SLIT) is registered throughout Europe and the UK for the treatment of seasonal allergic rhinoconjunctivitis in patients aged 5–65 years (18–65

years in UK).[14,16,38,25,39] Trials have shown an approximate 30% reduction in symptoms and 40% decrease in rescue medication during the season and improved quality of life (see Table 1). A pre-seasonal duration of 4 months at a daily dose of 75,000 SQ (containing15 µg *Phl p5*) was shown to be optimal.[14,16] Three years continuous daily treatment in adults aged 16-64 years was effective with a 30% reduction in seasonal symptoms.[16] Efficacy persisted for 2 years after discontinuation of immunotherapy.[16] Long-term benefit was confirmed in a 5 year multi-center European trial in 813 children aged 5-12 years with seasonal rhinoconjunctivitis.[40] Three years treatment with Grazax® was effective in reducing symptoms and rescue medications for both rhinoconjunctivitis and asthma that persisted for 2 years after discontinuation. On the basis of these results Grazax® is registered in Europe as a disease-modifying treatment in both adults and children. The GRASS trial showed that whereas Grazax® was effective, 2 years treatment was insufficient for tolerance.[20] The concept of a sublingual fast-dissolving once daily tablet has now been extended to other inhalant allergens, with demonstration of efficacy in rhinoconjunctivitis due to Ragweed,[41,42] in rhinoconjunctivitis due to house mite dust,[43] and in asthma due to house mite dust.[44]

Table 1. Grazax® Sublingual *Phleum pratense* tablet immunotherapy for seasonal grass pollen allergic rhinitis

Study	Extract	Length	Groups (N)	Design	Efficacy	Adverse events
Durham JACI 2006 [45]	*P. pratense*	18 wks	2,500 SQ (136) 25,000 SQ (139) 75,000 SQ (294) Placebo (286)	RDBPCT 8 weeks pre- and co-seasonal	16% reduction in SS and 28% MS with 75,000SQ vs placebo	Local reactions in 53%, local pruritus, oedema, throat irritation. 1 serious TRAE (uvula oedema)
Dahl JACI 2006 [38]	*P. pratense*	Treatment 3 yrs	*Dahl 2006* 75,000 SQ (316) Placebo (318)	RDBPCT 1 yr initially, extended to 3 yrs	30% reduction in SS, 38% in MS vs placebo at 1 yr	Local reactions in 46%, oral pruritus (44%), mouth oedema (19%), throat irritation (13%), and ear pruritus (12%). No serious TRAE or serious allergic reactions.
Durham JACI 2012 [16]		Follow up 2 yrs	75,000 SQ (189) Placebo (162)	Off-treatment 2 yrs	27% reduction CSMS at 5 yrs	
Maloney Ann Allergy 2014 [25]	*P. pratense*	16 wks pre-co-season	75,000 SQ (749) Placebo (414)	RDBPCT in adults and children	CSMS was reduced by 23% in the active group compared with placebo. 29% in the peak season.	Local reaction; throat irritation 23% and oral pruritus 19% in the active group. 3.5 and 2.7% in the placebo group respectively. Three systemic reactions.
Valovirta JACI 2018 [40]	*P. pratense*	Treatment 3 yrs Follow up 3 yrs	75,000 SQ (398) Placebo (414)	RDBPCT children 5-12 yrs, ARC to grass, no asthma.	No difference time to asthma development. Reduction 29.4% in asthma symptoms and medication.	Local pruritus and throat irritation in up to 61% of treatment group. No serious AEs.

Grazax®, (*Phleum pratense* SQ 75000 standardized quality units) is a lyophilized tablet that contains 15 µg of Phl p5 major allergen. The tablet is administered sublingually daily for a minimum of 2 months before and during the grass pollen season. It is recommended that the first dose of Grazax® is administered in the clinic with observation for at least 60 minutes and that subsequent doses are taken independently by the patient. Local side effects of itching and swelling in the mouth are common, occurring in 46-61% of individuals in phase 3 trials.[14,16,25,38] Local side effects occur within minutes and resolve within 1 hour with a median half-life of approximately 10 days with daily administration. These local side effects are, in general, mild well-tolerated and require no treatment. More severe local and systemic reactions have very rarely been reported, and no fatalities have occurred (see Section 5.1.1). There have been two reported cases of anaphylaxis in the literature.[46] These cases did not result in fatalities, serious adverse events (SAEs), or epinephrine use.

1.2.2 CLINICAL EFFICACY AND SAFETY FOR DUPIXENT® (DUPILUMAB 300MG SUBCUTANEOUS INJECTION)

Dupilumab has not been studied in patients with allergic rhinoconjunctivitis, but given the similar role of Type 2 immunity in atopic dermatitis, asthma, and allergic rhinitis, there is a strong rationale for using dupilumab in this trial.

Five phase 3 trials involved 2,912 participants 18 years and older with moderate to severe eczema.[26] The Summary of Product Characteristics (SmPC) dated June 28, 2019 for Dupixent® indicates the percentage of participants who had a ≥75% improvement in their Eczema Area and Severity Index (EASI) varied form 44-72% for dupilumab compared to 12-30% for placebo-treated participants.[47]

Dupilumab has been assessed in three phase 3 trials involving 2,888 patients with moderate-to-severe persistent asthma where it has been shown to reduce exacerbations, improve lung function and reduce maintenance corticosteroid requirements.[26,47] For example in one pivotal phase 3 trial involving 1,902 participants, dupilumab 300 mg every two weeks resulted in a 46% reduction in severe exacerbations (67% in those with blood eosinophils> $0.3x10^9$/dL) compared to placebo treatment.[48]

Dupilumab has also been studied in nasal polyps. In a phase 2 trial over 16 weeks in 60 adults with nasal polyps refractory to topical steroids, the combination of dupilumab with mometasone nasal spray compared to mometasone alone reduced the endoscopic nasal polyp score and improved nasal symptoms, including sense of smell.[29] In two multicenter phase 3 trials in adults 24 and 52 weeks in duration dupilumab significantly reduced polyp burden and improved symptom score, achieving all primary endpoints.[51]

Dupilumab is approved in the UK for treatment of moderate-severe atopic dermatitis that fails to respond adequately to emollients and topical therapy and in whom systemic therapy is indicated. Dupilumab is now also FDA, UK, and European Commission approved for use in severe asthma (eosinophilic type), and FDA and European Commission approved for nasal polyposis.[30,47,52]

Safety of Dupilumab 300mg subcutaneous injection (Dupixent®)

The approved dose of dupilumab in moderate to severe atopic dermatitis, moderate to severe asthma, and inadequately controlled chronic rhinosinusitis with nasal polyps is an initial subcutaneous injection of 600mg followed by 300mg every two weeks. The incidence of adverse events (AEs) was similar in dupilumab and placebo arms in trials from 16-52 weeks duration. A recent meta-analysis of atopic dermatitis studies revealed a lower risk of skin infections and eczema herpeticum, a marked reduction in exacerbations of atopic dermatitis and no difference from placebo in other types of infection (Table 2).[53] In patients with atopic dermatitis dupilumab was associated with a significant 2.24 fold increase in local injection site reactions and a slight 1.47-fold increase in the risk for developing headache (Table 2).

The injection site reactions likely relate to the 2ml volume for injection for the standard 300mg subcutaneous dose. In atopic dermatitis trials, there was a 2.64-fold increase in conjunctivitis with >90% of the conjunctivitis events rated as mild or moderate, and 75% resolved on treatment. Only 1 of 920 participants treated with dupilumab discontinued treatment because of conjunctivitis.[26] The cause for the conjunctivitis is unknown but may relate to antagonism of the effects of IL-13 on mucus secretion at mucosal surfaces. The effect may be peculiar to atopic eczema participants who exhibit impaired barrier function, since to date the effect has not been observed in dupilumab trials in asthma (as seen in Sections 4.8 and 6.4 of the Dupixent® SmPC).[47]

The 16 week safety data for dupilumab are reported in the package insert (Table 3). Data are derived from atopic dermatitis trials in patients treated with dupilumab for 52 weeks either as monotherapy or in conjunction with topical corticosteroids. The safety profile at 52 weeks is reportedly similar to week 16 data.

In asthma trials, the most common adverse reaction was injection site erythema (see Table 4). Anaphylaxis has been reported very rarely. In contrast to trials of dupilumab for atopic dermatitis, the frequency of conjunctivitis in asthma trials was very low and the prevalence similar between dupilumab and placebo-treated participants. The list of adverse reactions to dupilumab in the trials of dupilumab in asthma can be found in Table 2 of the Dupixent® SmPC.[47] The rate of conjunctivitis observed in CRSwNP was lower than the observed rate in atopic dermatitis trials (see

Table 5).30

Dose adjustment in the elderly, in relation to body weight or in those with renal impairment, is not required. Dupilumab has been approved down to age 6 in the United States for atopic dermatitis and age 12 in the United Kingdom for asthma and atopic dermatitis. The safety of dupilumab in patients with liver impairment has not been established.[47]

Table 2. Dupilumab AEs (meta-analyses of 8 studies in atopic dermatitis, 2,705 adults (>18 yr) 4-52 weeks duration.[53]

Adverse Events	Dupilumab N (%)	Placebo group N (%)	Risk ratio (95% Confidence intervals)	p value
Exacerbations of atopic dermatitis	193 (14.3)	292 (37.9%)	0.39 (0.33–0.46)	<0.001
Skin infections	120 (6.7)	121 (13.3)	0.54 (0.42–0.69)	<0.001
Herpes virus infection	102 (6.1)	43 (5.2)	1.21 (0.84–1.74)	0.30
Upper respiratory infections	110 (6.6)	53 (6.4)	1.03 (0.53–2.01)	0.94
Nasopharyngitis	261(15.7)	116 (13.9)	1.06 (0.87–1.31)	0.55
Urinary tract infections	25/1238 (2.0)	12/517 (2.3)	0.58 (0.28–1.19)	0.14
Conjunctivitis	133 (8.0)	30 (3.6)	2.64 (1.79–3.89)	< 0.001
Injection site reactions	221 (13.2)	54 (6.5)	2.24 (1.68–2.99)	< 0.001
Headache	136 (8.2)	45 (5.4)	1.47 (1.05–2.06)	0.03
Infrequent AEs and those reported in only one study				
Bacterial infection	25 (7.9)	7 (11.5)	0.69 (0.31–1.51)	0.35
Viral infection	17 (5.3)	6 (9.8)	0.54 (0.22–1.32)	0.18
Dermatitis and eczema	63 (19.8)	12 (19.7)	1.01 (0.58–1.75)	0.98
Nausea and vomiting	10 (3.1)	4 (6.6)	0.48 (0.16–1.48)	0.20
Musculoskeletal connective tissue	15 (4.7)	5 (8.2)	0.58 (0.22–1.52)	0.27
Back pain	9 (2.8)	5 (8.2)	0.35 (0.12–0.99)	0.05
Sinusitis	23 (1.7)	15 (1.9)	0.68 (0.10–4.68)	0.70
Influenza	19 (1.4)	19 (2.5)	0.68 (0.36–1.28)	0.23
Asthma	7 (1.6)	19 (6.0)	0.27 (0.12–0.64)	0.003

Table 3. Adverse Reactions Occurring in ≥1% of the Dupixent® Monotherapy Group or the Dupixent® + TCS Group in the Atopic Dermatitis Trials through Week 16

Adverse Reaction	Dupixent® Monotherapy[a]		Dupixent® + TCS[b]	
	Dupixent® 300 mg Q2Wc N=529 (%)	Placebo N=517 (%)	Dupixent® 300 mg[c] Q2Wc + TCS N=110 (%)	Placebo + TCS N=315 (%)
Injection site reactions	51 (10)	28 (5)	11 (10)	18 (6)
Conjunctivitis[d]	51 (10)	12 (2)	10 (9)	15 (5)
Blepharitis	2 (<1)	1 (<1)	5 (5)	2 (1)
Oral herpes	20 (4)	8 (2)	3 (3)	5 (2)
Keratitis[e]	1 (<1)	0	4 (4)	0
Eye pruritus	3 (1)	1 (<1)	2 (2)	2 (1)
Other herpes simplex virus infection[f]	10 (2)	6 (1)	1 (1)	1 (<1)
Dry eye	1 (<1)	0	2 (2)	1 (<1)

[a] Pooled analysis of 3 safety trials in atopic dermatitis.
[b] Analysis of one trial where participants were on background TCS therapy.
[c] Dupixent 600 mg at Week 0, followed by 300 mg every two weeks.
[d] Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.
[e] Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simplex.
[f] Other herpes simplex virus infection cluster includes herpes simplex, genital herpes, herpes simplex otitis externa, and herpes virus infection, but excludes eczema herpeticum.

Table 4. Adverse Reactions Occurring in ≥1% of the Dupixent® Groups in Asthma Trials 1 and 2 and Greater than Placebo (6 Month Safety Pool)

Adverse Reaction	Dupixent® 200 mg Q2W N=779 (%)	Dupixent® 300 mg Q2W N=788 (%)	Placebo N=792 (%)
Injection site reactions[a]	111 (14)	144 (18)	50 (6)
Oropharyngeal pain	13 (2)	19 (2)	7 (1)
Eosinophilia[b]	17 (2)	16 (2)	2 (<1)

[a] Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation.
[b] Eosinophilia: Blood eosinophils ≥3,000 cells/mcL, or deemed by the investigator to be an adverse event.

Table 5. Adverse Reactions Occurring in ≥1% of the Dupixent® Group in CRSwNP Trials 1 and 2 and Greater than Placebo (24 Week Safety Pool)

Adverse Reaction	Dupixent® 300 mg Q2W N=440 (%)	Placebo N=282 (%)
Injection site reactions[a]	28 (6)	12 (4)
Conjunctivitis[b]	7 (2)	2 (1)
Arthralgia	14 (3)	5 (2)
Gastritis	7 (2)	2 (1)
Insomnia	6 (1)	0 (<1)
Eosinophilia	5 (1)	1 (<1)
Toothache	5 (1)	1 (<1)

[a] Injection site reactions cluster includes injection site reaction, pain, bruising and swelling.
[b] Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial. conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

2. STUDY HYPOTHESES/OBJECTIVES

2.1 PRIMARY HYPOTHESES

In patients with moderate-severe seasonal allergic rhinitis, the combination of SLIT and dupilumab is more effective than double-placebo in suppressing the NAC response to grass pollen at year 3, one year after completion of study treatment.

2.2 SECONDARY HYPOTHESES

1. The combination of SLIT and dupilumab is more effective than double-placebo in inducing clinical tolerance to grass pollen.
2. The combination of SLIT and dupilumab is more effective than double-placebo in inducing clinical desensitization to grass pollen.
3. The combination of SLIT and dupilumab, SLIT plus dupilumab placebo, and double-placebo are safe and tolerable during two years of study treatment and one year after completion of study treatment.

2.3 PRIMARY OBJECTIVE

The primary objective is to compare the effect of the combination of SLIT and dupilumab versus double-placebo on the nasal allergen challenge (NAC) response to grass pollen at year 3, one year after completion of study treatment.

2.4 SECONDARY OBJECTIVES

1. To compare the effect of the combination of SLIT and dupilumab versus double-placebo on clinical tolerance to grass pollen.
2. To compare the effect of the combination of SLIT and dupilumab versus double-placebo on clinical desensitization to grass pollen.
3. To evaluate the safety and tolerability of the combination of SLIT and dupilumab, SLIT plus dupilumab placebo, and double-placebo arms.

2.5 EXPLORATORY OBJECTIVES

Clinical:

1. To compare the effect of the combination of SLIT and dupilumab versus SLIT plus dupilumab placebo on clinical tolerance to grass pollen.
2. To compare the effect of the combination of SLIT and dupilumab versus SLIT plus dupilumab placebo on clinical desensitization to grass pollen.
3. To compare the effect of SLIT plus dupilumab placebo versus double-placebo on clinical tolerance to grass pollen.
4. To compare the effect of SLIT plus dupilumab placebo versus double-placebo on clinical desensitization to grass pollen.

Mechanistic:

5. To compare the effect of the combination of SLIT and dupilumab, SLIT plus dupilumab placebo, and double-placebo on immune tolerance to grass pollen, as defined by down-regulation of local nasal and peripheral blood Th2 responses and induction of protective antibody responses.
6. To compare the effect of the combination of SLIT and dupilumab, SLIT plus dupilumab placebo, and double-placebo on immune desensitization to grass pollen,

as defined by down-regulation of local nasal and peripheral blood Th2 responses and induction of protective antibody responses.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY DESIGN

This is a randomized, double blinded trial in adults (n=108) with moderate to severe seasonal allergic rhinitis with allergic sensitization to grass pollen.

During the screening visit, participants will be asked for demographic information, complete a brief questionnaire concerning their allergic rhinitis, severity and duration, and impact on their quality of life, work or school performance and sleep. Any co-morbidities including asthma, eczema, or sinusitis; their past medical history; smoking history and medication history will be recorded. Participants will undergo skin prick testing with a panel of inhaled aeroallergens and with positive and negative controls. A blood sample will be taken for full blood count, total and specific IgE to grass and tree pollen, comprehensive chemistry and liver function tests.

Participants who meet eligibility criteria and choose to enroll will undergo a baseline visit. Thereafter participants will be randomized 1:1:1 to three parallel treatment arms as follows:

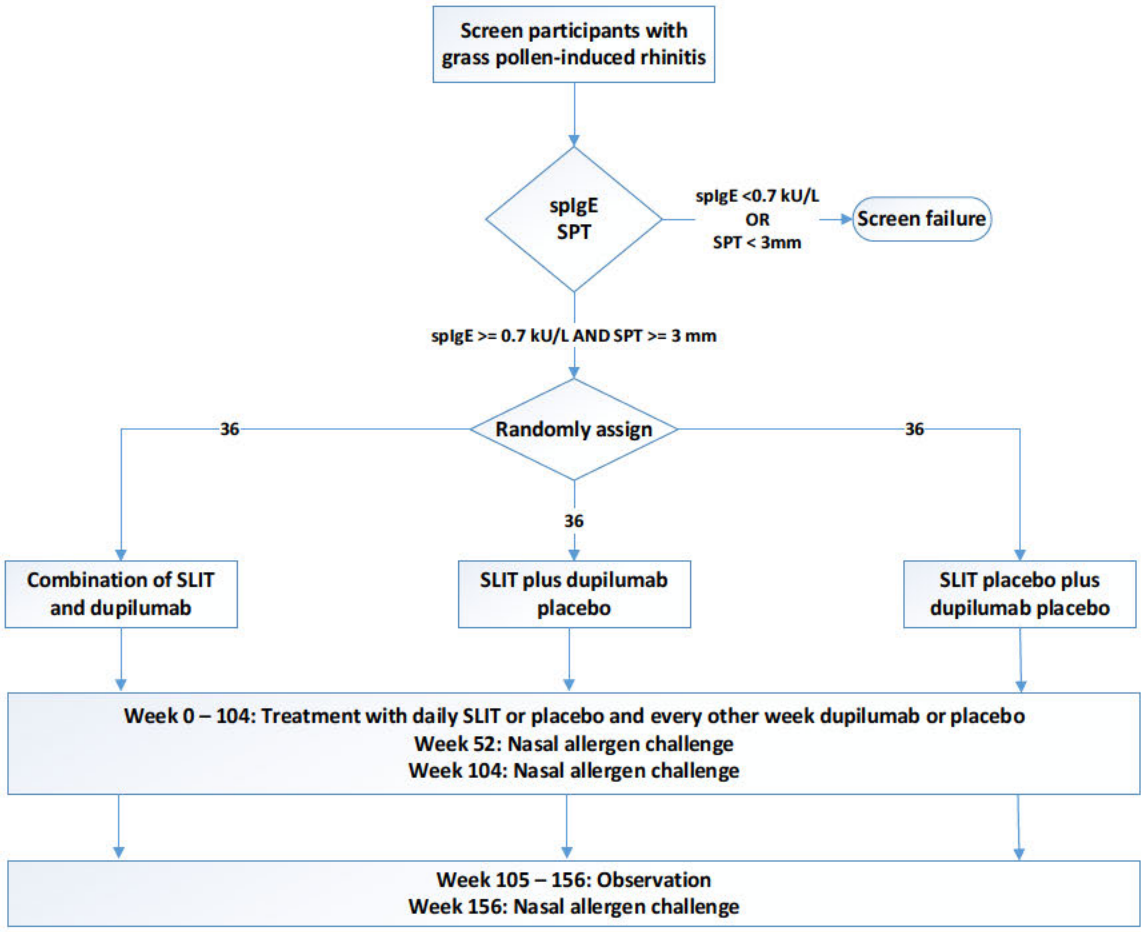
- Combination of SLIT and dupilumab (n=36)
- SLIT plus dupilumab placebo (n=36)
- SLIT placebo plus dupilumab placebo (i.e. double-placebo) (n=36)

Grazax® is a sublingual grass immunotherapy product approved for clinical use in the United Kingdom and will be used as SLIT in this study. It (and its matching placebo) will be self-administered daily by participants through week 104. Dupixent® is the brand name for dupilumab and is a monoclonal antibody against the IL-4 receptor. Dupilumab and its placebo will be administered every two weeks by subcutaneous injection through week 104. With appropriate training by study personnel, alternate doses of dupilumab (and other occasional doses as required) may be self-administered by participants at home. Dupilumab is approved for self-administration by patients. The treatment phase of 104 weeks will be followed by an observation phase of 52 weeks.

A NAC will be performed at baseline (Visit -1) and repeated annually after 1 and 2 years of study treatment and at 3 years (1 year after completion of study treatment). Annual NACs should be done at the same time every year, within +/-14 days of the preceding year's NAC. Blood, nasal brushings, and nasal fluid samples will be collected as outlined in Appendices 1 through 5.

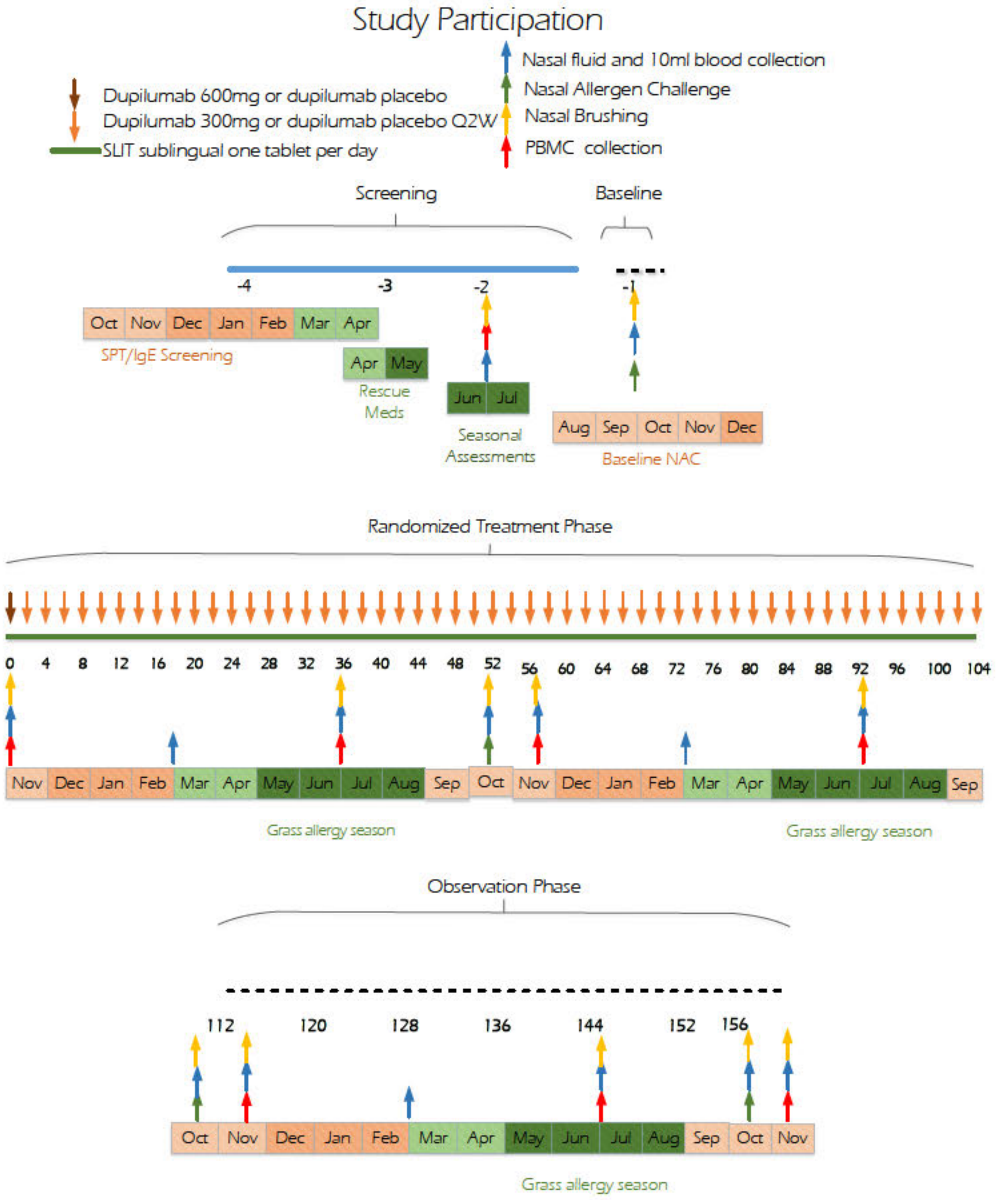
The study design which illustrates screening, treatment arm assignment and follow up for the treatment arms in the trial is shown in Figure 1 below.

Figure 1. Study Design



The plan for study participation for individuals is shown in Figure 2. Months listed are approximate and exact dates may be adjusted based on pollen count and participant availability.

Figure 2. Study Flow Chart



3.2 PRIMARY ENDPOINT

NAC (TNSS Area-under-Curve [$AUC_{0\text{-}1hr}$]) at year 3, one year after completion of treatment. The primary comparison will be between the combination of SLIT and dupilumab arm and the double-placebo arms (clinical tolerance endpoint).

3.3 SECONDARY ENDPOINTS

Clinical tolerance endpoints at year 3, one year after completion of study treatment. The comparison will be between the combination of SLIT and dupilumab and the double-placebo arms.

1. Peak nasal inspiratory flow (Delta PNIF $AUC_{0\text{-}1hr}$)
2. Size of early and late intradermal skin test response
3. Size of the skin prick test endpoint titration response
4. Seasonal outcomes
    a. Weekly seasonal symptoms (Visual Analogue Scale [VAS] 0-10 cms) and combined symptom medication scores (CSMS)
    b. Weekly rhinitis quality of life scores (Juniper mini-Rhinoconjunctivitis Quality of Life Questionnaire [miniRQLQ]) measured in-season
    c. Modified Rhinitis Symptom Utility Index (MRSUI) measured in-season and out-of-season
    d. Global Evaluations No. 1 and No. 2 after the season

Clinical desensitization endpoints at year 1 and 2 whilst on study treatment. The comparison will be between the combination of SLIT and dupilumab and the double-placebo arms.

5. TNSS $AUC_{0\text{-}1hr}$
6. Delta PNIF $AUC_{0\text{-}1hr}$
7. Size of early and late intradermal skin test response
8. Size of skin prick test endpoint titration response
9. Seasonal outcomes
    a. Weekly seasonal symptoms (VAS 0-10 cms) and CSMS
    b. Weekly rhinitis quality of life scores miniRQLQ measured in-season
    c. MRSUI measured in-season and out-of-season
    d. Global Evaluations No. 1 and No. 2 after the season

Safety Endpoints

10. The number, severity, and relatedness of local and systemic AEs and SAEs reported during screening, at baseline, during years 1 and 2 whilst on study treatment, and during year 3 (one year after completion of study treatment). Each treatment arm will be summarized separately.

3.4 EXPLORATORY ENDPOINTS

Clinical tolerance endpoints at year 3, one year after completion of study treatment. All pairwise comparisons not included in primary and secondary endpoints above will be reported.

1. TNSS $AUC_{0\text{-}1hr}$
2. Delta PNIF $AUC_{0\text{-}1hr}$
3. Size of early and late intradermal skin test response
4. Size of skin prick test endpoint titration response
5. Seasonal outcomes
    a. Weekly seasonal symptoms VAS 0-10 cms and CSMS
    b. Weekly rhinitis quality of life scores miniRQLQ measured in-season
    c. MRSUI measured in-season and out-of-season
    d. Global Evaluations No. 1 and No. 2 after the season

Clinical desensitization endpoints at year 1 and 2 whilst on study treatment. All pairwise comparisons not included in primary and secondary endpoints above will be reported.

6. TNSS $AUC_{0\text{-}1hr}$
7. Delta PNIF AUC0-1hr
8. Size of early and late intradermal skin test response
9. Size of skin prick test endpoint titration response
10. Seasonal outcomes
    a. Weekly seasonal symptoms VAS 0-10 cms and CSMS
    b. Weekly rhinitis quality of life scores miniRQLQ measured in-season
    c. MRSUI measured in-season and out-of-season
    d. Global Evaluations No. 1 and No. 2 after the season

Mechanistic endpoints at year 3, one year after study treatment (i.e., immune tolerance) and at year 1 and 2 whilst on study treatment (i.e., immune desensitization). All pairwise comparisons will be reported.

11. Mechanistic assessments of local immune responses in the nasal mucosa before and after the NAC.
12. Mechanistic assessments of peripheral blood leukocytes (including eosinophils, mast cells, and basophils) and mononuclear cell subsets after the NAC.
13. Mechanistic assessments of local immune responses and peripheral blood leukocytes (including eosinophils, mast cells, and basophils) and mononuclear cell subsets during natural allergen exposure In versus Out of the pollen season.

3.5 STRATIFICATION, RANDOMIZATION, AND BLINDING

Participants who sign the consent form and meet the eligibility criteria will be randomized to one of the three treatment arms administered in a double-blind, double-

dummy fashion in an approximately 1:1:1 ratio. The SACCC will be responsible for the development, validation, and implementation of the investigational medicinal product (IMP) treatment assignment and randomization system. This system will ensure protection of vital study data with user authentication protocols, dedicated servers, remote network backup, and 24-hour support.

Authorized study personnel will enter required data into the web-based system. Each participant's treatment will be randomly assigned by the system, and a randomization ID and blinded treatment assignment associated with that randomization will be associated with the participant. An unblinded randomization notification identifying the assigned treatment will be provided to the site's unblinded pharmacist and authorized unblinded study personnel. The participant will be assigned a specific IMP kit by the unblinded pharmacist from those available at the site that corresponds to the treatment assignment. Additionally, blinded, randomization notifications that do not contain the treatment assignment will be sent to authorized, blinded study and site personnel.

3.5.1 BLINDING

Double-blinding for administration of SLIT, SLIT placebo, dupilumab, and dupilumab placebo will be strictly maintained for all study participants and all of the clinical and laboratory teams on site throughout the treatment phase of the study and during the 1-year withdrawal phase after treatment is discontinued.

3.5.2 PROCEDURE FOR UNBLINDING

Before the study is complete, the blind for an individual participant should only be broken when appropriate medical management of the participant necessitates knowledge of treatment assignment.

In the event of a medical emergency, when the immediate knowledge of the actual treatment is essential for the management of the participant, the site investigator or designee can automatically obtain the participant's treatment assignments for both investigational products from the randomization system. The site investigator is encouraged to discuss the emergency unblinding with the DAIT/NIAID Medical Monitor prior to unblinding the participant, if possible.

If the randomization system is not available, the site staff may contact the SACCC Client Support Services for assistance in obtaining treatment assignment information. For more information and other unblinding pathways, please refer to the study Manual of Operations.

As soon as possible, the site investigator will provide a full account of unblinding to the DAIT/NIAID Medical Monitor, Protocol Chair, and the SACCC of the unblinding event. The DAIT/NIAID Medical Monitor will then notify the Data and Safety Monitoring Board (DSMB). A full account of the event will be recorded, including the date and time of the unblinding, the names of the individual(s) who made the decision, the reason(s) for unblinding, the participant(s) affected, individual(s) who were unblinded, and individual(s) who were notified.

Unblinding the treatment of an individual participant or subgroups of participants for unplanned interim analyses to support DSMB reviews and final analyses will require written approval from DAIT/NIAID.

An exception to the above rule is that Suspected Unexpected Serious Adverse Reaction (SUSAR) will be reported to the health authorities, DSMB, and Institutional Review Boards (IRB) or ethics review committee in an unblinded fashion as requested by current ICH and local guidance.

The final study report will contain any instances of unblinding prior to completion of the study along with the reason(s) for unblinding.

3.6 POLLEN SEASON

Daily pollen counts for grass pollen and birch pollen (*Betula*) will be supplied annually by the London Met office from a centrally located pollen trap (Islington, London) and data expressed as mean weekly pollen counts throughout the season (February - August) each year 2020-2023. *Grass pollen season* is defined in Table 6.

Table 6. Grass Pollen levels to define pollen season[53]

	Pollen Season	Peak pollen season	High pollen days
Start of season	1st day of 5 days (out of 7 consecutive days) each of these 5 days with ≥3 pollen/m^3 and with a sum of these 5 days of ≥30 pollen/m^3	1st day of 3 consecutive days, each with at least ≥50 pollen/m^3	The day(s) with at least 50 pollen/m^3
End of season	Last day of series of 5 days (out of 7 consecutive days) with ≥3 pollen/m^3 and with a sum of these 5 days of ≥30 pollen/m^3	Last day of at least 3 consecutive days, each with ≥50 pollen/m^3	

4. SELECTION OF PARTICIPANTS AND CLINICAL SITES / LABORATORIES

4.1 RATIONALE FOR STUDY POPULATION

Allergen immunotherapy is indicated in patients with moderate-severe persistent allergic rhinoconjunctivitis with/without mild-moderate controlled asthma and confirmed IgE-sensitivity to the relevant allergen as defined in the clinical history, and who remain inadequately controlled despite usual anti-allergic medications.[54] As defined by the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, 'Moderate-Severe' rhinitis implies sufficiently bothersome rhinitis symptoms that interfere with sleep, usual daily activities or school/work performance. 'Persistent' rhinitis is defined as symptoms for more than 4 days per week for a minimum of 4 weeks per year in at least the previous two consecutive years.

These recommendations are endorsed by the European Medicines Agency [56] and the recently published European Academy of Allergy and Clinical Immunology Guidelines on allergen immunotherapy for allergic rhinoconjunctivitis.[19]

The European Guidelines recommend immunotherapy in those who give a history of not responding adequately to treatment with oral or topical antihistamines and/or intranasal corticosteroids.[56] The guidelines highlight the important disease-modifying effects of immunotherapy with long-term suppression of symptoms and the need to treat for at least 3 years.[16] The guideline also identifies that polysensitization is not a contraindication, since several studies have highlighted that the clinical response to grass pollen immunotherapy is the same in polysensitised as in grass monosensitised individuals.[57] Similarly patients with seasonal asthma do as well as those without seasonal asthma,[58] although moderate-severe and uncontrolled *perennial* asthma is a contra-indication for immunotherapy.[56]

The above criteria are precisely the same as the entry criteria for the present study.

The population studied will be multi-ethnic and representative of the general population in London, United Kingdom. The study will include males and females. SLIT with Grazax® is approved down to age 5 years and Dupixent® is approved down to age 12, however, we will not recruit children in this study. For this study, the combination of allergen immunotherapy and IL-4Rα blockade is at proof of concept level and the visit frequency is high. Therefore, enrolling a pediatric population for this study is premature. There are no additional control populations necessary for this study.

4.2 INCLUSION CRITERIA

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

1. Participant must be able to understand and provide informed consent.
2. Adults age 18 to 65 years.
3. A clinical history of grass pollen-induced allergic rhinoconjunctivitis for at least 2 years with peak symptoms in May, June, or July.
4. A clinical history of moderate to severe rhinoconjunctivitis symptoms for at least 2 years interfering with usual daily activities or with sleep as defined according to the ARIA classification of rhinitis.
5. A clinical history of inadequately controlled rhinoconjunctivitis symptoms despite treatment with antihistamines and/or nasal corticosteroids during the grass pollen season for at least 2 years.
6. Positive skin prick test response at screening, defined as wheal diameter greater than or equal to 3 mm, to *Phleum pratense*.
7. Positive specific IgE at screening, defined as greater than or equal to IgE class 2 (0.7 kU/L) against *Phleum pratense*.
8. Removed in protocol version 3.0.

9. A woman of childbearing potential (WOCBP; for definition, see Appendix 6), regardless of birth control history, is required to consistently use one of the following highly effective methods of contraception throughout the study: hormonal (e.g. oral, transdermal, intravaginal, implant, or injection); intrauterine device (IUD) or system (IUS); vasectomized partner; bilateral tubal occlusion; or sexual abstinence (for definitions see contraceptive guidance in Appendix 6).

4.3 EXCLUSION CRITERIA

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

1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol.
2. Prebronchodilator forced expiratory volume (FEV_1) less than 70% of predicted value at either screening or baseline visit.
3. A clinical history of asthma requiring regular inhaled corticosteroids for > 4 weeks per year outside of the grass pollen season.
4. A clinical history of moderate to severe allergic rhinitis, as defined according to the ARIA classification of rhinitis, caused by either:
   a. an allergen to which the participant is regularly exposed OR
   b. tree pollen during tree pollen season treated with regular antihistamine or intranasal corticosteroids.
5. History of emergency visit or hospital admission for asthma in the previous 12 months.
6. History of chronic obstructive pulmonary disease.
7. History of recurrent acute sinusitis, defined as 2 episodes per year for the last 2 years, all of which required antibiotic treatment.
8. History of chronic sinusitis, defined as sinus symptoms lasting greater than 12 weeks that includes 2 or more major factors or 1 major factor and 2 minor factors. Major factors are defined as facial pain or pressure, nasal obstruction or blockage, nasal discharge or purulence or discolored postnasal discharge, purulence in nasal cavity, or impaired or loss of smell. Minor factors are defined as headache, fever, halitosis, fatigue, dental pain, cough, and ear pain, pressure, or fullness.
9. History of systemic disease affecting the immune system such as autoimmune diseases, immune complex disease or immunodeficiency.
10. Current symptoms of, or treatment for, upper respiratory tract infection, acute sinusitis, acute otitis media, or other relevant infectious process; serous otitis media is not an exclusion criterion. Participants may be re-evaluated for eligibility after symptoms resolve.
11. A past history of any malignant disease in the previous 5 years.

12. Any tobacco smoking within the last 6 months, or a history of greater than or equal to 10 pack years of cigarette use. Any vaping or electronic cigarette use within the last 6 months.
13. Previous immunotherapy with grass pollen allergen within the previous 5 years.
14. Previous treatment by dupilumab.
15. Previous Grade 4 anaphylaxis (WAO grading criteria) due to any cause.
16. History of anti-IgE, anti-IL-5, anti-IL-5 receptor, anti-IL-4/IL-13 receptor, or other monoclonal antibody treatment.
17. Current use of tricyclic antidepressants or monoamine oxidase inhibitors.
18. Ongoing systemic immunosuppressive treatment.
19. History of intolerance to the study therapy, rescue medications, or their excipients.
20. A positive pregnancy test.
21. Currently lactating/breast feeding.
22. The use of any investigational drug within 30 days of the screening visit.
23. The presence of any medical condition that the investigator deems incompatible with participation in the trial.
24. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or may impact the quality or interpretation of the data obtained from the study.
25. Eosinophilic esophagitis or a diagnosis of any hypereosinophilic syndrome.
26. Administration of live attenuated vaccines within four weeks of dupilumab or dupilumab placebo injections, before the first injection and throughout the treatment period.

4.4 SELECTION OF CLINICAL SITES/LABS

Imperial College London is in central London and readily accessible by public transport for the 3 million hay fever sufferers (1 in 4 of the London population of 12 million). The study is a natural extension of the successful GRASS trial which was a single center study located at Imperial College that targeted an identical study population and in which 108 participants were recruited from March to August (5 months) from the local clinic population and by advertisement in the local and national press and by the use of advertising on London Transport.

The group at Imperial College has a longstanding collaboration with the ITN and is experienced and fully equipped to fulfil the clinical and translational mechanistic aspects of the trial.

The primary outcome is an objective clinical surrogate, namely nasal allergen provocation that is standardized according to international guidelines and independent of

any local seasonal or geographic variations that might affect regional pollen counts and the generalizability of the findings. The potential limitations of using a single site have to be balanced against the heterogeneity in seasonal/environmental exposures, participant demographics, and study conduct/procedures that can complicate the conduct and interpretation of multi-center studies.

5. KNOWN AND POTENTIAL RISKS AND BENEFITS TO PARTICIPANTS

5.1 RISKS OF INVESTIGATIONAL PRODUCT OR INTERVENTION AS CITED IN INVESTIGATOR BROCHURE OR PACKAGE INSERT

5.1.1 SLIT: GRAZAX® AND GRAZAX® PLACEBO

Grazax® is approved for use in the UK for treatment of allergic rhinitis. Very commonly reported adverse reactions in adult and pediatric patients treated with Grazax® were local allergic reactions in the mouth which mostly were mild to moderate. In the majority of patients these reactions started early during treatment, lasted from minutes to hours after each intake of Grazax® and tended to subside spontaneously within 1 to 14 days. If significant local adverse reactions occur, treatment with antihistamines should be considered. Withdrawal due to local reactions may occur in up to 5% of participants due to local side effects of SLIT compared to 3% in placebo-treated participants.

Rare cases of severe systemic allergic reactions have been reported with Grazax® use. Therefore, medical supervision at the start of treatment is an important precaution. All participants will be observed by a study physician for one hour following the first dose of Grazax® and provided with an emergency telephone contact number for study personnel with 24-hour availability. The onset of systemic symptoms may include flushing, itching in the extremities and other areas of the body, general discomfort and agitation. In cases of severe systemic reactions including angioedema, difficulty swallowing or breathing, throat fullness or hypotension, Grazax® should be discontinued and a physician contacted immediately. Severe systemic reactions may be treated with adrenaline. Treatment with Grazax® should remain withheld until evaluation by a study physician.

If participants with concomitant asthma experience symptoms and signs indicating asthma deterioration, treatment should be discontinued and a study physician consulted immediately.

Adverse reactions are divided into groups according to the Medical Dictionary for Regulatory Activities (MedDRA) convention frequencies: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000). AEs are reported in Section 4.8 of the SmPC for Grazax® dated December 3, 2018.[60]

5.1.2 DUPILUMAB: DUPIXENT® AND DUPIXENT® PLACEBO

Dupilumab is generally safe and well tolerated. Warnings and precautions specified in the prescribing information include hypersensitivity reactions, conjunctivitis and

keratitis.[30] AE data for dupilumab are provided in Section 4.8 of the SmPC.[60] Additional safety data from the package insert are provided in Section 1.2.2.

5.2 RISKS OF INVESTIGATIONAL PRODUCT OR INTERVENTION CITED IN MEDICAL LITERATURE

5.2.1 SLIT: GRAZAX® AND GRAZAX® PLACEBO

See Section 1.2.1 for additional details of risk cited in the medical literature.

5.2.2 DUPILUMAB: DUPIXENT® AND DUPIXENT® PLACEBO

See Section 1.2.2 for details of risks cited in medical literature and the package insert.

5.2.3 COMBINATION THERAPY

There is no available data concerning the concurrent administration of Grazax® and Dupixent® in man. Both agents are well-tolerated with a defined profile of generally mild AEs, in particular mild-moderate, largely self-resolving reactions at the site of local administration for both products and the occurrence of mild-moderate conjunctivitis for Dupixent®, so far largely confined to participants with atopic eczema. The mechanism of action of Dupixent® is such that it is anticipated that the local allergy-related side-effects of sublingual Grazax® will likely be ameliorated by Dupixent®.

Grazax® will be administered sublingually daily and Dupixent® will be administered by subcutaneous injection every 2 weeks. On the day that Dupixent® is administered, this will be separated from Grazax® by a minimum interval of 6 hours. This duration was chosen because any reactions to Grazax® occur within 1 hour thereby allowing for attribution of any AEs to the appropriate study therapy.

5.3 RISKS OF OTHER PROTOCOL SPECIFIED MEDICATIONS

Besides Dupixent® and Grazax®, other protocol specified medications would include oral/ocular antihistamines; oral, nasal, and inhaled corticosteroids; and combination inhaled long-acting beta agonists with corticosteroids. Ocular antihistamines may rarely be associated with local irritation. Oral antihistamines may be associated with drowsiness. Nasal steroids may be associated with local irritation, sneezing, and rhinorrhea. Minor nasal bleeding may also occur. Inhaled corticosteroids may be associated with cough, hoarseness, and oral candidiasis. Rarely, systemic absorption of inhaled corticosteroids may lead to the side effects listed below under oral corticosteroids. Inhaled beta agonists may be associated tachycardia, palpitations, tremor, headache, hypokalemia, and elevations in serum glucose. Oral steroids when used continuously for prolonged periods of time (>2 weeks) may be associated with adrenal insufficiency, skin atrophy, osteoporosis, hypertension, diabetes, glaucoma, cataracts, dyspepsia and mood changes. However, in this trial, only short courses (up to 7 days) of oral corticosteroids will be dispensed and only after consultation with the study clinician and monitoring. Very few participants are likely to require systemic corticosteroids as rescue medication.

5.4 RISKS OF STUDY PROCEDURES

5.4.1 INTRADERMAL AND SKIN PRICK TESTS

Participants may experience mild to moderate pruritus and local swelling at the sites of skin pricks with allergen and the positive control (histamine dihydrochloride 10mg/ml). They may experience larger swellings and mild discomfort following intradermal testing. The symptoms are not bothersome and treatment with oral antihistamines is effective although almost never required. Although rare, theoretical risks do include systemic reactions, including anaphylaxis, after intradermal skin tests with standardized aeroallergen extracts.[60] A physician will always be present and drugs and equipment for treatment of anaphylactic reactions, including epinephrine drawn up in a syringe, will always be available.

5.4.2 NASAL ALLERGEN CHALLENGE (NAC)

The NAC will be performed using grass pollen extract (*Phleum pratense*) (ALK-Abelló). Application of the allergen to the nasal mucosa is undertaken using a disposable nasal pump spray (Bidose®; Aptar Pharma, France). Nasal challenge provokes immediate symptoms at 0-1 hour after challenge followed by milder delayed-in-time late responses at 1-10 hours (generally mild and not captured in this study). The participant will experience typical hay fever symptoms including nasal itching, nasal blockage, sneezing, nasal watery discharge, itchy eyes, watery eyes, and redness of the conjunctivae. If bothersome nasal and/or ocular symptoms persist after the period of 0-1 hour observation in the clinical unit, participants will be offered treatment with oral antihistamines. Unless bothersome symptoms persist, the participants will be discharged after one hour and provided with a telephone contact number with immediate access for 24 hours after challenge.

There is a remote risk of provoking mild asthma symptoms after a NAC. All participants' peak expiratory flow (PEF) will be recorded before and after nasal challenge. Inhaled bronchodilators and corticosteroids will be immediately available for treatment. As for any intervention with allergen to which an individual is sensitive, there is the theoretical risk of developing a systemic allergic/anaphylactic reaction, although this has never been observed in studies of several hundred participants over the past 30 years in the Section for Allergy and Clinical Immunology at NHLI, Imperial College. Nevertheless, a trained physician and injectable adrenaline, oxygen and intravenous equipment and fluids will be immediately available in the clinical unit during participants' NAC visits.

5.4.3 NASAL LAVAGE

Prior to nasal challenge, a saline nasal lavage will be performed with a commercially available preparation (Sinus Rinse®, NeilMed Pharmaceuticals) diluted in 240ml (8 oz.) of warm distilled water. This is a non-irritant, preservative free, pH neutral solution that contains sodium chloride, sodium bicarbonate, and iodine. Sinus Rinse® is widely available and no adverse effects are expected.

5.4.4 NASAL FLUID COLLECTION

Nasal fluid will be collected on 1 cm polycarbonate sponges that are inserted into the nostril using fine forceps, placed adjacent to the inferior turbinate, and left *in situ* for exactly 2 minutes before retrieval. Risks include slight discomfort and reflex eye watering.

5.4.5 NASAL BRUSHINGS

Cells from the nasal epithelium will be collected by nasal brushing. Risks include local burning with eye watering and rarely slight local bleeding. The symptoms resolve within minutes.

5.4.6 VENIPUNCTURE

Blood will be drawn from an antecubital vein using a 19 gauge butterfly (or similar) sterile cannula. Participants may experience some minor discomfort on skin puncture during insertion of the cannula. Blood samples will be taken with the participant sitting down. If they experience faintness or frank vaso-vagal syncope due to venipuncture, they will be assisted to lie flat and blood pressure and vital signs will be monitored until symptoms resolve. Oxygen and intravenous fluids will be available in the exceptionally unlikely event that they are required.

5.5 POTENTIAL BENEFITS

There is no assurance of therapeutic benefit from participation. Based on previous studies, it is likely that participants who are randomly assigned to receive immunotherapy with Grazax® will have an improvement in allergic rhinitis symptoms.[13] Given the randomization scheme described in Section 3.1, we estimate that at least 2/3 of participants will receive Grazax® and may receive some benefit from this study. The impact of dupilumab, however, is unknown. Some participants will not receive either immunotherapy with Grazax® or dupilumab; however, all participants in the study will have access to approved rescue medications. Participants with co-morbid atopic dermatitis and/or asthma may benefit from administration of dupilumab.

6. INVESTIGATIONAL AGENTS

6.1 CHARACTERISTICS OF INVESTIGATIONAL AGENTS

6.1.1 SLIT: GRAZAX® AND GRAZAX® PLACEBO

6.1.1.1 Name, Manufacturer, and Indication

Grazax® 75,000 SQ-T oral lyophilisate (Grazax®, ALK- Abelló Horsholm, Denmark) is standardized allergen extract grass pollen from Timothy grass (*Phleum pratense*). It is in the form of a white to off-white circular oral lyophilisate tablet. Grazax® has been used extensively in clinical trials.[13,25,38,39] The product characteristics are well described in a 2004 version of the Investigational Brochure and in the 2018 version of a SmPC.[60]

6.1.1.2 Formulation, Packaging, and Labeling

SQ Standardized Grass Allergy Immunotherapy (Grazax®, ALK- Abelló Horsholm, Denmark) is formulated as a freeze-dried oral lyophilisate/orally disintegrating tablet for oromucosal use. The active pharmaceutical ingredient is a standardized allergen extract derived from extraction and purification of grass pollen from Timothy grass (*Phleum pratense*). The biological activity of the allergen is expressed in standardized quality units. The recommended dosage is one oral lyophilisate (75,000 Standardized Quality Tablet units (SQ-T) or approximately 2800 bioequivalent allergy units (BAU), a measure of *Phleum pratense* SQ total biological potency defined by the FDA. This dose is equivalent to 15 µg of *Phleum pratense* 5. The non-active ingredients consist of fish gelatin, mannitol, sodium hydroxide and water.

Grazax® placebo is a tablet whose composition is identical to the active Grazax® tablet with the only exception being exclusion of the active pharmaceutical ingredient, *Phleum pratense* SQ. Grazax® and Grazax® placebo tablets will be supplied in blister packs by ALK-Abelló.

6.1.1.3 Dosage, Administration, and Storage

The first dose of Grazax® or Grazax® placebo tablet will be administered under investigator's supervision in the clinic. Participants will be observed for at least 60 minutes.

Home sublingual administration of Grazax® or Grazax® placebo tablets will occur daily during the first 2 years of the trial as specified in the Schedule of Events. Tablets should be removed from the blister packs with dry fingers and should be taken immediately after opening the blister. Each tablet should be placed underneath the tongue until fully dissolved (1–2 minutes). Swallowing should be avoided for about 1 minute. Food and beverage should not be consumed for the following 5 minutes. On days that participants receive dupilumab/placebo every two weeks, SLIT/placebo will be administered with a minimum interval of 6 hours. Study medication may be temporarily withheld at the investigator's discretion, for example due to illness of the participant.

The most recent SmPC can be found here:
https://www.medicines.org.uk/emc/product/315.

According to SmPC, Grazax® does not require any special storage conditions.[60]

Special Warnings and Precautions for Use

In case of oral surgery, including dental extraction, treatment with Grazax® should be stopped for 7 days to allow healing of the oral cavity.

Grazax® tablets are sensitive to moisture and blister packs should be stored unopened until use. The current formulation has been shown to be stable when stored at room temperature in unopened blisters.

6.1.2 DUPILUMAB: DUPIXENT® AND DUPIXENT® PLACEBO

6.1.2.1 Name, Manufacturer, and Indication

Dupilumab is approved for marketing as Dupixent® by Sanofi in the European Union currently, including the UK and is indicated in the treatment of asthma and moderate to severe atopic dermatitis in adult patients.

6.1.2.2 Formulation, Packaging, and Labeling

Dupixent® has the following pharmaceutical form:

- Solution for injection (injection)
- Clear to slightly opalescent, colorless to pale yellow solution, which is free from visible particulates.

Each single-use pre-filled syringe contains 300 mg of dupilumab in a 2 ml (150 mg/ml) aqueous buffered solution, pH 5.9. Excipients include L-arginine hydrochloride, L-histidine, sodium acetate, sucrose, and polysorbate 80.

The placebo for Dupixent® will also be provided in pre-filled syringes. It will be identical in appearance to active Dupixent®. Excipients are identical between placebo and active Dupixent®.

Study specific labels will be applied. Dupixent® and matching placebo will be supplied by Regeneron.

6.1.2.3 Dosage, Administration, and Storage

We will use the recommended dose of dupilumab for adult patients: an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every two weeks administered as subcutaneous injection. Administration of dupilumab will occur at a minimum interval of six hours from a SLIT dose. Participants will be observed for 30 minutes after the first three dupilumab injections. A minimum of 7 days and a maximum of 24 days will occur between dupilumab doses. Study medication may be temporarily withheld at the investigator's discretion, for example due to illness of the participant.

Dupixent® should be stored in refrigerated condition between 2º C and 8º C.

The shelf-life of Dupixent® is 30 months at 2-8º C. Pre-filled syringes may be kept at room temperature (up to 25° C) for a maximum of 14 days (Section 6.1 of the SmPC).[47]

The most recent SmPC can be found here:
https://www.medicines.org.uk/emc/product/8553.

6.2 DRUG ACCOUNTABILITY

An investigator is required to maintain adequate records of the disposition of the investigational product, including the date and quantity of drug that was received, the participants to whom drug was dispensed (participant by participant accounting), and an account of any drug accidentally or deliberately destroyed.

Records for receipt, storage, use, and disposition of the study drug will be maintained by the study site. A drug-dispensing log will be kept current for each participant and will contain the identification of each participant and the date and quantity of drug dispensed.

All records regarding disposition of the investigational product will be available for inspection by the clinical trial monitor.

6.3 ASSESSMENT OF PARTICIPANT COMPLIANCE WITH INVESTIGATIONAL AGENTS

Participants will be asked to return used Grazax® and Grazax® placebo blister packs and unused tablets at study visits every 4 weeks when they attend for alternate two weekly visits to receive dupilumab. Those participants with less than 75% compliance with study treatments will be counseled.

6.4 TOXICITY PREVENTION AND MANAGEMENT

6.4.1 TOXICITY PREVENTION

Participants will be counselled on the likelihood of local reactions and their usual short and self-limiting course. A 24-hour telephone link is available for participants to contact study clinicians if they have concerns. If bothersome, symptoms may be partially relieved by pre-treatment with a non-sedating oral anti-histamine (desloratidine) and/or ocular anti-histamine (olopatadine) which will be supplied if needed.

Participants will be monitored for both systemic and local side effects during study visits. There is no intention to modify the dose of either SLIT or dupilumab. SLIT should be withheld on days when there are any local inflammatory conditions or local bleeding in the mouth, for example from dental treatment. SLIT can be restarted thereafter with the same daily dose. Participants will be explicitly advised not to take more than one SLIT tablet daily – not for 'catchup' due to missed doses nor for any other reason.

6.4.2 TOXICITY MANAGEMENT

In the unlikely event that participants experience symptoms and signs of asthma, clinical features (PEF and oxygen saturation) will be assessed. Treatment will be initiated according to the severity of symptoms. Inhaled β_2 agonists will be given and if no response, nebulized β_2 agonist and ipratropium bromide driven by oxygen will be given and if needed, oral or intravenous corticosteroid will be given and maintained until recovery.

Cases of anaphylactic reactions have rarely been reported after Grazax®. The first dose of Grazax® is therefore given under medical supervision and participants observed for at least one hour after administration. In the extremely unlikely event that anaphylaxis occurs, participants will be treated with intramuscular adrenaline and oxygen followed by intravenous antihistamine and corticosteroid and observed for at least 4 hours after the event.

Given the increased incidence of conjunctivitis observed in the dupilumab trials in atopic dermatitis, conjunctivitis symptoms will be recorded if reported by participants.

Participants who volunteer bothersome eye symptoms that are not attributable to relevant allergen exposures will be referred for an eye assessment and examination by a consultant ophthalmologist affiliated with Royal Brompton Hospital/Imperial College London. The consulting ophthalmologist will be asked to assess whether there is conjunctival inflammation and offer an opinion as to whether this may be secondary to treatment as opposed to another cause.

6.5 PREMATURE DISCONTINUATION OF INVESTIGATIONAL AGENT

Study therapy may be prematurely discontinued for any participant for any of the reasons listed in Section 11.2.

Study therapy may also be prematurely discontinued for any participant if the investigator believes that the study treatment is no longer in the best interest of the participant.

Participants who discontinue or are discontinued from the use of study treatment will be invited to continue participating in the study and undergo evaluations per protocol for the remaining duration of the study.

7. OTHER MEDICATIONS

7.1 CONCOMITANT MEDICATIONS

Use of the following rescue medications is permitted. These medications are considered standard of care and will be provided by the study approximately 2 weeks before the start of the pollen season and throughout the pollen season:

- Antihistamine tablets (desloratidine)
- Nasal corticosteroid spray (fluticasone propionate aqueous nasal spray)
- Ophthalmic antihistamine drops (olopatadine)
- Short-acting beta2-agonist inhaler (albuterol)

Use of the following rescue medications will be provided only after participants are evaluated by a study clinician. Evaluations may occur by phone contact or clinic visit.

- Oral corticosteroid (prednisolone 5mg tablets)
- Corticosteroid inhaler (fluticasone propionate)
- Combination of long-acting beta-agonist and corticosteroid inhaler (salmeterol/fluticasone)

7.2 PROHIBITED MEDICATIONS

Use of the following medications is prohibited during study participation:

- Administration of live attenuated vaccines: live attenuated vaccines should not be given concurrently with dupilumab as clinical safety and efficacy has not been established (if needed, live vaccine should be administered to participants before commencement of dupilumab). These vaccines should not be given within 4 weeks of dupilumab or dupilumab placebo injection.
- Tricyclic antidepressants
- Monoamine oxidase inhibitors
- Anti-IgE, anti-IL-5, anti-IL-5 receptor, other monoclonal antibodies targeting the human immune system, or any other biologic therapies. Antiviral monoclonal antibodies are permitted.
- Refer to Appendix 7 for required medication washout periods prior to the NAC and skin prick testing

8. STUDY PROCEDURES / ASSESSMENTS

8.1 ENROLLMENT

The research study will be explained by a study clinician in lay terms to each potential research participant. The potential participant will sign and date an informed consent form that is countersigned at the same time by the study clinician before undergoing any study procedures.

8.2 SCREENING/BASELINE VISIT

The Schedules of Events for this trial are represented in Appendices 1-5. The timing of the screening visit is determined by whether the participant's first visit falls in or out of season (See Section 8.5).

8.3 STUDY VISITS OR STUDY ASSESSMENTS

8.3.1 GENERAL ASSESSMENTS

- Informed consent: Written informed consent will be obtained before any study assessments or procedures are performed.
- Eligibility criteria: Eligibility for study participation will be assessed during the screening period.
- Demographics: age and ethnicity.
- Medical history: A history will be taken to determine if the participant has had any clinically significant diseases or medical procedures other than the disease under study.
- Allergy history.
- Rhinoconjunctivitis severity screening evaluation (ARIA severity score).

- Directed physical examination: includes body systems: respiratory, cardiovascular, skin, and conjunctivae.
- Vital signs: blood pressure, temperature, pulse, and respiratory rate.
- Pulmonary Function Test (Spirometry, record one-second FEV_1 and forced vital capacity).
- AEs: Participants will be assessed at every visit for AEs. Prior to home administration of Dupixent or Dupixent placebo, participants will be asked whether there have been any AEs. If they report Yes, the study team will assess the changes before they proceed with the injection.
- Concomitant medications: All concomitant medications and their indications will be recorded at every visit. Prior to home administration of Dupixent or Dupixent placebo, participants will be asked whether there have been any changes in Concomitant medications. If they report Yes, the study team will assess the changes before they proceed with the injection.

8.3.2 LOCAL LABORATORY ASSESSMENTS

- Serum pregnancy test
- Urine pregnancy test (monthly)
- Hematology: Complete blood count with differential
- Comprehensive chemistry: albumin, bilirubin total, creatinine, glucose, potassium, protein total, sodium, alanine amino transferase (ALT or SGPT), Alkaline Phosphatase (ALP), urea.
- Total IgE and specific IgE to grass pollen (*Phleum pratense*) and birch pollen

8.3.3 CLINICAL ASSESSMENTS

Clinical allergy assessments comprise NACs and several forms of skin testing and provide eligibility information, clinical characterization and allergy status. It is important that prior to all such assessments, participants avoid medications that might unduly modify allergic responses independent of the study interventions. Certain procedures may generate aerosols and will be conducted only if they comply with local hospital guidelines at the time of the procedure. Washout periods for specific medications are shown in Appendix 7.

Potential aerosol generating procedures

- Nasal Allergen Challenge
- Visual Analogue Scale (Appendix 9)
- Peak expiratory flow testing
- Peak nasal inspiratory flow testing
- Pulmonary Function Testing (Spirometry, FEV1)

Non-aerosol generating procedures

- Skin prick test endpoint titration – *Phleum pratense*
- Intradermal skin test – *Phleum pratense*
- Skin prick test panel: Timothy grass pollen (*Phleum pratense*), silver birch (*Betula verrucosa*), mugwort (*Artemisia vulgaris*), house dust mite (*Dermatophagoides pteronyssinus*), cat hair (*Felis domesticus*), dog hair (*Canis familiaris*), *Aspergillus fumigatus, Cladosporium herbarum, Alternaria alternata*, negative control, and positive control (*histamine dihydrochloride*)

8.3.4 RHINITIS ASSESSMENTS

Participants may be asked to utilize a 21 CFR Part 11 compliant mobile application to submit this information.

- Weekly MiniRQLQ (Appendix 10) during pollen season
- Global Evaluation No. 1 (Appendix 12) after pollen season
- Global Evaluation No. 2 (Appendix 12) after pollen season
- Weekly CSMS during pollen season (Appendix 11)
- MRSUI (Appendix 13) in and out of pollen season

8.3.5 MECHANISTIC ASSESSMENTS

See Section 9 for detailed discussion of mechanistic assays.

8.4 UNSCHEDULED VISITS

Unscheduled visits may be performed in the event that participants experience an AE requiring medical attention, a disease exacerbation requiring treatment or because the participant prematurely terminates from the study (see Section 11.2).

8.5 VISIT WINDOWS

All scheduled study visits will aim to occur within the time limits specified below and may be adjusted based on pollen count and participant availability.

Table 7. Visit Windows all Participants (See Appendices 1-5)

Visit	Visit description	Visit Window
Visit -4	Screening	October 2020 to January 2022
Visit -3	Rescue medication dispensing visit	April 1 to July 31
Visit -2	Baseline In-season assessments	June 1 to July 31
Visit -1	Baseline NAC	September to January
Visit 0	Randomization – 1st dupilumab/dupilumab placebo dose	≥ 28 days after Visit -1 and before end of February
Visit 1	1st SLIT/SLIT placebo dose	≥12 hours from Visit 0 and ≥ 7 days prior to Visit 2.
Visits 2-53	Treatment visits	Every 2 weeks from Visit 0 through week 104 +/- 10 days (with at least 7 days between treatment visits)
Visits 54-65	Observation visits	Every 4 weeks from 108 to 156 +/- 14 days
S1	Out of season visit assessment year 1	January to April
S2, S7, S12	Pre-season visit	April to May
S3, S8, S13	In-season visits	May to August
S4, S9, S14	Out-of-season NAC visits	September to January 1, 2 and 3 calendar years after Visit -1 +/- 14 days
S5, S10, S15	Mechanistic draws post NAC visits	≥ 4 weeks post NAC visit (S4, S9, S14) and before end of February each year
S6, S11	Out of Season visit	January to April

9. MECHANISTIC ASSAYS

9.1 MECHANISTIC HYPOTHESES

The main mechanistic hypotheses being tested are whether combination of dupilumab with *Phleum pratense* SLIT will result in:

1. Down-regulation/deletion of grass pollen-driven Th2 responses in peripheral blood, nasal fluid and nasal epithelial cells.
2. Immune deviation in favor of grass pollen-driven Th1 responses in peripheral blood, nasal fluid and nasal epithelial cells.
3. Induction of grass pollen-driven regulatory responses in peripheral blood, nasal fluid and nasal epithelial cells.
4. Changes in downstream events, including:
   a. Reduction in allergen-specific IgE in sera or plasma.
   b. Development of allergen-specific IgG, IgG4, and IgA antibodies in nasal fluid and sera or plasma.
   c. Increased serum IgE-inhibitory activity (assessed by IgE-FAB in sera or plasma and IgE-mediated basophil activation in whole blood).

Depending on sample and technology available, additional fluids/cells may be used to test the hypotheses described above.

9.2 PROPOSED MECHANISTIC ASSAYS

Although specimens in this protocol are described in the context of assays to be performed, it should be noted that not necessarily all assays will be performed for all participants at each time point. Decisions to perform assays will be made based on statistical and scientific planning, hypotheses to be tested, and technologies available. Finally, clinical outcomes will be taken into account to determine the potential value of the assays. For example, if a clinical effect fails to occur, it may be decided that there is minimal value in performing certain mechanistic assays. The ITN sample sharing policy will apply for the provision of samples to study or outside investigators (www.immunetolerance.org).

Residual stored specimens may be used by the investigators for development of new immunologic assays or for cross-trial comparisons. Use of de-identified samples for novel assays will be submitted to the National Research Ethics Committee (NREC) for approval. The use of these de-identified samples will not require additional consent by participants.

9.2.1 LOCAL IMMUNE RESPONSES IN NASAL MUCOSA

Nasal fluid and epithelial brushings will be collected as listed in Appendix 1, 2 and 5.

Nasal fluid will be collected for protein analysis. Analytes to be measured in nasal fluid may include Th2 cytokines (IL-4, 5, and 13), Th1-cytokines (IFN-γ, IL-12, IL-27, and IFN-α), and regulatory cytokines (IL-10, TGF-b, and IL-35). Th2-related chemokines (MDC, TARC, and eotaxin), Th1-related chemokines (IP-10), and other inflammatory mediators may also be measured. In addition, local IgE-FAB inhibitory activity may be assessed and grass pollen-specific antibody levels (IgE, IgA, IgG and IgG4) may be measured in nasal fluid by ImmunoCAP or ELISA.

Nasal epithelial cells will be harvested by gently brushing the nasal inferior turbinates and RNA extracted. To avoid interfering with nasal fluid collections, nasal brushes will only be taken after nasal fluid has been collected. Gene expression may be assessed by methods such as RT-PCR, RNAseq, or nanostring for comparisons between treatment arms. Specific genes targeted for RT-PCR analysis may include genes for epithelial cell-derived chemokines (MDC, TARC, eotaxin, RANTES), adhesion molecules (ICAM-1), and cytokines such as IL-8, GM-CSF and those that may possibly be detected in trans-epithelial migratory effector cells (IL-4, IL-5, IL-9, IL-13, Interferon-gamma, IL-10 and TGF-beta). Transcription factors of interest could include GATA-3, STAT-6, T bet, and FOXP3. Epithelial Th2-inducing cytokines of interest could include IL-25, IL-33 and TSLP.

9.2.2 DNA-HLA GENOTYPES

Major Histocompatibility Complex (MHC) tetramers bind to the T-cell receptor in a Human Leukocyte Antigen (HLA) specific context. Therefore, DNA will be collected from participants to perform sequence-based HLA typing, such that appropriate candidates can be identified for tetramer analysis.

Additional genotyping (e.g. IL-4R alpha polymorphisms) may be performed in order to determine whether genetic profiles are associated with response to grass pollen immunotherapy or other study characteristics.

9.2.3 WHOLE BLOOD GENE EXPRESSION

Gene expression profiling may be performed on RNA isolated from peripheral whole blood using RNAseq, nanostring, RT-PCR, or other methods. The goal of these assays is to identify differences in transcriptional profiles between treatment arms and clinical outcome groups, and to monitor the durability of these potential changes after discontinuation of immunotherapy. These types of analyses may also explain why some individuals respond to treatment or may elucidate mechanisms resulting in adverse responses to treatment. Changes in whole blood gene expression could also be compared and contrasted with local (nasal) gene expression changes.

9.2.4 CELLULAR ASSAYS

T Cell Assays: To address the functional status of T-cell responses, various cell-based assays using previously frozen PBMCs can be used to estimate frequency, phenotype, cytokine, and transcriptional profile of allergen-specific cells.

MHC Class II tetramers may be used to identify & enumerate grass allergen-specific CD4 T cells using flow cytometry or CyTOF. Additional staining of surface markers may be performed to determine if treatment leads to the development of anergy, exhaustion, Th2 to Th1 deviation, or the induction of regulatory T cells.

Since tetramers are not currently available for all haplotypes, other T cell assays may also be performed. The CD154 and CD137 up-regulation assays may be used to monitor allergen-reactive effector and regulatory CD4 T cells, respectively with either flow

cytometry or CyTOF. Currently, these assays require PBMCs to be stimulated *in vitro* with grass allergen in the presence of anti-human CD40 blocking mAb. If flow cytometry is used, during acquisition, cells may be sorted and epigenetic or transcriptomic studies performed on the allergen-specific effector and regulatory cells.

The CD154 up-regulation assay can also be performed to measure cytokine production in allergen-specific CD4 cells. Intracellular staining for IL-4, IL-5, IL-13 and IFN-γ (Th1/Th2), IL-17 (Th17), along with IL-10 and TGF-β (Th3) could be performed and combined with surface staining to assess changes in effector CD4 subpopulations.

We may also use flow cytometry or CyTOF to determine the frequency of TH2A cells as this subset of Th2 cells may be a biomarker for allergy.[61] This assay can be reliably performed with as few as one million previously frozen, viable PBMCs. Work by Wambre, et al suggests that this subset includes the vast majority of allergen-specific CD4+ T cells as determined by tetramer analysis.[61]

The FluoroSpot assay could also be used to further explore the phenotype and evaluate the frequency of cytokine-producing antigen-specific cells. The FluoroSpot assay requires 18–48 hours of cell stimulation with allergen (*Phleum pratense* component proteins or whole *Phleum pratense* grass extract) and reveals frequencies of antigen-specific cells producing cytokines of interest, such as IL-4, IL-5, and IL-10. Therefore, it represents an additional functional readout of T-cell activity.

Whole Blood IgE-dependent Basophil Activation: IgE-dependent basophil activation will be assessed using fresh whole blood incubated with different concentrations of *Phleum pratense* allergen extract. Basophil surface CD63 expression will be monitored by flow cytometry to determine basophil activation levels.

Other Immune Cells: Using flow cytometry or CyTOF, we may perform detailed immunoprofiling of other cell types such as B cells, NK cells, dendritic cells, and others.

9.2.5 SERUM/PLASMA ASSAYS

Cytokines/Chemokine Assays: Whole blood (10 ml) will be collected as outlined in Appendices 1, 2, and 5 coincident with corresponding nasal fluid collections for measurement of Th2, Th1, regulatory and other cytokines/chemokines. ELISA, single-molecule digital immunoassays, or other methods may be used to measure levels of cytokines, chemokines and other inflammatory mediators in/out of season or elicited following a NAC.

Immunoglobulin assays: Serum antibody responses may be measured to determine levels of total and allergen-specific antibodies. These measurements could include testing for total IgE and IgG and allergen-specific IgE, IgG1, IgG4, IgA1 and IgA2. IgG1, IgG4, and IgA may be induced by immunotherapy and may act as blocking antibodies reducing clinical responses to allergen.

Component-resolved assays: ImmunoCAP™ may be used to measure levels of antibodies to *Phleum pratense* components. Levels of IgE, IgG4, and IgA to specific grass allergen components, such as *Phl p* 1, 2, 4, 5, 6, 7, 11, and 12 may be measured to evaluate changes in specific reactivity over time and between treatment arms.

IgE-facilitated antigen binding (FAB) assay: In addition to antibody testing, serum samples may be used in functional assays to measure serum inhibitory activity. The IgE-FAB inhibition assay uses flow cytometry to measure serum inhibitory activity of IgE-facilitated CD23-dependent binding of allergen-IgE complexes to B cells. Serum from SLIT plus dupilumab placebo, combination of SLIT and dupilumab, and double placebo arms may be assessed for its inhibitory activity for IgE-FAB. The time course and magnitude of changes in inhibitory activity for IgE-FAB may be compared with clinical symptoms, clinical scores, and allergen-specific IgE and IgG levels.

10. BIOSPECIMEN STORAGE

A major priority of the ITN, in partnership with the NIAID of the National Institutes of Health (NIH), USA, is the development of novel immunoassays in order to better understand mechanisms of tolerance and to develop biomarkers to predict the development and maintenance of clinical tolerance. As in all ITN-funded clinical trials, informed consent will be obtained from all participants for their samples to be stored for use in future studies. Biological specimens collected in this trial will be stored long-term in order to re-evaluate biologic responses as new research tools to study tolerance become available. The specimens will therefore be stored at the ITN sample repository for a minimum of 10 years. For research on stored samples that has not been defined in the protocol, approval from the relevant ethics committee will be obtained.

11. CRITERIA FOR PARTICIPANT AND STUDY COMPLETION AND PREMATURE STUDY TERMINATION

11.1 PARTICIPANT COMPLETION

Participants will have completed the study when they have attended the S15 Visit for mechanistic blood collection and skin prick test endpoint titration.

11.2 VISIT PARTICIPANT STOPPING RULES AND WITHDRAWAL CRITERIA

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

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. The participant is “lost to follow-up” (i.e. fails to respond to repeated email/text/phone calls following a scheduled appointment or other planned contact).
3. The participant dies.
4. The Investigator no longer believes participation is in the best interest of the participant.

5. Individual safety stopping rules are met. Individual stopping rules include:
   a. A grade 3 or higher AE that is possibly related or related to study treatment or procedures.
   b. Use of prohibited medications, including MAO inhibitors, tricyclic antidepressants, Anti-IgE (Xolair), or other monoclonal antibody treatments targeting the human immune system.
   c. Female participant pregnancy.

Participants prematurely terminated from the study will be followed as detailed in Section 11.4.

11.3 PARTICIPANT REPLACEMENT

Randomized participants who do not receive study drug will be replaced. Participant recruitment will continue until at least 108 participants are randomized and receive at least one dose of both study drugs.

11.4 FOLLOW-UP AFTER EARLY STUDY WITHDRAWAL

If a participant stops study treatment for any reason, he/she will be asked to attend ongoing study assessments as long as the study Principal Investigator judges that such assessments do not confer risks that are beyond what is described in the protocol.

If the withdrawn participant declines to attend for further study assessments, then they will be invited to undergo a single post-withdrawal visit within 4 weeks of the patient's decision to withdraw.

11.5 STUDY STOPPING RULES

- Any death that is possibly related or related to one of the investigational products (dupilumab/dupilumab placebo or SLIT/SLIT placebo) or a study procedure.
- Any grade 4 AE that is possibly related or related to one of the investigational products (dupilumab/dupilumab placebo or SLIT/SLIT placebo) or a study procedure.
- Any grade 3 AE that is possibly related or related to one of the investigational products (dupilumab/dupilumab placebo or SLIT/SLIT placebo) or a study procedure in three or more participants.

Grading for AEs can be seen in Section 12.2.3.

In case a study stopping rule is met, an immediate suspension of one or both investigational products (dupilumab/dupilumab placebo or SLIT/SLIT placebo) dosing or suspension of one or more study procedure(s) will be implemented. The decision as to which specific product(s) or procedure(s) is to be suspended will be made by the Principal Investigator and the DAIT/NIAID Medical Monitor based on which product(s) or procedure(s) was most likely related (depending on timing and clinical factors) with meeting the stopping rule. A rapid contact system will be established (i.e. email) to

inform all participants of temporary suspension of product dosing. If participants do not respond via email, they will be contacted by telephone until a response is received. The NREC and the MHRA will be notified (see Section12.8.2). An ad hoc DSMB meeting will be scheduled where all pertinent information will be discussed. The DSMB's recommendations as to whether suspended study activity(ies) may or may not be resumed will be further discussed with DAIT/NIAID and the decision will be relayed to the NREC and the MHRA for concurrence. If deemed appropriate, participants will be contacted by the rapid contact system to resume dosing.

12. SAFETY MONITORING AND REPORTING

12.1 OVERVIEW

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. AEs that are classified as serious according to the definition of health authorities must be reported promptly (per Section 12.5, Reporting of SAEs and AEs) to the Sponsor, DAIT/NIAID. Appropriate notifications will also be made to the site Principal Investigator, NREC, and MHRA.

Information in this section complies with Directives 2001/20/EC and 2011/C172/01 of the European Parliament and the Council, European Commission CT-3 guidance and with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50.[63]

12.2 DEFINITIONS

12.2.1 ADVERSE EVENT (AE)

Any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with study interventions or procedures (modified from Directive 2001/20/EC).[64]

For this study, AEs associated specifically with study therapy and study procedures will be defined as follows:

- **Study therapy regimen:**
    - SLIT involves taking a daily tablet under the tongue. This is frequently associated with oral itching and mild swelling. These symptoms may last from minutes to hours or longer in some cases. These symptoms will be recorded as AEs only if they are bothersome (i.e. interfere with usual daily activities or sleep) and/or require daily treatment with anti-histamine for more than two weeks. Any other event that meets the above-described general definition of an AE will be recorded as such.

- Dupilumab injection is associated with local swelling, redness, heat, minor itching, and discomfort. These reactions may last from 5 up to 60 minutes. Frequently there is persistent swelling at the injection site that may persist 24 to 48 hours. These symptoms will be recorded as AEs only if they are bothersome (i.e. interfere with usual daily activities or sleep). Any other event that meets the above-described general definition of an AE will be recorded as such.

- **Study mandated procedures:**
  - Skin prick tests are associated with local redness, itching and wheal formation at 5 to 30 minutes that resolves within 1 to 3 hours. This may also be associated with mild swelling which last for up to 6 to 48 hours. As long as these symptoms are not bothersome (i.e. interfere with usual daily activities or sleep), they will not be recorded as AEs. Any other event that meets the above-described general definition of an AE will be recorded as such.
  - NACs are associated with symptoms of itching, sneezing, watery discharge, nasal congestion, and eye symptoms which begin within minutes and last for 0 to 60 minutes. In some participants, nasal congestion and watery discharge may persist for 6 to 24 hours and occasionally up to 48 hours after discharge from the clinic. Unless these symptoms are bothersome and/or require treatment with an oral antihistamine, an intranasal decongestant or an intranasal corticosteroid for more than 2 days following the procedure, they will not be recorded as AEs. Any other event that meets the above-described general definition of an AE will be recorded as such.

12.2.2 SERIOUS ADVERSE EVENT (SAE)

A ‘serious adverse event’ is defined in Article 2(o) of Directive 2001/20/EC.

An AE or adverse reaction is considered “serious” if, in the view of either the investigator or DAIT/NIAID, the Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening event: An AE or suspected adverse reaction (SAR) is considered “life-threatening” if, in the view of either the investigator or DAIT/NIAID, the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE or SAR/AR that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical

judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

12.2.3 ADVERSE REACTION

An 'adverse reaction' is defined in Article 2(n) of Directive 2001/20/EC as follows:

- "all untoward and unintended responses to an IMP related to any dose administered."
- The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.
- The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

12.2.4 SUSPECTED ADVERSE REACTION

Any AE for which there is a reasonable possibility that the investigational drug (or investigational study therapy regimen) caused the AE. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

12.2.5 UNEXPECTED ADVERSE REACTION

An unexpected adverse reaction is defined as an adverse reaction the nature or severity of which is not consistent with the applicable product information SmPC or IB *Directive 2001/20/EC*).[60] The expectedness of an adverse reaction is determined by the Sponsor using the reference safety information ('RSI') that is contained in SmPC or IB.

For this Protocol, the applicable product information refers to the ALK SmPC for Grazax® and the Sanofi SmPC for Dupixent®.[47,60]

12.2.6 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)

SUSAR is a serious and unexpected adverse event that fulfills the definition of SAR.

12.3 GRADING AND ATTRIBUTION OF ADVERSE EVENTS

12.3.1 GRADING CRITERIA

12.3.1.1 Study Treatment Adverse Reaction

The study site will grade the severity of AEs for the following study treatment adverse reactions according to the following criteria:

Local Reactions:

- All local reactions to SLIT that meet the definition of an AE (see Section 12.2.1) and are not associated with systemic signs or symptoms will be graded according to Table 7. Local AEs to dupilumab will be graded based on the NCI's *Common Terminology Criteria for Adverse Events, Version 5.0*.

Systemic Allergic Reactions:

- If an immediate (0-1hr) systemic allergic reaction were to occur following administration of either SLIT or dupilumab, the reaction will be graded according to the WAO Subcutaneous Immunotherapy Systemic Reaction Grading System (see Appendix 14).
    - The following modification will apply only for SLIT: Under Grade 1 (Symptoms/signs of 1 organ system present), "throat clearing (itchy throat)" and under grade 2 gastrointestinal symptoms (abdominal cramps, vomiting or diarrhea) are considered local reactions to SLIT and do not constitute a systemic reaction unless accompanied by other manifestations of a systemic allergic reaction.

Table 7. Grading Table for Local Reactions to SLIT

Grade	Description
1	Bothersome (interfering with usual daily activities or sleep) OR moderate swelling of the tongue as assessed by the study physician that is unassociated with systemic signs or symptoms.
2	Bothersome, with associated moderate difficulty in swallowing or breathing and/or requiring a visit to the doctor for treatment OR severe swelling of the tongue as assessed by the study physician that is not associated with systemic signs or symptoms.
3	Bothersome, associated with severe difficulty in swallowing or breathing and/or requiring hospitalization
4	Life-threatening local reaction (i.e. upper airway obstruction requiring intubation, ICU admission, tracheostomy, etc.)

12.3.1.2 Selected Study Procedures

The study site will grade the severity of AEs for the following selected study procedures according to the following criteria:

Local Reactions:

- All local reactions to allergen skin testing and NACs that meet the definition of AEs (see Section 12.2.1) and are not associated with systemic signs or symptoms will be graded according to Table 8 and Table 9, respectively.

Systemic Reactions:

- All systemic reactions related to allergen skin testing or to the NAC procedure will be graded according to the WAO Subcutaneous Immunotherapy Systemic Reaction Grading System (see Appendix 14).
- The following modification will apply for NACs: Under Grade 1 (Symptoms/signs of 1 organ system present), "rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus and/or

nasal congestion)" as well as "cough perceived to originate in the upper airway, not the lung, larynx or trachea" are not considered systemic reactions to NACs.

Table 8. Grading Table for Local Reactions to Allergen Skin Testing

Grade	Description
1	Bothersome, (interfering with usual daily activities or sleep).
2	Bothersome, requiring medication
3	Bothersome, requiring a visit to the study physician/emergency room for treatment

Table 9. Nasal Allergen Challenge (NAC) procedure (local reactions)

Grade	Description
1	Nasal or oropharyngeal symptoms requiring more than a single dose of an oral antihistamine and/or an intranasal decongestant spray as rescue medication.
2	Nasal or oropharyngeal moderate to severe symptoms interfering with usual daily activities not requiring oral steroids as rescue medication.
3	Severe nasal or oropharyngeal symptoms requiring oral or systemic steroids.
4	Life threatening and/or requiring hospitalization for upper airway obstruction or other local reaction reason

12.3.1.3 Grading and Attribution of All Other Adverse Events

AEs not described in Section 12.3.1.1 or 12.3.1.2 will be graded based on NCI-CTCAE v5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).[63] AEs will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

- Grade 1 = mild AE.
- Grade 2 = moderate AE.
- Grade 3 = severe AE.
- Grade 4 = life-threatening AE.
- Grade 5 = death.

12.3.2 ATTRIBUTION ASSESSMENT

The relationship, or attribution, of an AE to the study therapy regimen or study procedure(s) will initially be determined by the Site Investigator and recorded on the appropriate AE electronic case report form (eCRF). Sponsor's determination of attribution will be made by DAIT/NIAID. For safety reporting, the Sponsor cannot downgrade the Site Investigator's causality assessment but can upgrade it. The relationship of an AE to study therapy regimen or procedure(s) will be determined using the descriptors and definitions provided in Table 10.

Table 10. Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
Unrelated Category		
1	Not Related	The AE is clearly not related: there is insufficient evidence to suggest a causal relationship.
Related Categories		
2	Possibly Related	The AE has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Related	The AE is clearly related.

12.4 COLLECTION AND RECORDING OF ADVERSE EVENTS

12.4.1 COLLECTION PERIOD

AEs/SAEs within 24 hours of study procedures will be collected during the screening period (visits -4 to visit -1). After the screening period, all AEs/SAEs will be collected from participants who undergo a baseline NAC (visit -1) until he/she completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

12.4.2 COLLECTING ADVERSE EVENTS

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

- Observing the participant.
- Interviewing the participant (e.g., using a checklist, structured questioning, diary, etc.).
- Receiving an unsolicited complaint from the participant.
- Receiving a report of an AE from the participant when they are prompted at the time of their home injections.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an AE, as defined in Section 12.3, *Grading and Attribution of Adverse Events*.

12.4.3 RECORDING ADVERSE EVENTS

Throughout the study, the investigator will record AEs and SAEs as described previously (Section 12.2, *Definitions*) on the appropriate eCRF(s) and source document(s) regardless of the relationship to study therapy regimen or study procedure.

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

12.5 REPORTING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

12.5.1 REPORTING OF ADVERSE EVENTS TO THE SPONSOR, DAIT/NIAID

The site investigator will report all AEs to the study Sponsor (DAIT/NIAID) in the AE eCRF via the SACCC. Timely reporting of AEs is required by Directives 2001/20/EC and 2011/C 172/01 of the European Parliament and the Council, European Commission CT-3 guidance 21 code of Federal Regulations and ICH E6 guidelines.[64,65]

Whenever possible, a diagnosis should be provided, rather than compilation of signs/symptoms, with grade of the event dictated by highest grade of the sign/symptom component.

12.5.2 REPORTING OF SERIOUS ADVERSE EVENTS TO THE SPONSOR, DAIT/NIAID

This section describes the responsibilities of the site investigator to report SAEs to the Sponsor via the AE/SAE eCRF.

Site investigators will report all SAEs (see Section 12.2.2) to the Sponsor, regardless of relationship or expectedness within 24 hours of discovering the event. For SAEs, all requested information on the AE/SAE eCRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE eCRF should be updated and submitted.

For additional information regarding SAE reporting, contact Rho Product Safety:

[redacted]

12.5.3 REPORTING OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS) TO THE MHRA AND NREC

The Sponsor (DAIT/NIAID) will ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to MHRA and NREC; and in any case no later than 7 days after knowledge by the sponsor of such a case; and that relevant follow-up information is subsequently communicated within an additional 8 days.

All other SUSARs will be reported to the MHRA and NREC as soon as possible, but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will report the following SUSARs:

- all SUSARs occurring in this clinical trial;

- all SUSARs related to the same active substance (regardless of pharmaceutical form and strength or indication investigated) in a clinical trial performed exclusively in a third country or exclusively in another Member State, if that clinical trial is sponsored by the same sponsor

In the cases where a SUSAR turns out to be fatal or life-threatening, whereas initially it was considered as non-fatal or not life-threatening, the non-fatal or non-life- threatening SUSAR should be reported as soon as possible, but within 15 days; the fatal or life-threatening SUSAR follow-up report should be made as soon as possible, but within a maximum of 7 days after first knowledge of the reaction being fatal or life-threatening.

12.5.4 ANNUAL SAFETY REPORTING TO THE MHRA AND NREC

The Sponsor (DAIT/NIAID) will submit once a year throughout the clinical trial an annual safety report to MHRA and NREC containing:

- Analysis of the participants' safety
- A line listing of all suspected serious adverse reactions (including all SUSARs)
- An aggregate summary tabulation of suspected serious adverse reactions

12.6 PREGNANCY REPORTING

The investigator shall be informed immediately of any pregnancy in a study participant. A pregnant participant shall be instructed to stop taking study treatment. The investigator shall counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy.

The investigator shall report to DAIT/NIAID (through the SACCC) all participant pregnancies within 24 hours of becoming aware of the event using the Pregnancy Reporting and Follow-up eCRF. All participant pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. The Pregnancy Reporting and Follow-up eCRF shall be updated and submitted to DAIT/NIAID (through the SACCC) when details about the outcome are available.

Information requested about the delivery shall include:

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

For all pregnancy complications in female participants resulting in a congenital abnormality, birth defect, miscarriage, and medically indicated abortion - an SAE shall

be submitted to DAIT/NIAID (through the SACCC) using the SAE reporting procedures described above.

12.7 REPORTING OF OTHER SAFETY EVENTS

Events may occur during a clinical trial which do not fall within the definition of SUSAR and thus are not participant to the reporting requirements for SUSARs.

An investigator shall promptly notify DAIT/NIAID (through the SACCC) about such events that are relevant to participant safety.

DAIT/NIAID shall notify the MHRA and NREC of any identified urgent safety events.[64]

12.8 REVIEW OF SAFETY INFORMATION

12.8.1 MEDICAL MONITOR REVIEW

The DAIT/NIAID Medical Monitor will receive monthly reports from the SACCC compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the study site(s) on appropriate forms.

In addition, the DAIT/NIAID Medical Monitor will review and make decisions on the disposition of the SAE and pregnancy reports received by DAIT/NIAID through the SACCC (See Sections 12.5.2, *Reporting of Serious Adverse Events*, and 12.6 *Pregnancy Reporting*).

12.8.2 DSMB REVIEWS

12.8.2.1 Planned DSMB Reviews

The DSMB shall review safety data at least yearly during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs, SAEs, and other safety events.

12.8.2.2 Ad hoc DSMB Reviews

In addition to the pre-scheduled safety reviews, the DSMB may be called upon for *ad hoc* reviews by the DAIT/NIAID Medical Monitor and/or Protocol Chair or Co-Chair when an event occurs that potentially impacts study participants' safety.

12.8.2.2.1 Temporary Suspension of drug dosing for ad hoc DSMB Review

A temporary suspension of investigational product(s), dosing, or study procedure(s) will be implemented in case a Study Stopping rule is met (See Section 11.5).

These study activities may not be resumed until all pertinent information is discussed with DAIT/NIAID, the DSMB, the NREC, and the MHRA, and all parties concur.

13. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

13.1 ENDPOINTS

Please refer to Sections 3.2, 3.3, and 3.4 which provide definitions of the primary, secondary and exploratory endpoints respectively.

13.2 MEASURES TO MINIMIZE BIAS

To minimize bias, participants who sign informed consent and meet the eligibility criteria will be randomized using a 1:1:1 ratio of participants assigned to the combination of SLIT and dupilumab, SLIT plus dupilumab placebo, and double-placebo arms respectively. Using a permuted block randomization design with varying block sizes (i.e., blocks are of different size and order of treatment within each block is permuted), randomization will be performed by the DAIT SACCC using a validated system that automates the random assignment of treatment arms to study identification numbers.

All study participants and study personnel involved in outcome assessments will be blinded to the participant's randomization status, as described in Section 3.5.1.

13.3 ANALYSIS PLAN

13.3.1 ANALYSIS SAMPLES

Screened sample: All participants who undergo screening procedures for purposes of eligibility.

Randomized sample: All participants who undergo random assignment. Participants will be analyzed according to the treatment arm to which they were randomized, regardless of the treatment they actually received.

Safety sample: All participants who undergo random assignment and who receive at least one dose of a study drug. Participants in the safety sample will be analyzed with the arm associated with the medication they actually received, regardless of their random assignment.

Modified intent-to-treat (mITT) sample: All participants who undergo random assignment, who receive at least one dose of both study medications, and complete the baseline NAC assessment (See Appendix 1 and 2). Participants will be analyzed according to the treatment arm to which they were randomized, regardless of the treatment they actually received.

Per protocol (PP) sample: All participants in the mITT sample for whom the primary endpoint is assessed and who are compliant with study treatment, defined as taking at least 50% of SLIT or SLIT placebo tablets and at least 75% of dupilumab or dupilumab placebo injections throughout the treatment period.

13.3.2 PRIMARY ANALYSIS OF PRIMARY ENDPOINT

The primary analysis will compare the mean TNSS $AUC_{0\text{-}1hr}$ between treatment arms using a longitudinal repeated measures model on data from the modified ITT sample at years 1, 2, and 3. The model will include fixed effects for treatment arm, time, and treatment arm by time interaction and will include covariates for baseline TNSS $AUC_{0\text{-}1hr}$. Since a nonlinear relationship between TNSS $AUC_{0\text{-}1hr}$ and time is expected, time will be treated as a categorical variable. An unstructured covariance structure will be used to model the correlation among time points within a participant. The primary objective will be addressed by applying a contrast in least squares means at year 3 between the combination of SLIT and dupilumab arm and double-placebo arm. The p-value associated with this contrast will not be adjusted for multiplicity.

13.3.3 SUPPORTIVE ANALYSES OF THE PRIMARY ENDPOINT

Supportive analyses of the primary endpoint will include replication of the primary analysis of the primary endpoint using participants included in the PP sample.

Subgroup analyses of the primary endpoint will include repeating the primary analysis of the primary endpoint using a longitudinal repeated measures model adjusting for treatment arm, time, baseline TNSS $AUC_{0\text{-}1hr}$, and the ratio of grass sIgE to total IgE (or grass skin prick test). An interaction term will also be included between the ratio of grass sIgE to total IgE and treatment arm (or grass skin prick test and treatment arm) to evaluate if the treatment effect on the primary endpoint is modified by differing levels of the ratio of grass sIgE to total IgE (or grass skin prick test).

There will be no methods of imputation used for missing data for the summaries, the primary analysis of the primary endpoint, or supportive analyses of the primary endpoint listed above. Sensitivity analyses of the primary endpoint will address the impact of missing data. First, we will compare demographic characteristics and baseline assessments among subgroups defined by study completion status to identify possible differences of interest. Then, while it is not expected, intermittent missing data will first be imputed using the Markov Chain Monte Carlo (MCMC) method which is appropriate for non-monotonic missing data. Monotone missing data (i.e., data missing after participants discontinue the trial early) will then be multiply imputed using a regression method adjusting for treatment arm, baseline TNSS $AUC_{0\text{-}1hr}$ and other covariates as appropriate. There will be 100 samples imputed for analysis. Results of the statistical analysis method on the 100 multiply imputed data sets will be summarized. The overall estimate will then be compared to the estimate derived from the primary inferential analysis model to assess the potential magnitude and direction of bias.

13.3.4 ANALYSES OF SECONDARY ENDPOINTS

All secondary endpoints will be treated as supportive. P-values computed for analyses of secondary endpoints will not be adjusted for multiplicity. Unless otherwise noted, all analyses will be performed on data from the modified ITT sample using a similar model methodology as described in Section 13.3.2.

13.3.4.1 Clinical Tolerance Endpoints

Peak nasal inspiratory flow, defined as the change in PNIF relative to the pre-allergen exposure PNIF measurement during the NAC (Delta PNIF $AUC_{0\text{-}1hr}$),), will be analyzed using a longitudinal repeated measures model on data from years 1, 2, and 3 with a covariate for baseline Delta PNIF $AUC_{0\text{-}1hr}$.

The size of the early intradermal test response will be analyzed using a longitudinal repeated measures model on data from years 1, 2, and 3 with a covariate for the size of the early intradermal test response at baseline. A similar model will be used to analyze the late intradermal test response.

The size of the skin prick test endpoint titration response will be analyzed using a longitudinal repeated measures model on data from years 1, 2, and 3 with a covariate for the size of the skin prick test endpoint titration response at Visit 0.

Weekly seasonal symptoms (VAS 0-10 cm), CSMS and miniRQLQ will be summarized separately using the trapezoidal rule to estimate the VAS AUC, CSMS AUC, and miniRQLQ AUC at baseline, year 1, 2, and 3 respectively. The AUC of pollen counts collected weekly during the pollen season in year 1, 2, and 3 will be estimated similarly. A longitudinal repeated measures model will be applied to VAS AUC, CSMS AUC, and miniRQLQ AUC from years 1, 2, and 3 with a time-varying covariate for the AUC of pollen count and a covariate for baseline VAS AUC, baseline CSMS AUC, or baseline miniRQLQ AUC respectively.

MRSUI will be analyzed using a longitudinal repeated measures model on data measured twice (in-season in June/July and out-of-season in November/December) in years 1, 2, and 3 with a time-varying covariate for baseline in-season and out-of-season MRSUI.

Global Evaluation No. 1 will be analyzed using a longitudinal repeated measures model on data from years 1, 2, and 3 with a covariate for baseline Global Evaluation No. 1.

Global Evaluation No. 2 will be analyzed using a longitudinal repeated measures model on data from years 1, 2, and 3 without any additional covariates.

Using each of the above models, Secondary Objective 1 will be addressed by applying a contrast in least squares means at year 3 between the combination of SLIT and dupilumab arm and double-placebo arm.

13.3.4.2 Clinical Desensitization Endpoints

Using the models specified in Section 13.3.2 and in Section 13.3.4.1, Secondary Objective 2 will be addressed by applying a separate contrast in least squares means at year 1 and 2 between the combination of SLIT and dupilumab arm and double-placebo arm.

13.3.4.3 Safety Endpoints

AEs will be summarized during screening, at baseline, and during year 1, 2, and 3 separately. Frequency of AEs will be tabulated by SOC and preferred term, as well as by seriousness, severity, and treatment relatedness. Frequency of SAEs will be tabulated by SOC and preferred term, as well as by severity and treatment relatedness. Frequency of AEs and SAEs by severity will be tabulated across all severity scales, as well as within each severity scale separately. The proportion of participants experiencing at least one AE related to the study therapy regimen during year 1, 2, and 3 will also be reported. AE summaries during screening will be performed using the Screening Sample. All other AE summaries will be performed separately in each treatment arm using the Safety Sample.

13.3.5 ANALYSES OF EXPLORATORY ENDPOINTS

All exploratory endpoints will be treated as supportive. P-values computed for analyses of exploratory endpoints will not be adjusted for multiplicity. Unless otherwise noted, all analyses will be performed on data from the modified ITT sample and will be analyzed using a similar model methodology as described in Section 13.3.2 and 13.3.4.1.

13.3.5.1 Clinical Tolerance Endpoints

Using the models specified in Section 13.3.2 and in Section 13.3.4.1, Exploratory Objective 1 will be addressed by applying a contrast in least squares means at year 3 between the combination of SLIT and dupilumab arm and SLIT plus dupilumab placebo arm. Similarly, Exploratory Objective 3 will be addressed by applying a contrast in least squares means at year 3 between the SLIT plus dupilumab placebo arm and the double-placebo arm.

13.3.5.2 Clinical Desensitization Endpoints

Using the models specified in Section 13.3.2 and in Section 13.3.4.1, Exploratory Objective 2 will be addressed by applying a separate contrast in least squares means at year 1 and 2 between the combination of SLIT and dupilumab arm and SLIT plus dupilumab placebo arm. Similarly, Exploratory Objective 4 will be addressed by applying a separate contrast in least squares means at year 1 and 2 between the SLIT plus dupilumab placebo arm and the double-placebo arm.

13.3.5.3 Mechanistic Endpoints

Details and methodology for analyses of mechanistic endpoints will be provided in a separate mechanistic analysis plan.

13.3.6 DESCRIPTIVE ANALYSES

Descriptive analyses will be reported by treatment arm. Continuous baseline measures will be summarized with means and their 95% confidence intervals, and/or median with first and third quartiles, as appropriate. Categorical baseline and demographic characteristics and study disposition will be reported as frequencies and proportions.

13.4 INTERIM ANALYSES

13.4.1 INTERIM ANALYSIS OF EFFICACY DATA

No formal interim analyses of efficacy data will be performed for this study.

13.4.2 INTERIM ANALYSIS OF SAFETY DATA

The DSMB will receive at least annual safety reports on study participants. However, no formal interim analysis of safety data will be conducted.

13.4.3 FUTILITY ANALYSIS

No formal interim analysis of futility will be performed for this study.

13.5 STATISTICAL HYPOTHESES

All analyses of primary, secondary, and exploratory endpoints will be based on two-sided superiority tests. For example, the null and alternative hypotheses for the primary endpoint are:

- Null hypothesis: The mean TNSS $AUC_{0\text{-}1hr}$ at year 3 in the combination of SLIT and dupilumab and double-placebo arms are equal.
- Alternative hypothesis: The mean TNSS $AUC_{0\text{-}1hr}$ at year 3 in the combination of SLIT and dupilumab and double-placebo arms are not equal.

13.6 SAMPLE SIZE CONSIDERATIONS

Sample size for this trial was determined by calculating the total enrollment necessary to provide at least 80% power to detect an expected difference in the mean TNSS $AUC_{0\text{-}1hr}$ at year 3 comparing the combination of SLIT and dupilumab arm to the double-placebo arm.

Estimates used for this sample size calculation are based on the mean in the placebo arm (3.81) and a range of standard deviations for TNSS $AUC_{0\text{-}1hr}$ observed in the GRASS study[20]: placebo (1.73), SLIT (1.53), and pooled placebo and SLIT arms (1.64).

Using this range of standard deviations and an ANOVA test with a two-sided alpha level of 0.05, a total of 90 participants with TNSS $AUC_{0\text{-}1hr}$ at year 3 (30 participants per arm) will allow us to detect a reduction of at least 29% - 33% in the mean TNSS $AUC_{0\text{-}1hr}$ at year 3 between the combination of SLIT and dupilumab and double-placebo arms. This exceeds the 20% minimally clinically important difference recommended by the WAO.

Assuming 6 participants per arm (16.6%), will not complete the NAC assessment at year 3, a total sample size of N=108 randomized participants who receive at least one dose of study drug and complete the NAC assessment at baseline is required. This assumed discontinuation rate approximates and is slightly more conservative than the discontinuation rate observed in the GRASS study (13.2%).

Repeated measures analysis (as is planned for the primary analysis of the primary endpoint) provides more statistical power than cross-sectional analysis, since the greater total number of observations over all participants and time points increases the degrees of freedom available for hypothesis tests. Hence, with the current sample size, the power to detect the stated differences is anticipated to be greater than 80%.

14. IDENTIFICATION AND ACCESS TO SOURCE DATA

14.1 SOURCE DATA

Source documents and source data are considered to be the original documentation where participant information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial.

14.2 ACCESS TO SOURCE DATA

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

15. PROTOCOL DEVIATIONS

15.1 PROTOCOL DEVIATION DEFINITIONS

The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted.

Protocol Deviation – Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

Major Protocol Deviation – A major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that impacts the research participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. In addition, protocol deviations that include willful or knowing breaches of human participant protection regulations, or policies, inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, will be considered major deviations.

Non-Major Protocol Deviation – A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not impact the research participant' rights, safety or well-being, or the integrity of the study data.

15.2 REPORTING AND MANAGING PROTOCOL DEVIATIONS

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

16. ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

16.1 STATEMENT OF COMPLIANCE

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the NREC. Any amendments to the protocol or to the consent materials will also be approved by the NREC before they are implemented.

16.2 INFORMED CONSENT PROCESS

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The Principal Investigator/Protocol Chair or attending physician listed on the Site-Specific Information form will review the consent and answer questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in English. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing and the form will be re-reviewed and documented after study treatment is completed (Week 104). The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

16.3 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management. Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated quarterly. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the

protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

16.4 PRIVACY AND CONFIDENTIALITY

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study Sponsor or their representatives.

17. PUBLICATION POLICY

The ITN policy on publication of study results will apply to this study. Authorized participants may find details regarding the policy statement on the ITN internet website at http://www.immunetolerance.org.

18. REFERENCES

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APPENDIX 1. SCREENING AND BASELINE ASSESSMENTS

	2020 - 2021			
	Screening	**Rescue Medication Dispensing visit**	**Baseline In Season Assessments**	**Baseline NAC**
Visit	**-4**	**-3[2]**	**-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 (FEV1, FVC, PEFR)	X[3]			
Adverse events	X	X	X	X
Concomitant 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
VAS[1]				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				
CSMS[1]			X	
MiniRQLQ[1]			X	
MRSUI			X	
Global Evaluation No. 1				X
Mechanistic Assessments				
PBMCs			X	
Serum FAB antibody assay			X	
Serum pre/8hr post NAC				X
Serum archive			X	
Whole blood flow cytometry (BAT)			X	
DNA methylation			X	
Nasal brushings			X	X
Nasal fluid cytokines			X	X
Whole Blood – RNA in season and pre/ 8hr post NAC			X	X
Whole Blood - DNA (genotyping)			X	

[1] Collected every week during grass pollen season from mid-May to end of July.

[2] Can be combined with visit -4 for those participants screened after 1 April.

[3] May be conducted at any time up until and including visit -1 and/or substituted with Peak Expiratory Flow if required.

APPENDIX 2. SCHEDULE OF EVENTS TREATMENT YEAR 1

	Dosing Year 1																												
Week	0	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	
Visit	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
General Assessments																													
Directed physical exam	X																												
Vital signs	X	X																											
Adverse events[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization	X																												
Study Medications																													
Dupixent®/Dupixent® placebo[1,2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Grazax®/Grazax® Placebo[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Rhinitis Assessments																													
MRSUI	X																												
Local Laboratory Assessments																													
Urine pregnancy test[4]	X			X		X		X		X		X		X		X		X		X		X		X		X		X	

[1] Randomization dose (visit 0) will be 600 mg, all other doses 300 mg.

[2] Dupixent®/Dupixent® placebo may be administered in-clinic or self-administered as detailed in section 3.2.

[3] Grazax®/Grazax® placebo taken once daily.

[4] To be carried out within 4 weeks prior to any injection. If a visit was missed, this may be completed at an even-numbered visit as needed or performed at home.

Clinical Assessments																												
Skin prick test endpoint titration – Phleum pratense	X[5]																											
Mechanistic Assessments																												
PBMCs	X[6]																											
Serum FAB antibody assay	X[6]																											
Serum archive	X[6]																											
Whole blood flow cytometry (BAT)	X[6]																											
DNA methylation	X[6]																											
Nasal brushings	X[6]																											
Nasal fluid cytokines	X[6]																											
Whole blood -RNA	X[6]																											

[5]Clinical assessments are collected 1-3 hours, according to clinical judgement, prior to Dupixent®/Dupixent® placebo administration.

[6]Mechanistic assessments are collected 1-3 hours, according to clinical judgement, prior to Dupixent®/Dupixent® placebo administration.

[7]Prior to home administration of Dupixent or Dupixent placebo, participants will be asked whether there have been any AEs or changes in Concomitant medications. If they report Yes, the study team will assess the changes before they proceed with the injection.

APPENDIX 3. SCHEDULE OF EVENTS TREATMENT YEAR 2

	Dosing Year 2																								
Week	**54**	**56**	**58**	**60**	**62**	**64**	**66**	**68**	**70**	**72**	**74**	**76**	**78**	**80**	**82**	**84**	**86**	**88**	**90**	**92**	**94**	**96**	**98**	**100**	**102**	**104**
Visit	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**52**	**53**
General Assessments																										
Adverse events	X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X	X
Study Medications																										
Dupixent®/Dupixent® placebo[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Grazax®/Grazax® Placebo[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local Laboratory Assessments																										
Urine pregnancy test[3]		X		X		X		X		X		X		X		X		X		X		X		X		X

[1] Dupixent®/Dupixent® placebo may be administered in-clinic or self-administered as detailed in section 3.1.

[2] Grazax®/Grazax® placebo taken once daily.

[3] To be carried out within 4 weeks prior to any injection. If a visit was missed, this may be completed at an even-numbered visit as needed or performed at home.

APPENDIX 4. SCHEDULE OF EVENTS OBSERVATION YEAR 3

	Observation Year 3												
Week	**108[1]**	**112[1]**	**116[1]**	**120[1]**	**124[1]**	**128[1]**	**132[1]**	**136[1]**	**140[1]**	**144[1]**	**148[1]**	**152[1]**	**Un**
Visit	**54**	**55**	**56**	**57**	**58**	**59**	**60**	**61**	**62**	**63**	**64**	**65**	**Early Term**
General Assessments													
Vital signs													X
Directed physical exam													X
Pulmonary Function Testing (FEV1, FVC, PEFR)													X
Adverse events	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
Pregnancy questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X
Local Laboratory Assessments													
Hematology													X
Comprehensive chemistry													X
Specific and Total IgE													X

[1] Phone visit.

APPENDIX 5. SCHEDULE OF EVENTS IN AND OUT OF 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	Jan-Apr	Apr-May	May-Aug	Sep-Jan	Sep-Feb	Jan-Apr	Apr-May	May-Aug	Sep-Jan	Sep-Feb	Jan-Apr	Apr-May	May-Aug	Sep-Jan	Sep-Feb
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 (spirometry)				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[1]				X					X					X	
VAS	X			X	X	X			X	X	X			X	X

[1] To ensure the NAC is done at the same time each year, the yearly NAC should be performed +/-14 days from the calendar date of the baseline out-of-season NAC (V-1).

	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	Jan-Apr	Apr-May	May-Aug	Sep-Jan	Sep-Feb	Jan-Apr	Apr-May	May-Aug	Sep-Jan	Sep-Feb	Jan-Apr	Apr-May	May-Aug	Sep-Jan	Sep-Feb
Visit	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15
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															
CSMS[2]			X					X					X		

	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	Jan-Apr	Apr-May	May-Aug	Sep-Jan	Sep-Feb	Jan-Apr	Apr-May	May-Aug	Sep-Jan	Sep-Feb	Jan-Apr	Apr-May	May-Aug	Sep-Jan	Sep-Feb
Visit	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15
MiniRQLQ[2]			X					X					X		
MRSUI			X		X			X		X			X		X
Global Evaluation No. 1[3]				X					X					X	
Global Evaluation No. 2[3]				X					X					X	
Mechanistic Assessments															
PBMCs			X		X			X		X			X		X
Serum FAB antibody assay			X		X			X		X			X		X
Serum pre/8hr post NAC				X					X					X	
Serum archive	X		X	X	X	X		X	X	X	X		X	X	X
Whole blood flow cytometry (BAT)			X		X			X		X			X		X
DNA methylation			X		X			X		X			X		X

[2] Collected every week during grass pollen season each year.

[3] Collected after the grass pollen season, annually.

	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	Jan-Apr	Apr-May	May-Aug	Sep-Jan	Sep-Feb	Jan-Apr	Apr-May	May-Aug	Sep-Jan	Sep-Feb	Jan-Apr	Apr-May	May-Aug	Sep-Jan	Sep-Feb
Visit	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15
Nasal brushings[4]			X	X	X			X	X	X			X	X	X
Nasal fluid cytokines	X		X	X	X	X		X	X	X	X		X	X	X
Whole blood - RNA			X	X[5]	X			X	X[5]	X			X	X[5]	X

[4] Nasal brushings are collected 6 to 8 hours post NAC

[5] Pre- and Post-NAC

APPENDIX 6. DEFINITION OF WOMEN OF CHILDBEARING POTENTIAL, AND CONTRACEPTION GUIDANCE

(Refer to https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdfhttps:/www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf)

Definition of Women of Childbearing Potential

For the purpose of this document, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Contraception Guidance

One highly effective birth control method must be used in this study. For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - oral
  - injectable
  - implantable[2]
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomized partner[2, 3]
- sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

[3] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

APPENDIX 7. MEDICATION WASHOUT PERIODS

Medication Washout Periods Before Nasal Allergen Challenge and Intradermal Tests

Medications	Time
Oral β-agonists	
Conventional release (e.g., Salbutamol, Ventolin)	12 hours
Modified release (e.g., Bricanyl)	2 days
Leukotriene modifiers (e.g., Montelukast, Singulair, Zafirlukast, Accolate)	3 days
Oral steroid (e.g., prednisone, prednisolone)	14 days
Theophylline product	14 days
Short-acting preparation (e.g., Nuelin SA, Slo-Phyllin, Aminophylline)	24 hours
Long-acting preparation (e.g., Uniphyllin Continus, Phyllocintin Continus)	2 days
Certain antihypertensive medications (Beta-blockers, Calcium channel inhibitors)	2 days
Rhinitis Medications	**Time**
Sodium Cromoglicate (e.g., Rynacrom, Vividrin)	7 days
Antihistamines (e.g., Cetirizine, Desloratadine, Neoclaritin, Fexofenadine, Telfast, Levocetirizine, Xyzal. Loratadine, Chlorphenamine, Piriton, Atarax, Zaditen)	5 days
Decongestants (e.g. pseudoephedrine, phenylephrine)	3 days
Antihistamine-decongestant tablets/liquids (e.g., Zyrtec D, Claritin-D)	5 days
Nasal corticosteroids (e.g., Flixonase NS, Flixonase Nasules, Nasonex, Nasacort, Fluticasone Propionate, Nasonex, Beclomethasone, Beconase, Betnesol, Vista-Methasone, Budesonide, Rhinocort Aqua)	14 days

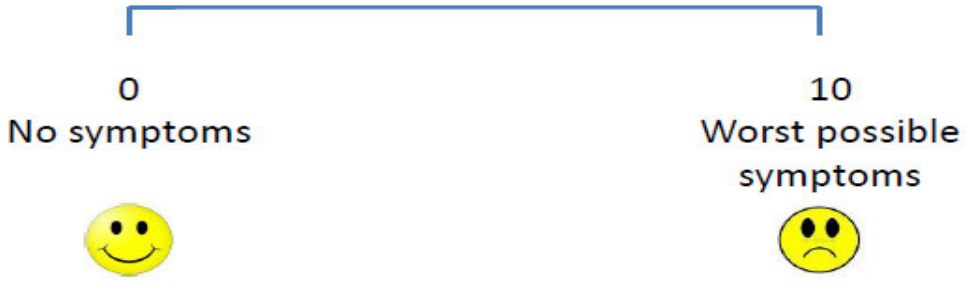
APPENDIX 8. TNSS VALIDATED SYMPTOM SCORING

Symptom	Score
Sneezing	0-3
Rhinorrhoea	0-3
Nasal congestion/blockage	0-3
Pruritus	0-3
Total Maximum Score	12
Positive outcome is an increase of ≥ 5 points from baseline	

Parameter		Points
Sneezing	None	0
	1-2	1
	3-4	2
	5 or more	3
Rhinorrhoea	None	0
	Mild	1
	Moderate	2
	Severe	3
Nasal congestion/blockage	None	0
	Mild	1
	Moderate	2
	Severe	3
Pruritus	None	0
	Mild	1
	Moderate	2
	Severe	3

APPENDIX 9. VISUAL ANALOGUE SCALE

Please place a vertical mark along the line where you feel the severity of your symptoms lie currently.



APPENDIX 10. MINI RHINOCONJUNCTIVITIS QUALITY OF LIFE QUESTIONNAIRE (MINIRQLQ)[66]

MINI RHINOCONJUNCTIVITIS QUALITY OF LIFE QUESTIONNAIRE (MiniRQLQ)

SELF-ADMINISTERED
UNITED KINGDOM VERSION

QOL TECHNOLOGIES LTD.

™

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MARCH 2006

MINI RHINOCONJUNCTIVITIS QUALITY OF LIFE QUESTIONNAIRE
(ENGLISH FOR UK VERSION)
SELF-ADMINISTERED

PATIENT ID_____

DATE_____

Page 1 of 2

Please complete **all** questions by circling the number that best describes how **troubled** you have been during the **last week as a result of your nose/eye symptoms.**

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
ACTIVITIES							
1. REGULAR ACTIVITIES AT HOME AND AT WORK (your occupation or tasks that you have to do regularly around your home and/or garden)	0	1	2	3	4	5	6
2. RECREATIONAL ACTIVITIES (indoor and outdoor activities with friends and family, sports, social activities, hobbies)	0	1	2	3	4	5	6
3. SLEEP (difficulties getting a good nights sleep and/or getting to sleep at night)	0	1	2	3	4	5	6
PRACTICAL PROBLEMS							
4. NEED TO RUB NOSE/ EYES	0	1	2	3	4	5	6
5. NEED TO BLOW NOSE REPEATEDLY	0	1	2	3	4	5	6

MINI RHINOCONJUNCTIVITIS QUALITY OF LIFE QUESTIONNAIRE
(ENGLISH FOR UK VERSION)
SELF-ADMINISTERED

PATIENT ID_____

DATE_____

How **troubled** have you been during the **last week** as a result of these symptoms?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
NOSE SYMPTOMS							
6. SNEEZING	0	1	2	3	4	5	6
7. STUFFY/BLOCKED NOSE	0	1	2	3	4	5	6
8. RUNNY NOSE	0	1	2	3	4	5	6
EYE SYMPTOMS							
9. ITCHY EYES	0	1	2	3	4	5	6
10. SORE EYES	0	1	2	3	4	5	6
11. WATERING EYES	0	1	2	3	4	5	6
OTHER SYMPTOMS							
12. TIREDNESS AND/OR FATIGUE	0	1	2	3	4	5	6
13. THIRST	0	1	2	3	4	5	6
14. FEELING IRRITABLE	0	1	2	3	4	5	6

APPENDIX 11. CSMS: SEASONAL WEEKLY COMBINED SYMPTOM MEDICATION SCORE

ITN084AD-Study CONFIDENTIAL

Participant Hospital Number	Participant Initials	Participant Study Number	Date (dd/mmm/yyyy)	CSMS
			□□/□□□/202□	CSMS

CSMS: Seasonal weekly Combined Symptom Medication Score:

Please complete the questions and the visual analogue scale below every Wednesday throughout the hay fever season. Your answers should refer only to the full week before you complete it. Please hand back the paper sheet to a member of the team at your next visit.

Over the past week, how often have you used your rescue medication for your hay fever? Please circle the appropriate answer, to the best of your knowledge / memory:

Antihistamines (Desloratadine tablets and/or Opatonol eye drops)

	SCORE (please circle one number)
Not used this week	0
On 1 day this week	1
On 2 days this week	2
On 3 days this week	3
On 4 days this week	4
On 5 or more days this week	5

Nasal spray (Mometasone)

	SCORE (please circle one number)
Not used this week	0
On 1 day this week	1
On 2 days this week	2
On 3 days this week	3
On 4 days this week	4
On 5 or more days this week	5

Please place a vertical mark along the line to reflect the severity of your hay fever this last week.

(For Office Use) Weekly VAS score		Weekly total medication score (WMS)	
Weekly Combined Symptom & Medication Score =(VAS+WMS)/2			

Name, Signature and Date of the person completing the form:

Name: _____ Signature: _____ Date: □□/□□□/202□

Data source-CSMS-v1-06Jul2020. Please keep in patient hospital record 1

APPENDIX 12. GLOBAL EVALUATIONS NO. 1 AND 2

Global Evaluation No. 1

The participant should be asked: "How do you assess the severity of your hay fever symptoms overall during this grass pollen season (Tick each single symptom)?

Rhinoconjunctivitis/ Hay fever symptom		Symptoms			
		0 (None)	1 (Mild)	2 (Moderate)	3 (Severe)
Nasal symptoms					
1.	Runny nose				
2.	Blocked nose				
3.	Sneezing				
4.	Itchy nose				
Eye symptoms					
1.	Itchy eyes				
2.	Watery eyes				

Global Evaluation No. 2

The participant should be asked: "How was your hay fever this year compared with years before you started immunotherapy treatment (Tick only one)?

Assessment						
Much better (+3)	Better (+2)	A little better (+1)	The same (0)	A little worse (-1)	Worse (-2)	Much worse (-3)
☐	☐	☐	☐	☐	☐	☐

APPENDIX 13. MODIFIED RHINITIS SYMPTOM UTILITY INDEX

MODIFIED RHINITIS SYMPTOM UTILITY INDEX			
Participant's Initials ___ ___ ___	Staff's Initial's ___ ___ ___	Completion Date ___/___/___	Visit ___

[Interview] "I would like to ask about symptoms you may have had DURING THE PAST 2 WEEKS from [your/his/her] nose and eyes, how frequently you had these symptoms, and how bothered by these symptoms you were."

1. How many days have you had a stuffy or blocked nose during the past 2 weeks?

   None.....0 [SKIP TO 3]
   1-3 days..... 1
   4-7 days..... 2
   8-14 days.....3

2. On average, how bothersome was your stuffy or blocked nose during the past 2 weeks?

   Not bothered at all.....0
   Somewhat bothered.....1
   Bothered a lot.....2

3. How many days have you had a runny nose during the past 2 weeks?

   None.....0 [SKIP TO 5]
   1-3 days..... 1
   4-7 days..... 2
   8-14 days.....3

4. On average, how bothersome was your runny during the past 2 weeks?

   Not bothered at all.....0
   Somewhat bothered.....1
   Bothered a lot.....2

5. How many days have you had sneezing during the past 2 weeks?

   None.....0 [SKIP TO 7]
   1-3 days..... 1
   4-7 days..... 2
   8-14 days.....3

6. On average, how bothersome was your sneezing during the past 2 weeks?

   Not bothered at all.....0
   Somewhat bothered.....1
   Bothered a lot.....2

7. How many days have you had itching, watery eyes during the past 2 weeks?

   None.....0 [SKIP TO 9]
   1-3 days..... 1
   4-7 days..... 2
   8-14 days.....3

8. On average, how bothersome were your itching, watery eyes during the past 2 weeks?

Not bothered at all.....0
Somewhat bothered.....1
Bothered a lot.....2

9. How many days have you had itching nose or throat during the past 2 weeks?

None.....0 [SKIP TO 11]
1-3 days..... 1
4-7 days..... 2
8-14 days.....3

10. On average, how bothersome was your itching nose or throat during the past 2 weeks?

Not bothered at all.....0
Somewhat bothered.....1
Bothered a lot.....2

MODIFIED RHINITIS SYMPTOM UTILITY INDEX HANDCARD

Handcard One: Questions 1, 3, 5, 7, 9

None.....0
1-3 days.....1
4-7 days.....2
8-14 days.....3

Handcard Two: Questions 2, 4, 6, 8, 10

Not bothered at all.....0
Somewhat bothered.....1
Bothered a lot.....2

APPENDIX 14. WAO SUBCUTANEOUS IMMUNOTHERAPY SYSTEMIC REACTION GRADING SYSTEM

World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (see text)				
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Symptom(s)/ sign(s) of one organ system present[i] **Cutaneous** Generalized pruritus, urticaria, flushing or sensation of heat or warmth[ii] **or** Angioedema (not laryngeal, tongue or uvular) **or** **Upper respiratory** Rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) **or** Throat-clearing (itchy throat) **or** Cough perceived to come from the upper airway, not the lung, larynx, or trachea **or** **Conjunctival** Conjunctival erythema, pruritus or tearing **Other** Nausea, metallic taste, or headache	***Symptom(s)/ sign(s) of more than one organ system present*** **or** **Lower respiratory** Asthma: cough, wheezing, shortness of breath (e.g., less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) **or** **Gastrointestinal** Abdominal cramps, vomiting, or diarrhea or **Other** Uterine cramps	**Lower respiratory** Asthma (e.g., 40% PEF or FEV1 drop, NOT responding to an inhaled bronchodilator) **or** **Upper respiratory** Laryngeal, uvula or tongue edema with or without stridor	**Lower or Upper respiratory** Respiratory failure with or without loss of consciousness **or** **Cardiovascular** Hypotension with or without loss of consciousness	Death
Patients may also have a feeling of impending doom, especially in grades 2, 3, or 4. **Note:** children with anaphylaxis seldom convey a sense of impending doom and their behavior changes may be a sign of anaphylaxis, e.g., becoming very quiet or irritable and cranky.				