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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A STUDY TO EVALUATE THE EFFICACY OF DUPILUMAB AS AN ADJUNCT FOR SUBCUTANEOUS GRASS IMMUNOTHERAPY TO REDUCE PROVOKED ALLERGIC RHINITIS SYMPTOMS USING THE NASAL ALLERGEN CHALLENGE MODEL

Compound:	REGN668 (dupilumab)
Clinical Phase:	2a
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Amendment 2 Date of Issue:	*See appended electronic signature page*
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[redacted]

Amendment 2

The purpose of this amendment is to respond to feedback received from the FDA.

The following table outlines the changes made to the protocol and the affected sections:

Change and Rationale for Change	Section Changed
As requested by the FDA, added a secondary endpoint which is the "Change and percent change from baseline in the TNSS AUC post NAC over the first hour of the challenge (0-1 hr post peak TNSS) at week 17 for dupilumab + SCIT as compared to dupilumab + placebo for SCIT."	Clinical Study Protocol Synopsis: Objective(s) and Endpoints Section 2.2 Secondary Objectives Section 4.2.2 Secondary Endpoints
Added a footnote to clarify that the NAC happens after 16 weeks of study treatment at week 17.	Section 5.1.1.2, Figure 1 Study Flow diagram
Changed text regarding the follow-up of pregnancies in dupilumab studies. The changes were made based on a decision made by the program team, which aligns with the current dupilumab label.	Section 6.2.2 Exclusion Criteria, #33 Section 9.4.3. Other Events that Require Accelerated Reporting to Sponsor
As requested by the FDA, added text that "The Placebo SCIT will have an identical appearance to the Grass SCIT" for clarification.	Section 7.1.2 Timothy Grass SCIT: Reference Treatment
Added the following footnote to the schedule of events table for clarification: 18. The visit should be conducted as close as possible to the designated study schedule date and the window for the days used only as needed.	Section 8.1.1 Footnotes for the Schedule of Events Table; footnote #18
Added text to clarify that treatment with prohibited medications is allowed during the study if medically necessary as judged by the investigator (ie, as needed for allergic symptoms related to SCIT or SCIT placebo or related to study procedures).	Section 7.7.1 Prohibited Medications (after Randomization) and Procedures
Added text to clarify the grading of severity of AEs by Common Terminology Criteria for Adverse Events (CTCAE).	Section 9.5.1 Evaluation of Severity
As requested by the FDA, corrected the type-o in the statistical hypothesis for superiority testing (ie, corrected from "week 24" to "week 17."	Section 10.1 Statistical Hypothesis
Minor editorial changes:	Section 8.1 Schedule of Events Section 10.2 Justification of Sample Size

Amendment 1

The following table outlines the changes made to the protocol for Amendment 1 and the affected sections:

Change and Rationale for Change	Section Changed
Change the detailed description of concentrations delivered during the NAC (4 BAU, 10 BAU, 40 BAU, 100 BAU, 400 BAU, 1000 BAU) to incorporate flexible language instead, including one highest dose, and refer to the Study Operations Manual for the actual dilutions that will be given. Rationale: This level of detail is better suited to the Study Operations Manual because we are finding during writing of the Study Operations Manual, that these doses will need to be adjusted for ease of dilution preparation. One highest dose has been suggested by multiple site PIs as has been done in similar studies.	Section 5.2 Screening
Clarify that any AEs or SAEs that are related to any study procedure, including the NAC procedure, should be reported as AEs and SAEs. The protocol currently states "The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of study, with the exception of symptoms that occur in response to the NAC on the day of the NAC. Allergic symptoms that occur in response to the NAC are not to be reported as AEs, as they will be recorded as outcome measures". The protocol now reads as follows "However, AEs that occur in response to the NAC that are outside of expected symptoms which are recorded in response to the NAC, or SAEs, should be reported as AEs and SAEs". Additional text was added to Section 9.5.2, "Relationship of Adverse Events to Study Procedures" Rationale: To clarify that reporting of AEs and SAEs related to study procedures.	Section 9.4.1 Adverse Events Section 9.5.2 Evaluation of Causality

Change and Rationale for Change	Section Changed
Correct typos and make clarifications. Rationale: Since the protocol has been circulated to study sites, we have received feedback to correct typos and inconsistencies	Synopsis Added study procedures section Section 3.2.7 Rationale for Primary Endpoint Section 3.2.8.1 Rationale of allergen-Specific IgG4 to IgE in Serum Section 3.2.8.5 Basophil Sensitivity Test for Timothy Grass Section 3.2.8.6 Frequency of Circulating Th2A Cells Section 3.2.8.7 Type 2 Inflammation in the Nasal Mucosa in Response to a NAC as Measured by RNA Sequence and Gene Expression Analysis Section 5.2 Screening Section 5.3.1 Randomization Section 6.2.2 Exclusion Criteria, #1, #6, #8 Table 1 SCIT Up Titration and Maintenance Regimen (corrected the sequence in the injection number) Table 2 Dosing Schedule for Dupilumab/Placebo with Respect to SCIT/Placebo (reference in the footnote) Section 7.3.2 Study Drug Discontinuation (Dupilumab or Placebo for Dupilumab and SCIT or Placebo for SCIT) Section 7.7 Concomitant Medications and Procedures Table 3 Schedule of Events Section 8.1.1 Footnotes for the Schedule of Events Section 8.2.1.1 NAC and NAC Assessments: TNSS, TOSS, PNIF, and Total Sneezes Section 8.2.1.4 Nasal Brushing Section 8.2.2.4 Spirometry Section 8.2.2.5 Peak Expiratory Flow Section 8.2.2.6 Laboratory Testing Section 9.4.2 Serious Adverse Events Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Study To Evaluate The Efficacy Of Dupilumab As An Adjunct For Subcutaneous Grass Immunotherapy To Reduce Provoked Allergic Rhinitis Symptoms Using The Nasal Allergen Challenge Model
Site Location(s)	North America
Objective(s)	The primary objective is to assess whether 16 weeks of treatment with dupilumab as an adjunct to Timothy Grass subcutaneous immunotherapy (SCIT) improves upon the efficacy of Timothy Grass SCIT to reduce provoked allergic rhinitis symptoms, as measured by Total Nasal Symptom Score (TNSS) after nasal allergen challenge (NAC) with Timothy Grass extract at week 17. The secondary objectives of the study are: • To assess whether 16 weeks of treatment with dupilumab as compared to placebo reduces provoked allergic rhinitis symptoms, as measured by TNSS after nasal allergen challenge (NAC) with Timothy Grass extract • To assess whether 16 weeks of treatment with dupilumab as compared to dupilumab + SCIT reduces provoked allergic rhinitis symptoms, as measured by TNSS after nasal allergen challenge (NAC) with Timothy Grass extract • To assess changes in serum Timothy Grass-specific IgG4, serum Timothy Grass-specific IgE, and ratio of serum Timothy Grass-specific IgG4 to IgE over 16 weeks of treatment with dupilumab + SCIT as compared to SCIT monotherapy • To evaluate the safety and tolerability of 16 weeks of treatment with dupilumab as an adjunct to Timothy Grass SCIT
Study Design	This is a phase 2a, multicenter, randomized, double-blind, parallel group, 4-arm study of dupilumab as an adjunct to grass SCIT in adult subjects with a history of allergic rhinitis. The entire study will be conducted outside of Timothy Grass allergy season. The 4 arms are: 1. Timothy Grass SCIT up-titrated to a 4,000 Bioequivalent allergy unit (BAU) maintenance dose + dupilumab subcutaneous (SC) [300 mg every 2 weeks (Q2W), after 600 mg loading dose]

	2. Timothy Grass SCIT up-titrated to a 4,000 BAU maintenance dose + placebo for dupilumab 3. Placebo for SCIT plus dupilumab (SC 300 mg Q2W, after 600 mg loading dose) 4. Placebo for SCIT plus placebo for dupilumab
Study Duration	The duration of the study is approximately 24 weeks excluding the screening period, including 16 weeks on study drugs and 8 weeks follow-up
End of Study Definition	The end of study is defined as the last visit of the last subject.
Population	Adult subjects with a history of allergic rhinitis
Sample Size:	Approximately 100 subjects, 25 per treatment group
Target Population:	Male and female subjects aged 18 to 55 with a history of Timothy Grass pollen–induced seasonal allergic rhinitis
Treatment(s)	
Study Drug	Dupilumab
Dose/Route/Schedule:	300 mg SC Q2W after loading dose of 600 mg SC on day 1
Reference Drug	Timothy Grass Extract SCIT
Dose/Route/Schedule:	Cluster SCIT up-titration regimen of Timothy Grass extract over 8 weeks followed by maintenance SC injections for the following 8 weeks (regimen described in Table 1)
Placebo	Placebo for dupilumab
Route/Schedule:	SC Q2W with loading dose after placebo loading dose SC on Day 1
Placebo	Placebo for SCIT
Route/Schedule:	Cluster SCIT up-titration regimen of placebo over 8 weeks followed by maintenance SC injections for the following 8 weeks
Endpoint(s)	
Primary:	The primary endpoint is the percent change in the area under the curve (AUC) for TNSS (0-1 hr post peak TNSS) in response to a NAC at week 17 from the pretreatment baseline TNSS AUC (0-1 hr post peak TNSS) for dupilumab + SCIT as compared to placebo +SCIT monotherapy.
Secondary	• Change from baseline in TNSS AUC post NAC over the first hour after the challenge (0-1 hr post peak TNSS) at week 17 for dupilumab + SCIT as compared to SCIT monotherapy

	• Change and percent change from baseline in TNSS area under curve (AUC) post NAC over the first hour of the challenge (0-1 hr post peak TNSS) at week 17 for dupilumab monotherapy as compared to placebo • Change and percent change from baseline in the TNSS AUC post NAC over the first hour of the challenge (0-1 hr post peak TNSS) at week 17 for dupilumab + SCIT as compared to dupilumab + placebo for SCIT. • Change and percent change from baseline (last pretreatment measurement) to week 17 in serum Timothy Grass sIgG4 for dupilumab + SCIT as compared to SCIT monotherapy • Change and percent change from baseline (last pretreatment measurement) to week 17 in serum Timothy Grass sIgE for dupilumab + SCIT as compared to SCIT monotherapy • Change from baseline (last pretreatment measurement) to week 17 in log transformed value of serum Timothy Grass sIgG4 to Timothy Grass sIgE ratio for dupilumab + SCIT as compared to SCIT monotherapy • Incidence rates of treatment emergent adverse events (TEAEs) and serious TEAEs through end of study
Procedures and Assessments	Efficacy will be assessed during the study at specified study site visits by the investigator(s) and include measurements of TNSS after NAC, TOSS after NAC, PNIF after NAC, intradermal skin challenge testing, and SPT with serial allergen titration. Safety will be assessed by vital signs, physical examination, clinical laboratory tests, ECGs, and clinical evaluations. All AEs that occur from the time of the informed consent until the end of the study will be monitored by the investigator.
Statistical Plan	**Sample Size Consideration:** It is estimated that with 25 subjects per group, at the 2-sided 5% significance level, the study will have 80% power to detect a difference of 29% between dupilumab plus SCIT and placebo plus SCIT monotherapy with respect to percent change from baseline in TNSS AUC (0-1 hr) at week 17, assuming that the mean percent changes from baseline values are -55% and -26% and a common standard deviation of 35% for dupilumab plus SCIT and placebo plus SCIT monotherapy, respectively.

Efficacy Analysis Sets:

The full analysis set includes all randomized subjects. Efficacy analyses will be based on the treatment allocated at randomization (as randomized).

The per protocol set includes all subjects in the FAS except for those who are excluded because of major protocol violations. A major protocol violation is one that may affect the interpretation of study results.

Analysis Methods:

Primary Efficacy Analyses

The primary endpoint will be analyzed by using the multiple imputation with analysis of covariance (ANCOVA) model. Missing data will be imputed 40 times to generate 40 complete data sets by using the Statistical Analysis System (SAS) procedure MI. Each of the 40 complete datasets will be analyzed using an ANCOVA model with treatment and relevant baseline as covariates. The SAS MIANALYZE procedure will then be used to generate valid statistical inferences by combining results from the 40 analyses using Rubin's formula.

All observed data will be used for analysis. Sensitivity analysis such as ANCOVA model with last observation carry forward (LOCF) method will also be conducted. Additional details on sensitivity analyses will be provided in the statistical analysis plan.

Secondary Efficacy Analyses

The continuous secondary efficacy endpoints will be analyzed using the same approach as that used for the analysis of the primary endpoint.

The biomarker related continuous endpoint will be analyzed using a rank based ANCOVA model with treatment and relevant baseline as covariates. The LOCF method will be used to impute the missing data.

Safety Analyses

Safety analysis will be based on the safety analysis set. This includes reported TEAEs and other safety information (eg, clinical laboratory evaluations, vital signs, and 12-lead ECG results).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under curve
BAU	Bioequivalent allergy unit
BUN	Blood urea nitrogen
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
EC50	50% of maximal activation
ECG	Electrocardiogram
ECP	Eosinophil cationic protein
EDC	Electronic data capture
EPR	Early phase reaction
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDL	High-density lipoprotein
HIV	Human Immunodeficiency Virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IFN-γ	Interferon Gamma
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IL-4	Interleukin 4
IL-4Rα	Interleukin 4 receptor alpha

IL-5	Interleukin 5
IL-13	Interleukin 13
ISR	Injection site reactions
IRB	Institutional Review Board
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LPR	Late phase reaction
MedDRA	Medical Dictionary for Regulatory Activities
NAC	Nasal allergen challenge
MI	Multiple imputation
NIMP	Non-investigational Medical Product
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NP	Nasal polyposis
PBMC	Peripheral Blood Mononuclear Cells
PBO	Placebo
PCSV	Potentially clinically significant value
PK	Pharmacokinetic
PNIF	Peak nasal inspiratory flow
POM	Proof of mechanism
PT	Preferred term
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RNA	Ribonucleic acid
sIgE	Specific immunoglobulin E
sIgG4	Specific immunoglobulin G4
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SCIT	Subcutaneous immunotherapy
SD	Standard deviation

SLIT	Sublingual immunotherapy
SOC	System organ class
SPT	Skin prick test
SQ	Standardized Quality
SUSAR	Suspected unexpected serious adverse reaction
TARC	Thymus and activation-regulated chemokine
TEAE	Treatment-emergent adverse event
Th2	Type 2 t-cells
Th2A	Th2A are a unique Th2 subcell in allergic individuals
TNSS	Total nasal symptom score
TOSS	Total ocular symptom score
WBC	White blood cell

1. INTRODUCTION

Subcutaneous immunotherapy (SCIT) is a disease modifying treatment option for patients with allergic rhinitis triggered by aeroallergens (such as pollen, animal dander, or dust). SCIT is recommended when pharmacological therapies are not sufficient to control symptoms. During SCIT, increasing doses of the inciting allergen are administered, followed by a maintenance dose for several years, with the goal of inducing immunological changes leading to symptom amelioration while on therapy, as well as sustained desensitization off SCIT (immune tolerance). The pathobiology of allergic disease is complex, involving many cell types and genetic susceptibility. Data suggest that SCIT results in memory T and B cell responses, allergen-specific immunoglobulin shifts from immunoglobulin E (IgE) to immunoglobulin G4 (IgG4), decreased Type 2 cytokines in tissues, decreased tissue migration of eosinophils and decreased mediator release from tissue mast cells, basophils and eosinophils (Akdis, 2011) (Larche, 2006). The increase in allergen-specific IgG4 (sIgG4) titers observed in SCIT may inhibit effector cell activation by binding to allergen, thereby blocking binding to high affinity IgE pre-loaded on Fc (epsilon) receptors expressed on mast cells and basophils (Flicker, 2003).

Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines and IgE. IL-4 and IL-13 play key roles in the pathophysiology of allergic diseases, as demonstrated by dupilumab's efficacy shown in clinical studies in atopic diseases such as atopic dermatitis (AD), asthma, nasal polyposis (NP) and eosinophilic esophagitis. This is the basis for the rationale to evaluate whether dupilumab may enhance allergy immunotherapy. Dupilumab has clinically demonstrated down-modulation of the Type 2 pathway and has the potential to complement the immunoregulatory mechanisms of allergen immunotherapy. IL-4 and IL-13 are important cytokines that trigger class switching in B-cells (Lundgren M, 1989) and dupilumab has been shown to suppress serum total and specific immunoglobulin E (sIgE) over time in all studies where measured; serum total IgE decreased by ~30% after 12 weeks of weekly 300 mg treatment in AD; for sIgE, studies in AD and asthma patients show a ~40% reduction at week 16 and ~50% reduction at week 24 (Regeneron unpublished data). In a post-hoc analysis of a dupilumab dose-ranging study in moderate-to-severe asthma patients with comorbid allergic rhinitis, patients had a significant reduction in reported rhinitis symptoms with dupilumab compared to placebo. Because of these data and the role of IL-4 and IL-13 in immunoglobulin class switching, we anticipate that dupilumab as an adjunct to SCIT, will enhance the change of allergen specific IgG4/IgE ratio in SCIT + dupilumab treated subjects as compared to subjects treated with SCIT alone. In patients with AD, dupilumab modulated several Type 2 chemokines, including CCL17 (thymus and activation-regulated chemokine [TARC]) in serum and skin tissue, therefore we anticipate that dupilumab will modulate Type 2 chemokines and cytokines in subjects with a history of allergic rhinitis, which may improve tolerability of SCIT up-dosing (Beck, 2014) (Hamilton, 2014). A reduction in the production of Type 2 cytokines and chemokines by dupilumab is also likely to potentiate the reduction of provoked allergic rhinitis symptoms by SCIT.

There is an unmet need for a more efficacious treatment of allergic disease. SCIT can provide long-lasting protection from allergic disease, but it also carries a risk of adverse reactions, has variable efficacy between patients, and can take at least 3 years to induce immune tolerance (Durham, 1999) (Durham, 2012) (Leung, 2010) (Durham, 2016). At the start of SCIT, patients receive injections of increasing doses of the allergen at weekly intervals over several weeks to months, under tightly monitored medical supervision. The gradual dose escalation enables tolerability to therapy and mitigates risk of severe hypersensitivity reactions related to allergen administration. Side effects occur in 40-50 % of patients ranging from mild reactions (eg, swelling, injection site reaction, de novo allergic response, and urticaria) to life-threatening reactions (eg, asthma exacerbation and anaphylaxis) (Frew, 2006a). Asthma is a major risk factor for life-threatening systemic reactions to SCIT and therefore moderate-severe asthma is a contraindication to SCIT. Therefore with proper patient selection, risk of severe reactions can be mitigated (Frew, 2010) (Frew, 2006a). Induction of Type 2 pathway cytokines upon SCIT initiation can transiently exacerbate allergic symptoms, resulting in SCIT dose limitations during up-titration in some patients. Blockade of these cytokines by dupilumab may improve tolerability of the desensitization process, in addition to improving overall safety and efficacy by further suppression of IgE production.

Therefore, dupilumab may: 1) limit symptoms of the desensitization process so that maximal SCIT uptitration may be achieved 2) improve the efficacy of the sensitization process via its suppressive effect on IgE production, and 3) reduce allergic symptoms directly by other mechanisms including the inhibition of allergen specific Type 2 t-cells (Th2) cell number and function with downstream effects on mast cells, eosinophils, and basophils.

This trial is a 4-arm, placebo-controlled, double-blind, randomized, parallel-group, proof-of-concept study over a 16 week treatment period followed by an 8 week safety follow-up period in approximately 100 subjects with a history of Timothy Grass-induced allergic rhinitis. Allergy to Timothy and rye grasses are the most prevalent seasonal allergies and grass immunotherapy is the most studied form of allergen immunotherapy (Salo, 2014). The primary objective will be to assess whether dupilumab in combination with SCIT can reduce provoked allergic symptoms more than SCIT alone by Total Nasal Symptom Score (TNSS) after nasal allergen challenge (NAC) with Timothy Grass allergen. The entire 17 week study will be conducted outside of grass allergy season so that environmental allergens do not interfere with the provoked allergy symptoms by the NAC. TNSS is a patient-reported composite symptom assessment of congestion, itching, rhinorrhea and sneezing. Cluster SCIT dosing (multiple injections per week) accelerates the onset of efficacy of SCIT. Therefore, up-titration of SCIT over 8 weeks (rather than conventional regimen of 12 weeks) plus 8 weeks of maintenance SCIT will be investigated in this study with the goal to show early induction of treatment response. We hypothesize that efficacy of SCIT, as measured by an improvement in TNSS in response to NAC, will be significantly augmented by dupilumab. The secondary objectives will assess safety and tolerability of dupilumab as an adjunct to SCIT, whether dupilumab monotherapy reduces provoked allergic rhinitis symptoms more than placebo, and whether dupilumab in combination with SCIT changes Timothy Grass-specific IgG4, Timothy-Grass specific IgE, and the ratio of Timothy-grass specific IgG4/IgE more than SCIT alone. Exploratory objectives will assess early-phase (0–1 hr) and late-phase (1-6 h) nasal and skin responses following nasal and intradermal allergen administration, Total Ocular Symptom Score (TOSS) after NAC, serum

TARC, and total IgE. Additional biomarkers, to be included in a separate Exploratory Biomarker Report, will include basophil sensitivities to grass allergen, allergen-specific Th2A cells, and changes in type 2 inflammation in the nasal mucosa after NAC as measured by RNA sequencing and nasal fluid cytokine concentration.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To assess whether 16 weeks of treatment with dupilumab as an adjunct to Timothy Grass SCIT improves upon the efficacy of Timothy Grass SCIT to reduce provoked allergic rhinitis symptoms, as measured by TNSS after NAC with Timothy Grass extract at week 17

2.2. Secondary Objectives

- To assess whether 16 weeks of treatment with dupilumab as compared to placebo reduces provoked allergic rhinitis symptoms, as measured by TNSS after NAC with Timothy Grass extract
- To assess whether 16 weeks of treatment with dupilumab as compared to dupilumab + SCIT reduces provoked allergic rhinitis symptoms, as measured by TNSS after nasal allergen challenge (NAC) with Timothy Grass extract
- To assess changes in serum Timothy-grass-specific IgG4, serum Timothy Grass-specific IgE, and ratio of serum Timothy Grass-specific IgG4 to IgE over 16 weeks of treatment with dupilumab + SCIT as compared to SCIT monotherapy
- To evaluate the safety and tolerability of 16 weeks of treatment with dupilumab as an adjunct to Timothy Grass SCIT

2.3. Other Objectives

- To assess whether 16 weeks of treatment with dupilumab as an adjunct to Timothy Grass SCIT improves upon the efficacy of Timothy Grass SCIT to reduce provoked allergic conjunctivitis symptoms, as measured by TOSS after NAC with Timothy Grass extract.
- To assess whether 16 weeks of treatment with dupilumab as compared to placebo reduces provoked allergic conjunctivitis symptoms, as measured by TOSS after NAC with Timothy Grass extract.
- To assess the changes in both early-phase (0–1 hr) and late-phase (1-6 hr) skin responses following Skin Prick Test with Serial Allergen Titration and intradermal administration of Timothy Grass, respectively, over 16 weeks of treatment with dupilumab monotherapy (+ placebo for SCIT), SCIT monotherapy (+ placebo for dupilumab), dupilumab + SCIT, and placebo for SCIT + placebo for dupilumab

- To assess changes in peak nasal inspiratory flow (PNIF) after NAC over 16 weeks of treatment with dupilumab monotherapy (+ placebo for SCIT), SCIT monotherapy (+ placebo for dupilumab), dupilumab + SCIT, and placebo for SCIT + placebo for dupilumab
- To assess total sneeze count after NAC over 16 weeks of treatment with dupilumab monotherapy (+ placebo for SCIT), SCIT monotherapy (+ placebo for dupilumab), dupilumab + SCIT, and placebo for SCIT + placebo for dupilumab
- To assess changes in serum TARC over 16 weeks of treatment with dupilumab monotherapy (+ placebo for SCIT), SCIT monotherapy (+ placebo for dupilumab), dupilumab + SCIT, and placebo for SCIT + placebo for dupilumab
- To assess changes in serum total IgE over 16 weeks of treatment with dupilumab monotherapy (+ placebo for SCIT), SCIT monotherapy (+ placebo for dupilumab), dupilumab + SCIT, and placebo for SCIT + placebo for dupilumab

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

Dupilumab in combination with SCIT will reduce provoked allergic rhinitis symptoms, as measured by TNSS after NAC, two-fold as compared to SCIT alone.

3.2. Rationale

3.2.1. Rationale for Study

This study is a double blind, placebo-controlled, parallel design study in grass allergic subjects. Four treatment groups are required to provide informative controls and minimize bias on clinical endpoints: dupilumab + SCIT, placebo for dupilumab + SCIT, dupilumab + placebo for SCIT and placebo for dupilumab + placebo for SCIT. In addition, this study will allow the evaluation of dupilumab monotherapy on clinical rhinitis symptoms and related biomarkers.

3.2.2. Rationale for Study Design

Dupilumab, with and without SCIT, will be tested in a 4-arm, double-blind, randomized, parallel-group, proof-of-concept study of 16 week treatment period in approximately 100 subjects with a history of Timothy Grass-induced allergic rhinitis using change from baseline in TNSS area under curve (AUC) post NAC over the first hour after the challenge (0-1 hr post peak TNSS) as the primary endpoint.

3.2.3. Rationale for Dose Selection

3.2.3.1. Dose and Regimen of Dupilumab

Dupilumab at 300 mg every 2 weeks (Q2W) with a loading dose of 600 mg on day 1 will be used in this study, as this regimen is Food and Drug Administration (FDA) approved for AD and is effective in asthma. Based on the pharmacokinetic profile of dupilumab, this dose regimen is expected to saturate binding to IL-4Ra, providing maximum inhibition of signaling and hence suppression of type 2 inflammation and Ig class switching to IgE. Moreover, this dose of dupilumab significantly reduces sIgE by 12 weeks (Regeneron unpublished data), which should improve upon the sIgG4/IgE ratio elicited by SCIT by 17 weeks to therefore improve upon the efficacy of SCIT as measured by TNSS in response to NAC after 17 weeks. Subjects may administer the dupilumab at home after receiving the loading dose at the study site (and training to self-administer at home), but they will be given the opportunity to receive dupilumab at the study site as well. The loading dose will allow subjects to achieve efficacious concentrations quickly for this short study. Dupilumab will be started one day prior to initiation of the SCIT regimen, and for subsequent doses dupilumab will be administered Q2W and will always be given on a different day than SCIT to assist with interpretation of adverse effects due to each agent. Dupilumab will be dosed as follows: subjects will be given a loading dose of 600 mg dupilumab subcutaneous (SC) or placebo on day 1, followed 2 weeks later by 300 mg Q2W SC, and to continue 300 mg Q2W SC for a total of 16 weeks. In previous studies in patients like those expected to be enrolled in this study dupilumab has a safety profile similar to placebo except for an increased incidence of injection site reactions. Other common adverse events (AEs) were headache, nasopharyngitis, and upper respiratory tract infection and these were most commonly mild to moderate in severity. In patients with AD, conjunctivitis and Herpes simplex were also reported at an increased incidence in patients receiving dupilumab compared to placebo (Beck 2014) (Wenzel, 2016) (Bachert 2016).

3.2.3.2. Dose and Regimen of SCIT

On the day following dupilumab dosing (up to 7 days after dupilumab loading dose), subjects will begin an up-titration regimen of Timothy Grass SCIT beginning at 1 bioequivalent allergy unit (BAU) up to 4,000 BAU, in a modified cluster regimen over 8 weeks, and then maintained on 4,000 BAU for the remaining 8 weeks (Table 1). This dosing regimen has previously been shown to give significant clinical efficacy and consistent kinetics of the sIgG4 and sIgE response (Frew, 2006b), (Shamji, 2012). Using a modified cluster regimen over 8 weeks to reach a 4,000 BAU maintenance dose, the most common AEs were fatigue, urticaria, wheezing, chest tightness and flushing (Ewbank, 2003). As referenced previously, safety of modified cluster uptitration of SCIT versus conventional up-titration appears to have similar local and systemic AE profile (Creticos, 1992). Additionally, as recommended by the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology to reduce local and systemic AEs during cluster SCIT, subjects will be pre-medicated with an oral H1 antihistamine prior to cluster SCIT dosing on all dosing days (Cox, 2011). However, oral H1 antihistamines are never to be administered within 5 days prior to a study visit for NAC as antihistamines will interfere with the NAC.

3.2.4. Rationale for Dose of SCIT and Up-titration Regimen

Per clinical guidelines, immunotherapy is typically initiated 12-16 weeks before the allergen season to treat seasonal allergic rhinitis. Immunotherapy is often continued for a duration of 3-5 years to reach greater efficacy and achieve allergen immunotolerance. In clinical studies, efficacy is typically assessed after 8-12 months of treatment (Bachert, 2016) (Scadding, 2017) to investigate the maximal efficacy of SCIT on reduction of clinical symptoms during natural pollen exposure (Bachert, 2016) or by NAC after ≥ 8-12 months (Scadding, 2017). SCIT reduces symptoms by 25-30% relative to placebo in these studies.

Few studies have evaluated efficacy at time points earlier than 8 months. However, the onset of symptom relief and increase in sIgG4 levels with SCIT occurs after reaching maintenance dose (ie, at the end of the up-titration phase [Ewbank, 2003]). With conventional SCIT up-titration regimens, this can take 8-12 weeks of weekly dosing. Cluster dosing, multiple injections per week, is an alternative to accelerate the onset of efficacy. In a house dust mite SCIT study, 6 week cluster dosing showed a marginal, but observable advantage to a 12 week conventional up-titration on clinical measures and a 50% more rapid rise in sIgG4. Adverse events rates were slightly lower with the cluster regimen than the conventional up-titrations, 3% and 4%, respectively (Tabar, 2005). A meta-analysis of 567 participants in 8 trials showed that cluster SCIT has similar effect in the reduction of both rhinitis symptoms and the requirement for anti-allergic medication compared with conventional SCIT. The safety of cluster SCIT showed that no differences existed in the incidence of either local or systemic adverse reaction between the cluster group and control group (Feng, 2014). The current study proposes to evaluate the highest recommended dose of SCIT (4,000 BAU) provided in a modified cluster regimen so that an observable change in treatment groups can be assessed in 17 weeks. Efficacy will be assessed by changes in rhinitis symptoms after NAC (Section 4.2).

3.2.5. Rationale for Choice of Allergen and Its Route of Administration

Grass SCIT immunotherapy was selected as an experimental model to test the effect of dupilumab on SCIT due to the availability of precedent clinical and biomarker data. Few well-controlled studies have been conducted with other allergens (Canonica, 2013). Besides grass specific immunotherapy sublingual immunotherapy (SLIT) and SCIT, there are limited studies of other allergen immunotherapies demonstrating efficacy in a NAC study. The advantage of studying seasonal allergens, (ie, grass pollen), compared to perennial allergens (ie, cat, house dust mite), is that pollens induce broader symptomatology, induce sneezing, itchiness and nasal congestion, whereas the predominant symptom associated with perennial allergens is nasal congestion. Hence, a study of grass pollen will inform about the efficacy of dupilumab as an adjuvant to SCIT treatment on broad rhinitis symptoms. One limitation of using a seasonal allergy is that timing of study and seasonality are key considerations; this study must be conducted outside of pollen season to minimize the impact of environmental allergen exposure on study results.

3.2.6. Rationale for Nasal Allergen Challenge

This study will use the NAC to assess the efficacy of dupilumab with or without SCIT on allergic symptoms outside of grass allergy season. The NAC is a well-recognized nasal provocation model that reproduces direct allergen contact of the upper airways in a controlled clinical setting allowing for rapid proof-of-mechanism (POM) in smaller numbers of patients than natural exposure studies (Eckman, 2010) (Paterniti, 2011). Intranasal instillation of allergen causes local allergic symptoms, such as nasal congestion, itching, sneezing and rhinorrhea, which peak within the first hour of the early phase reaction (EPR) (Scadding, 2015a). Within minutes of local allergen exposure, IgE-mediated basophil and tissue mast cell degranulation occurs with the release of mediators, which cause blood vessel dilation and vascular leakage immediately leading to these nasal symptoms. Therefore, the change in TNSS score after NAC with Timothy Grass extract is selected for POM as a reliable, reproducible, and controlled method of measuring allergy symptoms for this study. Each subject will undergo a baseline NAC at screening and a repeat NAC at the end of treatment.

3.2.7. Rationale for Primary Endpoint

As a primary endpoint, the percent change in the AUC for TNSS (0-1 hr post peak TNSS) in response to a NAC at week 17 from the pretreatment baseline TNSS AUC (0-1 hr post peak TNSS) will be assessed for dupilumab in combination with SCIT vs SCIT monotherapy (+ placebo for dupilumab). During the up-titration phase of the NAC, TNSS will be measured every 10 minutes during the first hour until attainment of a TNSS score ≥ 7, and then TNSS will be measured at 5 minutes, 15 minutes, 30 minutes, 45 minutes, one hour, then hourly up to 6 hours post-NAC. Peak symptoms occur between 0-1 hours after NAC, therefore the primary endpoint will measure the AUC of TNSS over the first hour after peak TNSS is achieved (Regeneron unpublished data). A 20-30% reduction in symptoms is considered a clinically meaningful response (Meltzer, 2016) (Pawankar, 2011). Compared to natural exposure or environmental chamber, nasal provocation is a controlled and customized administration of allergen, resulting in a more reliable and reproducible assessment of efficacy with a smaller sample size. Additionally, environmental chamber studies are limited to one site as chambers at different sites vary considerably by allergen exposure.

3.2.8. Rationale for Other Endpoints

3.2.8.1. Ratio of Allergen-Specific IgG4 to IgE in Serum

Immunotherapy induces both cellular and humoral regulatory immune mechanisms. Humoral mechanisms involve the induction of allergen specific antibodies, especially of the IgG4 isotype, which is thought to have a protective effect against IgE-mediated allergic symptoms. IgG4 competes with IgE, blocking IgE-mediated effector cell activation, suppresses histamine release and inhibits antigen-presentation of IgE-allergen complex by dendritic and B-cells (James, 2012). The gradual increase in serum allergen-specific IgG4, IgE-blocking factor and decrease in allergen-specific IgEs have been associated with clinical desensitization in SCIT for grass (Shamji, 2012) and was consistently observed across different studies. At the start of SCIT, serum sIgG4s are low/undetectable. In response to the initiation of SCIT, a 2-fold increase in sIgG4 and a transient increase in sIgE is observed (Scadding, 2017) (Creticos, 1992)

(Suarez-Fueyo, 2014). An approximately 8-fold increase in the ratio of sIgG4/sIgE was associated with a reduction in symptoms induced by nasal allergen provocation after 1-year of SCIT (Scadding, 2017). A higher ratio of sIgG4/sIgE in patients tolerant to some allergens (eg, birch, cat, peanut) compared to their symptomatic controls was observed (Geroldinger-Simic, 2011) (Du Toit, 2013) (Burnett, 2013). Compared to the individual levels of sIgG4 or sIgE, the ratio of sIgG4/IgE is thought to be more reflective of the competition for allergen binding between IgG4 and IgE and has so far shown better correlation with clinical improvement. Given that the induction of sIgG4 and the suppression of sIgE is the most well-known phenomenon associated with immunotherapy and dupilumab has been shown to suppress specific IgE in past studies, we aim to test if skewing of sIgG4/IgE ratio will be one of the immunological effects of dupilumab as an adjunct to SCIT treatment.

3.2.8.2. Nasal: Early-Phase (0–60 min) and Late-Phase (6 hr) Reaction to Nasal Allergen Challenge

Response to nasal allergen challenge has been used as a surrogate for seasonal symptoms in past clinical trials of corticosteroid treatment for allergic rhinitis. The concentration of cytokines/chemokines and other mediators in the nasal fluid were recorded as a measure of inflammatory response. The early phase reaction (EPR) was characterized by the induction of tryptase and histamine, which were thought to reflect mast cell activation and degranulation in the nasal epithelium. Existing data from multiple studies consistently reported peak induction of tryptase at 5-minutes post challenge, followed by rapidly declining levels within 60 minutes and then dropping back to baseline within 2 hours. The late phase reaction (LPR) is thought to reflect type 2 inflammation mediated by Th2-cells and eosinophils that migrate to the site of inflammation. The gradual increase in eosinophil cationic protein (ECP), eotaxin, eotaxin-3, IL-4, IL-5, IL-13, IFNγ IL-9 can be detected at pg/mL to ng/mL concentrations from 1 to 2 hours onwards. Typically, Type 2 cytokine levels in nasal fluid also increase some hours after challenge: IL-5 at 6–9 h (Nicholson, 2011) (Linden, 2000); IL-13 at 6–8 h (Erin, 2005a) (Nicholson, 2011); and IL-4 at 5–6 h (Wagenmann, 2005). IL-10 was reported to increase in nasal fluid 6 hours post allergen challenge (Bensch, 2002). IFN-γ levels did not show significant induction in published studies, which is consistent with a primarily type 2 mediated inflammation following NAC (Scadding, 2012).

Allergen specific immunotherapy with Timothy Grass has been shown to decrease both the early phase and late phase reaction post-NAC, as measured by the decrease of tryptase, eotaxin, IL-9 and IL-4 in the nasal fluid collected from patients on immunotherapy compared to placebo (Scadding, 2015b). We hypothesize that dupilumab treatment as an adjunct to SCIT treatment may further suppress the tissue specific allergic response to allergen challenge, as well as further decrease the induction of type-2 cyotkines and chemokines in late phase reactions compared to SCIT alone.

Two techniques could be used to collect and study mediators in nasal fluid. Key considerations include acceptability to patients, collection of adequate volumes, and adequate concentration to allow the planned immunoassays. Generally, techniques involving direct absorbance from the mucosa provide optimal results (Klimek, 1999a) (Klimek, 1999b) (Lü, 2010) (Riechelmann, 2003). In a comparison study by Scadding GW and colleagues, nasal sponges were shown to be superior to strip paper method (higher sample volume and statistically significant induction of ECP, IL-5, IL-13 were detected post NAC) (Scadding, 2012). In a Regeneron/Sanofi sponsored NP study with dupilumab, sufficient volumes of nasal fluid were collected by the sponge method and TARC, ECP and eotaxin-3 levels within detectable range for ELISA-based assays (Regeneron/Sanofi unpublished data), which also supports our selection of nasal sponge as the method of nasal fluid collection.

3.2.8.3. Skin: Early-Phase (0–60 min) and Late-Phase (6 hr) Skin Reaction to Allergen Challenge

The SPT with serial allergen titration assesses the early phase reaction (EPR) at 0-60 min. The intradermal allergen injection will be performed to assess late phase reaction (LPR) at 6 hours. The early phase reaction is characterized by histamine release and is thought to reflect cutaneous mast cell degranulation upon allergen exposure. The allergen-induced cutaneous LPR is characterized by an influx of inflammatory cells, including basophils, eosinophils, activated CD4+-cells, and neutrophils which arrive at the site of inflammation some hours after provocation.

Allergen specific immunotherapy with Timothy Grass has been shown to decrease both the early phase reaction after SPT, and late phase reaction after intra-dermal allergen challenge, as measured by the decrease of wheal size post challenge (Scadding, 2015b). In addition, short term grass SCIT treatment (13 weeks) led to significant and lasting reduction of LPR with statistical significance 12 months after the end of SCIT (Chaker, 2015a) (Chaker, 2015b). We hypothesize that dupilumab as an adjunct to SCIT treatment may further reduce skin allergic response to Timothy Grass and can further decrease LPR compared to SCIT alone. Based on expected reduction of IgE levels 12 weeks after dupilumab treatment in past AD studies, a reduction in mast cell activation may result in reduction in EPR and therefore reduced wheal sizes may also be expected.

3.2.8.4. Serum TARC and Total IgE

Serum TARC and total IgE are markers of Type 2 immune activity. Dupilumab significantly suppressed both TARC and total IgE in studies of adult AD, NP, and asthma patients.

3.2.8.5. Basophil Sensitivity Test for Timothy Grass

The allergen-specific decrease in basophil sensitivity following SCIT has been described for olive pollen allergy, birch pollen allergy and Timothy Grass allergy (Gokmen, 2012) (Lalek, 2010) (Nopp, 2009). In a 40-patient, 15-month, placebo-controlled study for allergic rhinitis, patients who received either SLIT or SCIT for Timothy Grass, basophil sensitivity for Timothy Grass was shown to decrease as early as one month after SCIT treatment and continues to decline at 15-months (Aasbjerg, 2014). In the above study, basophil activation was measured by high CD203 expression and high percentage of CD63+ cells. Basophil sensitivity was

measured by the concentration of allergen (ng/mL), sufficient to give a 50% of maximal activation (EC50) (Aasbjerg, 2014). For the current study of dupilumab as an adjunct for grass SCIT study, instead of EC50, basophil sensitivity will be measured by the threshold concentration of Timothy Grass sufficient to activate basophils in patient whole blood.

Basophil and mast cell activation are critical steps in mediating immediate allergic symptoms upon allergen exposure. The activation of basophil and mast cells is an IgE-mediated event, where cross-linking of grass-specific IgEs bound to high affinity Fc (epsilon) receptors on mast cells and basophils trigger immediate degranulation. In a study investigating the biomarker profile of dupilumab in patients with AD (Regeneron unpublished data) as well as other dupilumab studies, dupilumab suppressed both total and allergen-specific IgEs. In general, dupilumab suppresses total IgE by ~50% with 12 to 16 weeks of treatment. Based on the anticipated effect of dupilumab in reducing IgE, we hypothesize that dupilumab + grass SCIT may further reduce basophil sensitivity over grass SCIT alone. This improvement could be linked to allergic symptom reduction during dupilumab treatment as an adjunct for grass SCIT.

The exploratory basophil sensitivity testing will not be reported in the clinical study report.

3.2.8.6. Frequency of Circulating Th2A Cells

One important area of investigation is to determine the effect of dupilumab as an adjunct to SCIT treatment on changes in allergic T-cell responses. At week 4 (300mg/QW or Q2W) dupilumab effectively reduced CD3+ T-cells in AD skin lesions and suppressed Th2 inflammatory pathways genes (eg, CCL13, CCL17 and CCL18), as shown by past studies in atopic dermatitis (Hamilton, 2014). These data indicate that dupilumab has direct suppressive effect on Th2 cells. However, due to the extreme low frequency of allergen-specific T-cells in circulation, conventional immunophenotyping of Th2 cells has not been successful in capturing changes in allergen-specific T-cells during specific immunotherapy. Th2A cells are allergen-specific Th2 cells with a characteristic surface marker signatures (CRTH2+, CD27−, CD154+, CD161+, CD45RB−, and CD49d+ (Wambre, 2017). Using these markers, Wambre et al. reported a significant reduction in the frequency of pro-allergic Th2A cell subsets from subjects receiving active grass tablets (SLIT) compared to those receiving placebo. This method has also been implemented in assessing changes in allergen specific T-cells in a 2-year longitudinal grass immunotherapy study performed by the Immune Tolerance Network, where frequency of allergen-specific Th2 cells paralleled clinical outcomes (Renand, 2017) .Therefore, monitoring allergen-specific Th2 cells may reveal important mechanistic insight into the amelioration of allergic symptoms by dupilumab as an adjunct to SCIT treatment.

The exploratory Th2A analyses will not be reported in the clinical study report.

3.2.8.7. Type 2 Inflammation in the Nasal Mucosa in Response to a NAC as Measured by RNA Sequence and Gene Expression Analysis

The sponsor hypothesizes that dupilumab may suppress the homing of eosinophils and Th2-cells to the tissue, thus reducing the induction of genes and inflammatory pathways associated with type 2 inflammation post NAC. Existing data in the literature suggest that type 2 inflammation in asthmatic or allergic rhinitis patients could be detected by gene expression analysis of nasal tissue samples, collected either by nasal brushing or nasal curettes. For instance, RNA

expression analysis of type 2-associated genes in nasal brushings from 50 asthmatic patients and 50 healthy controls have identified "Th2-high" and "Th2-low" subjects differentiated by the expression of 70 genes associated with type 2 pathways, including IL-13, IL-5, and periostin. The analysis also revealed that Th2-high subjects were more likely to have atopy, atopic asthma, higher blood eosinophil counts and rhinitis, compared with Th2-low subjects. Nasal IL-13 expression was 3.9-fold higher in asthmatic participants who experienced an asthma exacerbation in the past year (Poole, 2014). In a study of allergic rhinitis patients treated with prednisone or placebo, nasal challenge with Timothy Grass was performed. Eight hours post NAC, significant increases in eosinophil related gene-expression were detected in the nasal sampling of placebo-treated patients compared to baseline, but not in prednisone-treated patients (Leaker, 2017). These data suggest that transcriptome analysis of nasal brushings could be used to assess underlying type 2-driven inflammation.

The exploratory nasal secretion and brushing analyses will not be reported in the clinical study report.

3.2.8.8. Rationale for Study Duration

The time course of SCIT efficacy is not well established with limited data published regarding short-term efficacy endpoints. Clinical guidelines and experience indicate that symptomatic improvement can be demonstrated shortly after the patient reaches a maintenance dose (Ewbank, 2003). It is thought the onset of action could coincide with induction of sIgG4, which plateaus after reaching maintenance dose. While conventional up-dosing schedules require 8-12 weeks, we propose an 8-week cluster up-titration regimen to accelerate time to maintenance dose and onset of action of SCIT. Dupilumab has resulted in rapid, potent suppression of type 2 biomarkers within 4-12 weeks of treatment in all indications tested to date. Thus, a 16 week treatment duration is expected to be sufficient to evaluate the effects of dupilumab with and without SCIT.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, co-morbid atopic conditions, years with aeroallergen disease, sex, etc), disease characteristics including medical history, and medication history for each subject.

4.2. Primary and Secondary Endpoints

4.2.1. Primary Endpoint

The primary endpoint is the percent change in AUC for TNSS (0-1 hr post peak TNSS) in response to a NAC at week 17 from the pretreatment baseline TNSS AUC (0-1 hr post peak TNSS) for dupilumab + SCIT as compared to placebo +SCIT monotherapy.

4.2.2. Secondary Endpoints

- Change from baseline in TNSS AUC post NAC over the first hour after the challenge (0-1 hr post peak TNSS) at week 17 for dupilumab + SCIT as compared to SCIT monotherapy
- Change and percent change from baseline in TNSS AUC post NAC over the first hour of the challenge (0-1 hr post peak TNSS) at week 17 for dupilumab monotherapy as compared to placebo
- Change and percent change from baseline in the TNSS AUC post NAC over the first hour of the challenge (0-1 hr post peak TNSS) at week 17 for dupilumab + SCIT as compared to dupilumab + placebo for SCIT.
- Change and percent change from baseline (last pretreatment measurement) to week 17 in serum Timothy Grass sIgG4 for dupilumab + SCIT as compared to SCIT monotherapy
- Change and percent change from baseline (last pretreatment measurement) to week 17 in serum Timothy Grass sIgE for dupilumab + SCIT as compared to SCIT monotherapy
- Change from baseline (last pretreatment measurement) to week 17 in log-transformed value of serum Timothy Grass sIgG4 to Timothy Grass sIgE ratio for dupilumab + SCIT as compared to SCIT monotherapy
- Incidence rates of treatment-emergent adverse events (TEAEs) and serious TEAEs through end of study

4.2.3. Exploratory Endpoints

- Change and percent change from baseline in the peak TNSS at week 17 for dupilumab + SCIT as compared to SCIT monotherapy and for dupilumab monotherapy as compared to placebo
- Change and percent change from baseline in TOSS AUC post NAC over the first hour of the challenge (0-1 hr post peak TNSS) at week 17 for dupilumab + SCIT as compared to SCIT monotherapy and for dupilumab monotherapy as compared to placebo
- Change and percent change from baseline (last pretreatment measurement) to week 17 in Skin Prick Test with Serial Allergen Titration, as measured by AUC of the wheal sizes (diameter) over the course of 0 hour to hour 1 after the challenge (early phase reaction)
- Change and percent change from baseline (last pretreatment measurement) to week 17 in the wheal size (diameter) induced by skin Timothy Grass intradermal injection 6 hrs after the challenge (late phase reaction)
- Change and percent change from baseline (last pretreatment measurement) to week 17 in PNIF AUC over the course of 0 hour to hour 1 and hour 1 to hour 6 after the challenge (early and late phase reaction)

- Change and percent change from baseline (last pretreatment measurement) to week 17 in sneeze count AUC over the course of 0 hour to hour 1 and hour 1 to hour 6 after the challenge (early and late phase reaction)
- Change and percent change from baseline (last pretreatment measurement) to week 17 in serum TARC
- Change and percent change from baseline (last pretreatment measurement) to week 17 in serum total IgE

4.3. Pharmacokinetic Variables

Concentration of functional dupilumab in serum at each time point, obtained prior to dosing, will be measured (C_{trough})

4.4. Anti-Drug Antibody Variables

Anti-drug antibody variables include ADA status and titer as follows:

- Total subjects with treatment emergent response
- Treatment emergent - defined as a positive response in the ADA assay post first dose when baseline results are negative.
- Total subjects with treatment boosted response
- Treatment boosted – defined as a positive response in the ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baselines results are positive.

Samples positive in the ADA assay will be assessed for titer:

- Titer category
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤10,000)
  - High (titer >10,000)

5. STUDY DESIGN

5.1. Study Description and Duration

This is a Phase 2a, multicenter, randomized, double-blind, parallel group, 4-arm study of dupilumab as an adjunct to grass SCIT and consists of a 12 week screening period, 16 week treatment period and a 8 week post treatment follow-up period in subjects with a history of allergic rhinitis to grass pollen.

5.1.1. Dosing and Administration

5.1.1.1. Dupilumab or Dupilumab Placebo

Dupilumab will be administered SC, as a 600 mg loading dose and then 300 mg Q2W. Dupilumab 150 mg/mL: Each single-use, pre-filled glass syringe with snap-off cap delivers 2.0 mL of a 150 mg/mL solution (300 mg).

Placebo matching dupilumab is prepared in the same formulation without the addition of protein (ie, active substance, anti-IL-4Rα monoclonal antibody).

After the loading dose, subjects will have the option to administer dupilumab or dupilumab placebo (or have a caregiver administer it) outside the study site. The study staff will train the subject/caregiver on preparation and administration of dupilumab or dupilumab placebo on day 1 and will administer the first 2 injections required for the loading dose. Subjects will be monitored at the study site for a minimum of 30 minutes after the first 2 doses of dupilumab or dupilumab placebo (loading dose) and blood pressure and heart rate determined. The subject (or caregiver) will administer dupilumab or dupilumab placebo outside of the study site during subsequent weeks of the study.

Subjects who prefer to have the study site staff administer dupilumab or dupilumab placebo may choose to have injections administered in the study site.

The procedure for preparing the dupilumab or dupilumab placebo dose for SC injection will be provided in the pharmacy manual. Subcutaneous injection sites should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms, so that the same site is not injected for 2 consecutive weeks. To allow for adequate assessment of possible injection site reactions (ISRs), dupilumab or dupilumab placebo should be administered only into areas of normal-looking skin. Instructions for recording and reporting ISRs will be provided in the study reference manual.

Detailed instructions for transport, storage, preparation, and administration of dupilumab or dupilumab placebo will be provided by the site to the subject (or caregiver). Subjects will complete a dosing diary to document compliance with self-injection of dupilumab or dupilumab placebo outside the study site.

5.1.1.2. SCIT and Placebo Matching SCIT

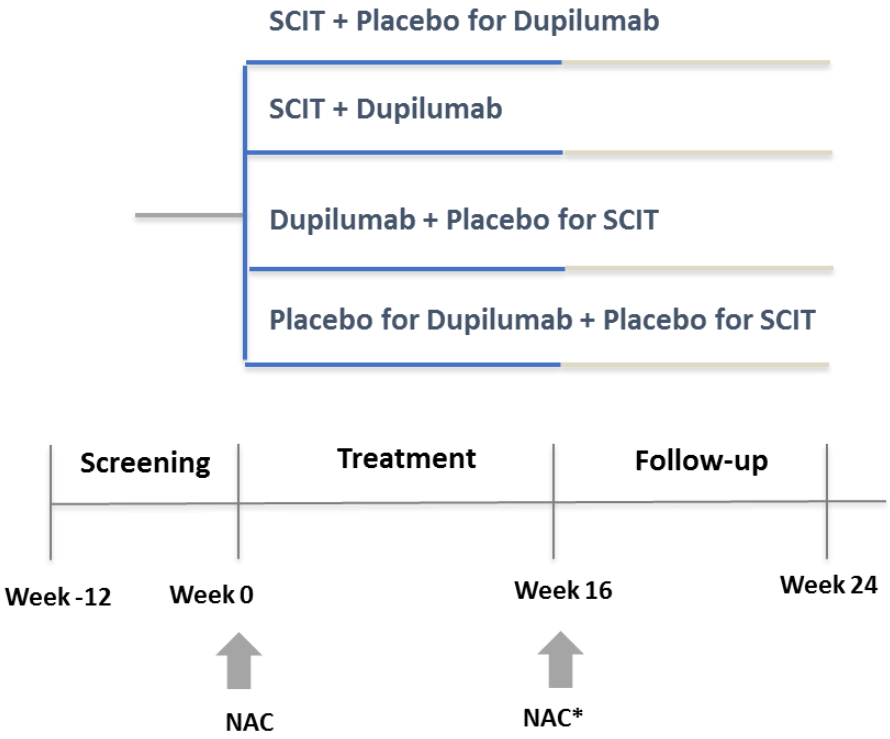
SCIT will be up-dosed for 8 weeks to a 4,000 BAU dose, followed by an 8-week maintenance dose. (See Table 1 for SCIT schedule).

Placebo matching SCIT is prepared in the same formulation (SCIT diluent) without the addition of Timothy Grass extract.

All SCIT visits will be supervised in an in-clinic study site setting where trained study physicians, who are experts in Allergy and Immunology and who are experienced SCIT providers, are present. Subjects will be observed for at least 30 minutes after any SCIT injection. Standing orders from a study physician will be provided for all clinical study personnel to immediately (ie, prior to study physician notification) initiate treatment of reactions, including but not limited to intramuscular administration of epinephrine, based on their own clinical judgment. For all SCIT visits subjects must be pre-medicated with an H1 anti-histamine

(loratadine 10 mg orally) 1-6 hours prior to each injection visit, as recommended by clinical guidelines to reduce local and systemic reactions during the cluster SCIT. (Cox, 2011) (Nielsen, 1996). Loratadine will be supplied to study sites as a non-investigational medicinal product (NIMP).

Figure 1: Study Flow Diagram



*The NAC happens after 16 weeks of study treatment at week 17.

5.2. Screening

After obtaining informed consent, subjects will be assessed for eligibility during a 3-part screening period. The 3-part screening period is up to 12 weeks. As this is an off-season study that must begin and end outside of grass season, sufficient screening time is necessary so that subjects may be enrolled efficiently. During screening visit 1, subjects with a history of allergic rhinitis to grass pollen will undergo a medical history, physical examination, SPT for Timothy Grass, and blood draw for Timothy Grass specific IgE. If the subject meets criteria with a positive SPT for Timothy Grass and for Timothy Grass specific IgE as per Inclusion/Exclusion criteria, they will be invited for screening visit 2. At screening visit 2 they will undergo a pregnancy test if applicable, spirometry, electrocardiogram (ECG), serologic testing for chronic viral infections (Human Immunodeficiency Virus Infection [HIV] and Hepatitis B and C), hematology, chemistry, urinalysis, will be evaluated for the study eligibility criteria, and will undergo a baseline nasal brushing. The baseline nasal brushing must occur while TNSS≤2 and it must be at least 28 days prior to the screening visit 3/Entry visit, so that the nasal mucosa may re-epithelialize and return to a resting state prior to NAC. If the subject reports nasal symptoms and has a TNSS>2 at Screening visit 2, they can be rescheduled for screening visit 2 when they

are no longer symptomatic- for re-evaluation by TNSS. The baseline nasal brushing should not be performed if the 28 day waiting period until the NAC will compromise the subject's ability to complete the 16 week treatment period and final week 17 NAC prior to the subsequent allergy season (eg, subjects cannot have any expected seasonal or environmental allergic symptoms at the week 17 NAC visit). If however, the full 16 week treatment period and week 17 NAC visit is expected to be completed prior to the subsequent allergy season, subjects should undergo baseline nasal brushing. Forgoing the baseline nasal brushing in this case will not be considered a protocol deviation, but the event will be recorded and justified. It is expected that subjects who are enrolled in the final month of the enrollment period, as described in the Study Operations Manual, will not undergo the baseline nasal brushing.

At screening visit 3/Entry visit (day -1), subjects may not have taken anti-histamines for at least 5 days. If the subject reports having taken anti-histamines within 5 days of Screening visit 3, they can be rescheduled for Screening visit 3.

At screening visit 3/Entry visit, subjects will be observed for approximately 10 minutes and a resting/baseline TNSS≤2 must be achieved, signifying that the subject does not have active nasal symptoms at rest (due to viral infection, sinusitis, allergies, etc.), prior to NAC. If the subject has a TNSS>2, signifying that they have active nasal symptoms at rest, they can be rescheduled for Screening visit 3. TNSS (measured on a 0-12 scale) is a composite symptom assessment of congestion, itching, rhinorrhea (each graded on 0-3 scale, 3 being severe), and sneezing (2 being 3-4 sneezes and 3 being >5 sneezes). TNSS report will be included in the Study Operations Manual.

If the subject has a resting/baseline TNSS ≤2 and therefore has no appreciable nasal symptoms at rest, a NAC and skin testing for early and late phase reactions will be performed as follows:

- NAC will be performed using increasing doses of Timothy Grass extract every 10 minutes up to 1 hour (up-titration phase), or until a TNSS ≥7 is reached. An example of concentrations are as follows: 14 BAU/ml, 41 BAU/mL, 123 BAU/mL, 370 BAU/mL, 1111 BAU/mL, and 3333 BAU/mL; please refer to the study manual for exact concentrations.
- The peak TNSS will be recorded.
- The Timothy Grass extract concentration that was used to attain TNSS ≥7 must be recorded.
- Subjects will be observed for the subsequent hour and the TNSS will be recorded at 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, and then hourly up to 6 hours.
- In addition to TNSS, the following will be measured at baseline, approximately every 10 minutes during the up-titration phase, and during the subsequent hour after peak TNSS is achieved (at 5 minutes, 15 minutes, 30 minutes, 45 minutes, and 1 hour) and hourly up to 6 hours:
    - PNIF; (measured in nasal patency, L/min)
    - Total sneezes
    - TOSS

Grass allergic subjects will be eligible for enrollment based on having a TNSS ≤2 prior to the screening NAC (time 0), peak TNSS ≥7 within the first hour during the up-titration phase. Additionally for eligibility, between the first non-zero dose of and approximately 10 minutes after the highest/peak dose, subjects must experience either a >20% drop in PNIF or >/=3 sneezes must be counted.

5.3. Randomized Treatment Period (16 Weeks)

5.3.1. Randomization

A total of 100 adult subjects with a history of allergic rhinitis to grass pollen who successfully complete screening procedures will be randomized 1:1:1:1 into the 4 treatment arms (n=25 in each arm) as follows:

1. SCIT up-titrated as described up to a 4,000 BAU maintenance dose + dupilumab (SC 300 mg Q2W, after 600 mg loading dose)
2. SCIT up-titrated as described up to a 4,000 BAU maintenance dose + placebo for dupilumab
3. Placebo for SCIT plus dupilumab (SC 300 mg Q2W, after 600 mg loading dose)
4. Placebo for SCIT plus placebo for dupilumab

Note: Randomization (visit 4) must occur within 2 weeks after NAC (visit 3)

5.3.2. Study Design Safety Considerations for SCIT

- All SCIT visits will be supervised in an in-clinic study site setting where trained study physicians are available.
- Subjects will be observed for at least 30 minutes after any SCIT injection.
- Standing orders from a study physician will be provided for all clinical study personnel to immediately (ie, prior to study physician notification) initiate treatment of reactions, including intramuscular administration of epinephrine, based on their own clinical judgment.
- A crash cart will be available in close proximity (within 50 feet) of all patient study site rooms.
- On days when SCIT or placebo SCIT are given, subjects must be pre-medicated with an H1 anti-histamine (loratadine 10 mg orally) 1-6 hours prior to each injection visit, as recommended by clinical guidelines to reduce local and systemic reactions during cluster SCIT (Cox, 2011) (Nielsen, 1996). Loratadine will be supplied to study sites as a NIMP.
- Patients will be dosed Q2W SC with dupilumab or placebo for dupilumab on separate days from the study-site SCIT or placebo for SCIT dose escalation.
- SCIT dosing related allergic symptoms and adverse events will be captured throughout the study.

5.4. Post-Treatment Follow-up Period (8 Weeks):

All subjects who complete or prematurely discontinue the treatment will be assessed for safety, laboratory, and clinical assessments as noted in the Schedule of Events (Table 3) 8 weeks after the end-of-treatment.

The duration of the 8-week follow-up period is based on the time expected for drug concentrations to approach the lower limit of quantification after the last dose of dupilumab.

5.5. End of Study Definition

The end of study is defined as the last visit of the last subject.

5.6. Planned Interim Analysis

No interim analysis is planned. An unblinded first-step analysis may be performed once all subjects in the study have completed the 16-week treatment period and performed NAC at week 17 as specified in the protocol (visit 16 or earlier for those subjects who are withdrawn prematurely from the study). If performed, this first-step analysis will be considered the final analysis for the primary endpoint and secondary efficacy endpoints up to end of treatment NAC visit 16 (week 17). A description of the statistical methods to be employed and blinding implications are in Section 10.4.3.4.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF SUBJECTS

6.1. Number of Subjects Planned

Approximately 100 subjects will be randomized (25 per treatment group) at approximately 20 planned sites in North America in geographies where Timothy Grass is the relevant grass species.

6.2. Study Population

6.2.1. Inclusion Criteria

A subject must meet the following criteria to be eligible for inclusion in the study:

1. Male and female subjects aged 18 to 55
2. History of grass pollen–induced seasonal allergic rhinitis
3. Grass pollen allergy confirmed by both:
    a. Positive SPT with Timothy Grass extract (mean wheal diameter at least ≥5 mm greater than a negative control)
    b. Positive serum Timothy Grass-specific IgE (≥0.35KU/L)
4. Positive NAC with Timothy Grass extract at screening with peak TNSS score ≥7 out of 12
5. Between the first non-zero dose and approximately 10 minutes after the highest dose of NAC, participants must experience either a >20% drop in PNIF or >/=3 sneezes must be counted

6. Provide informed consent signed by study subject
7. Able to understand and complete study-related questionnaires
8. Willing and able to comply with study site visits and study-related procedures

6.2.2. Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Significant rhinitis (causing TNSS >2), sinusitis, outside of the grass pollen season, or due to daily contact with other allergens causing symptoms that is expected to coincide with the baseline or the final NAC assessments as assessed by the investigator
2. Subjects who anticipate major changes in allergen exposure in their home or work environments that are expected to coincide with the baseline or the final NAC assessments as assessed by the investigator
3. At screening NAC, 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.
4. Any contraindications to SCIT (ie, severe cardiovascular disease, malignancies, autoimmune disease, use of beta blocker, asthma severe enough to require chronic medication, acute infection)
5. Patients with any laboratory findings showing evidence of organ dysfunction or any clinically significant deviation from the normal range, as decided by the investigator at the screening visit, including but not limited to:

    - Clinically significant/active underlying hepatobiliary disease.

        OR,

    - Alanine aminotransferase (ALT) >3 upper limit of normal (ULN).

    Abnormal laboratory values at screening:

    - Creatine phosphokinase (CPK) >10 ULN

        OR,

    - Platelets <100 000 cells/mm^3.

        OR,

    - Eosinophils >1500 cells/mm^3.

6. Use of any concomitant medications within the following time period preceding any screening visit or any screening NAC visit (visit 3) including antihistamines (5 days), leukotriene inhibitors (7 days), mast cell inhibitors (7 days), intranasal corticosteroids and/or inhaled corticosteroids (14 days), oral or topical decongestants (5 days), topical calcineurin inhibitors (4 weeks), beta blockers (5 days). Participants may be re-evaluated for eligibility after the time period for taking these concomitant medications has passed.

7. Use of systemic corticosteroids within 4 weeks of screening visits or any NAC visits
8. Abnormal lung function as judged by the investigator with FEV_1<80% of predicted
9. A clinical history of asthma requiring chronic medication such as regular inhaled corticosteroids for >4 weeks per year
10. A clinical history of asthma with 2 or more asthma exacerbations requiring hospitalizations or systemic corticosteroids in the previous year
11. History of emergency visit or hospital admission for asthma in the previous 12 months
12. History of significant recurrent sinusitis, defined as 3 episodes per year for the last 2 years, all of which required antibiotic treatment
13. History of chronic sinusitis (with or without nasal polyps) as defined as: presence of 2 or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
    - ± facial pain/pressure;
    - ± reduction or loss of smell;
    - for ≥12 weeks;
14. Any gross mechanical nasal obstruction, or history of nasal or sinus surgery that would interfere with the conduct of the NAC, as per judgment of the investigator
15. Tobacco smoking (ANY) within the last year
16. Any history of grade 4 anaphylaxis due to any cause as defined by the Common Terminology Criteria for Adverse Events (CTCAE) grading criteria for immunotherapy (Appendix 1)
17. History of chronic obstructive pulmonary disease
18. History of other chronic disease (other than asthma, atopic dermatitis, allergic rhinitis) requiring therapy (eg, heart disease, diabetes, hypertension) that, in the opinion of the investigator, would represent a risk to the subject's health or safety in this study or the subject's ability to comply with the study protocol
19. History of previous allergy immunotherapy (SCIT, sublingual immunotherapy, or oral immunotherapy) in the last 5 years
20. Any previous exposure to dupilumab
21. Treatment with an investigational drug within 2 months or within 5 half-lives (if known), whichever is longer, prior to screening
22. Member of the clinical site study team or his/her immediate family
23. Known or suspected immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency, or prolonged infections suggesting an immune-compromised status, as judged by the investigator

24. History of patient-reported alcohol or drug abuse within 6 months prior to screening
25. History of bleeding disorders or treatment with anticoagulation therapy
26. Subjects tested positive for HIV antibody, Hepatitis B surface antigen, or Hepatitis C antibody
27. Use of anti-IgE therapy within 6 months prior to screening.
28. Treatment with a live (attenuated) vaccine within 3 months prior to screening and during the study.
29. Active chronic or acute infection requiring systemic treatment with antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks prior to the screening visit. NOTE: subjects may be rescreened after the infection resolves.
30. History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.
31. Established diagnosis of a primary immunodeficiency disorder (eg, Severe Combined Immunodeficiency, Wiskott Aldrich Syndrome, DiGeorge Syndrome, X-linked Agammaglobulinemia, Common Variable Immunodeficiency), or secondary immunodeficiency eg, HIV.
32. Pregnant or breastfeeding women, women planning to become pregnant or breastfeed during the study
33. Women of child bearing potential* who are not sexually abstinent and are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 12 weeks after the last dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening;
    b. intrauterine device (IUD); intrauterine hormone releasing system (IUS);
    c. bilateral tubal ligation;
    d. vasectomized partner;
    e. and or sexual abstinence †, ‡.

    *Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

    †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 subject.

‡Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

34. Subjects unable to understand and comply with clinical protocol
35. Planned or anticipated use of any prohibited medications and procedures (as detailed in Section 7.7.1) during study treatment
36. Adults lacking capacity to consent themselves into the study.

6.3. Premature Withdrawal from the Study

A subject has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a subject from the study if it is no longer in the interest of the subject to continue in the study, or if the subject's continuation in the study places the scientific outcome of the study at risk (eg, if a subject does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided.

Subjects who are withdrawn prematurely from the study treatment will be asked to complete study assessments, as described in Section 8.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 7.3.2.

6.4. Replacement of Subjects

Subjects prematurely discontinued from study drugs (SCIT or placebo for SCIT and dupilumab or placebo for dupilumab) will not be replaced.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

7.1.1. Dupilumab Injection: Investigational Treatment

Dupilumab at 300 mg Q2W with loading dose of 600 mg or equivalent placebo will be started on the day of randomization. Dupilumab will be dosed as follows: subjects will be given a loading dose of 600 mg dupilumab SC or placebo, followed by 300 mg Q2W SC for a total of 16 weeks.

Dupilumab 150 mg/mL: Each single-use, prefilled glass syringe with snap-off cap delivers 300 mg of study drug (2.0 mL of a 150 mg/mL solution).

Placebo matching dupilumab is prepared in the same formulation without the addition of protein (ie, active substance, anti-IL-4Rα monoclonal antibody). The matching placebo formulation will be used: 2 mL placebo matching 300 mg dupilumab formulation.

Subcutaneous injection sites of dupilumab or placebo for dupilumab should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site is not injected for 2 consecutive administrations.

Instructions on dose preparation are provided in the pharmacy manual.

7.1.2. Timothy Grass SCIT: Reference Treatment

Timothy Grass SCIT will be given using cluster dose escalation regimen over 8 weeks then maintenance therapy will be given described below. SCIT will be started no earlier than 1 day after the dupilumab loading dose and up to 1 week after the dupilumab loading dose. Dosing of dupilumab should never be performed on the same day and administration site as SCIT.

The Grass SCIT protocol will comprise 1-3 SC injections per week visit of allergen following the up-titration regimen described below over 8 weeks followed by the maintenance SC injections for the following 8 weeks as shown in Table 1. The recommended target maintenance dose for SCIT is 4,000 bioequivalent allergy units (BAU) (Table 1), which is equivalent to approximately 20 mcg *Phlem Pratense 5* (major Timothy Grass allergen) (Cox, 2011) (Frew, 2006b). During weeks 1-3 of the up-dosing phase, 3 doses of SCIT will be given per visit: the first (lowest dose for that visit) will be given, the subject will be monitored for 30 minutes, and if the dose is well tolerated, the next higher scheduled dose for that visit will be given. The subject will then be monitored for the next 30 minutes, and if the dose is well tolerated, the next higher scheduled dose for that visit will be given. During weeks 4-5 of the up-dosing phase, 2 doses of SCIT will be given: the first (lowest dose for that visit) will be given, subject will be monitored for 30 minutes, and if the dose is well tolerated, the next higher scheduled dose for that visit will be given. During weeks 6-8 of the up-dosing phase, 1 dose of SCIT will be given. During the maintenance phase, one dose will be given per visit as per Table 1.

Placebo SCIT will be given in the same manner as the Grass SCIT, following the same protocol, but instead of active agent, diluent will be given. The Placebo SCIT will have an identical appearance to the Grass SCIT. The first (lowest dose for that visit) will be given, the subject will be monitored for 30 minutes, and if the dose is well tolerated, the next higher scheduled dose for that visit will be given.

On days when SCIT or placebo SCIT are given, subjects must be pre-medicated with an H1 anti-histamine (loratadine 10 mg orally) 1-6 hours prior to each injection visit, as recommended by clinical guidelines to reduce local and systemic reactions during cluster SCIT. (Cox, 2011) (Nielsen, 1996). Reactions associated with SCIT or SCIT placebo should be recorded as AEs (Section 9.5), and attributed to SCIT or SCIT placebo or as interpreted by the study investigator (Section 9.5).

Table 1: SCIT Up-Titration and Maintenance Regimen

Week No	Injection No	Subcutaneous Dose of SCIT (BAU)
1	1	1
1	2	4
1	3	10
2	4	20
2	5	40
2	6	70
3	7	100
3	8	150
3	9	250
4	10	400
4	11	700
5	12	1000
5	13	1500
6	14	2000
7	15	3000
8	16	4000
10	17	4000
13	18	4000
16	19	4000

7.1.3. Timing of Dupilumab/placebo and SCIT/placebo

Dupilumab dosing starts prior to SCIT dosing as shown in Table 2. Dupilumab/placebo are never to be given on the same day as SCIT/ placebo.

Table 2: Dosing Schedule for Dupilumab/Placebo with Respect to SCIT/Placebo

Dose	Dupilumab/Placebo[1]	SCIT/Placebo
NAC		
Randomization (V4)	X[2]	
Week 1		X[3, 5]
Week 2	X[4]	X[5]
Week 3		X[4, 5]
Week 4	X[4]	X[5]
Week 5		X[4, 5]
Week 6	X[4]	X[5]
Week 7		X[4, 5]
Week 8	X[4]	X[5]
Week 9		
Week 10	X[4]	X[5]
Week 11		
Week 12	X[4]	
Week 13		X[4, 5]
Week 14	X[4]	
Week 15		
Week 16	X[4]	X[5]
NAC		

1. Dupilumab/placebo dosing must given ± 3 days of the visit window.
2. Dupilumab or placebo for dupilumab loading dose is given day of randomization. Subsequent dupilumab/placebo dosing is given Q2W
3. SCIT/placebo should be given 1 to 7 days following dupilumab/dupilumab placebo loading dose. Subsequent SCIT/placebo dosing follows dosing regimen as depicted in Table 1.
4. During week 2, week 4, week 6, week 10, and week 16, when both dupilumab/placebo and SCIT/placebo are given in the same week, SCIT/placebo and dupilumab/placebo are NOT to be given on the same day (can be 1 day to 7 days apart) AND SCIT/placebo and dupilumab/placebo are to be given in a different anatomical location.
5. For SCIT/placebo visits, subjects are to be premedicated with an antihistamine as described in Section 5.1.1.2.

7.2. Rescue Treatments

If required, subjects who experience allergic reactions will be treated with rescue treatment including but not limited to IM or SC administration of epinephrine, as determined by trained study staff. Subjects may also take oral antihistamines as needed for allergic rhinitis symptoms during the course of the study, however oral antihistamines may not be used within 5 days prior to or during a visit for NAC or skin testing. If subject uses oral antihistamines within 5 days prior to or during a visit for NAC or skin testing they must be rescheduled.

7.3. Dose Modification and Study Treatment Discontinuation Rules

7.3.1. Dose Modification

Dose modification of dupilumab or dupilumab placebo is not allowed.

Dose modification/reduction of SCIT is allowed for an individual subject according to the following specifications:

> Subjects who develop either local or systemic side effects after an up-dosing visit of SCIT may require administration of the same dose at the next visit, a dosage reduction at the next visit, or a planned series of visits to achieve the same dose, as determined by the principal investigator.

If subjects develop side effects during the up-dosing phase of SCIT, such as repeated large immediate local reactions or grade 1-2 systemic reactions requiring dosage adjustments, the principal investigator (PI), in consultation with the medical monitor, may decide to reduce the planned maintenance dose of SCIT of 4000 BAU down to between 400 BAU and 4000 BAU but no lower than 400 BAU.

7.3.2. Study Drug Discontinuation (Dupilumab or Placebo for Dupilumab and SCIT or Placebo for SCIT)

If one study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) is discontinued, all study drugs (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) must be discontinued.

Subjects who permanently discontinue from study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) and who do not withdraw from the study will be asked to return to the study site within 2 weeks of stopping study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT), if possible, to undergo their end of treatment visit, including NAC. Anti-histamines may not be taken within 5 days of NAC.

Subjects who permanently discontinue from study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) and who opt to withdraw from the study will be asked to complete study assessments as per end of treatment visit immediately, within 2 weeks of stopping study drug **(**dupilumab or placebo for dupilumab and SCIT or placebo for SCIT), if possible, including NAC, per Section 8.1.2.

7.3.3. Reasons for Permanent Discontinuation of Study Drug (Dupilumab or Placebo for Dupilumab and SCIT or Placebo for SCIT)

Subjects will be permanently discontinued from study treatment in the event of:

- Anaphylactic reaction to study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT)
- Evidence of pregnancy
- Any infection that:
  - Requires parenteral treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agent
  - Requires oral treatment with such agents for longer than 2 weeks
  - Is opportunistic, such as tuberculosis and other infections whose nature or course may suggest an immunocompromised status
- Severe laboratory abnormalities, such as:
  - Neutrophil count $\leq 0.5 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$
    - ALT and/or aspartate aminotransferase (AST) values >3 x ULN with total bilirubin >2 x ULN, excluding confirmed Gilbert's Syndrome
  - Confirmed AST and/or ALT >5 x ULN (for more than 2 weeks)
- Other reasons that may lead to the permanent discontinuation of study treatment include:
  - Certain AEs deemed related to the study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) (eg, severe and prolonged ISRs) or study procedures

7.3.3.1. Reasons for Temporary Discontinuation of Study Drug (Dupilumab or Placebo for Dupilumab and SCIT or Placebo for SCIT)

Study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) dosing may be temporarily suspended in the event of:

- Clinically important laboratory abnormalities, such as:
  - Neutrophil count $\leq 1.0 \times 10^3/\mu L$ but $>0.5 \times 10^3/\mu L$
  - Platelet count $\leq 100 \times 10^3/\mu L$ but $>50 \times 10^3/\mu L$
  - CPK >10 ULN
- Short-term, self-limiting conditions (eg, infections resolving spontaneously or requiring ≤2 weeks of oral anti-infective treatment), with the exception of upper respiratory infections
- Other intercurrent illnesses

After the condition leading to suspension of dosing resolves, study treatment may resume.

A decision to temporarily discontinue study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) and/or to reinstitute study treatment should be discussed with the medical monitor. The investigator may suspend study treatment at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the subject's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation. Resumption of study treatment after temporary discontinuation requires consultation and agreement between the investigator and the medical monitor. In the case of SCIT or placebo for SCIT, if it was temporarily discontinued during the up-dosing phase, the investigator may need to modify the up-dosing regimen at his/her discretion and will inform the medical monitor of any modification of the up-dosing regimen.

7.4. Management of Acute Reactions

7.4.1. Acute Injection Reactions

7.4.1.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. All systemic reactions must be reported as AEs (as defined in Section 9.4.1) and graded using the grading scales as instructed in Section 9.5.1.

Acute systemic reactions following injection of either dupilumab/placebo or SCIT/placebo should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

7.5. Method of Treatment Assignment

Approximately 100 subjects will be randomized at baseline in a 1:1:1:1 ratio into one of 4 treatment arms (n=25/arm) described in Section 5.3.1 according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee).

7.5.1. Blinding

With the exception of the designated study pharmacist(s)/designee at the study site who prepares and gives the SCIT or SCIT placebo, and the provisions in Section 7.5.2 , this study will remain blinded to all individuals until the pre-specified unblinding to conduct the primary analyses.

The designated study pharmacist(s)/designee at the study site who prepares and gives the SCIT or SCIT placebo may not perform the NAC and nasal and skin assessments (outcome measures).

For dupilumab and placebo for dupilumab, blinded study drug kits coded with a medication numbering system will be used. In order to maintain the blind, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct.

Dupilumab anti-drug antibody and drug concentration results will not be communicated to the sites, and the sponsor operational team will not have access to results associated with patient identification until after the final database lock.

7.5.2. Emergency Unblinding

Unblinding of treatment assignment for a subject may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy).

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected subjects will be unblinded.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the subject
  - The investigator will notify Regeneron and/or designee before unblinding the subject, whenever possible

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

7.6. Treatment Logistics and Accountability

7.6.1. Packaging, Labeling, and Storage

Dupilumab/dupilumab placebo: A medication numbering system will be used to label blinded dupilumab/dupilumab placebo. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

SCIT and SCIT placebo (SCIT diluent) will display the product lot number on the label.

Both study drug dupilumab/ dupilumab placebo, and SCIT/SCIT placebo will be stored at the site [redacted] storage instructions will be provided in the pharmacy manual.

7.6.2. Supply and Disposition of Treatments

Study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) will be shipped [redacted] to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) will be returned to the sponsor.

7.6.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT). These records should contain the dates, quantity, and study medication:

- dispensed to each subject,
- returned from each subject (if applicable), and
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

7.6.4. Treatment Compliance

All study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

7.7. Concomitant Medications and Procedures

Any treatment administered from the time of informed consent to the time before the administration of study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) will be recorded as pretreatment medication. Any treatment administered from the first dose of study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) to the end of the follow-up period will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

The NIMP loratadine that is given before each SCIT (or placebo for SCIT) dose will also be recorded as a concomitant medication.

7.7.1. Prohibited Medications (After Randomization) and Procedures

Prohibited medications are not to be used after randomization except as noted in Section 7.2. Treatment with prohibited medications is allowed during the study if medically necessary as judged by the investigator (ie, as needed for allergic symptoms related to SCIT or SCIT placebo or related to study procedures).

Use of leukotriene inhibitors, mast cell inhibitors, corticosteroids including systemic, intranasal, or inhaled corticosteroids, oral or topical decongestants, systemic or topical calcineurin inhibitors, beta blockers, long-acting beta agonist (LABA), and long-acting muscarinic antagonist (LAMA) will be prohibited for the duration of the study.

7.7.2. Permitted Medications and Procedures

Use of standard of care medications not listed as prohibited will be allowed. Antihistamines will be allowed during the study with the exception of within 5 days of and including the day of NAC.

8. STUDY SCHEDULE OF EVENTS AND PROCEDURES

8.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 3.

Table 3: Schedule of Events

	Screening Period				Treatment Period														
Study Procedure	**V1**	**V2**	**NAC V3**	**R[1] V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**EOT NAC V16**	**V17**	**Unscheduled Visit (if applicable)[13]**	**EOS V18**	**ET**
Week (W)					**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**13**	**16**	**17**	**20**		**24**	
Study Day	**+1 to -84**			**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**71**	**92**	**113**	**120**	**141**		**169**	
Window in Weeks	**±1**				**-1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**		**±3[18]**	
Screening/Baseline																				
Inclusion/Exclusion	X	X	X	X																
Informed Consent	X																			
[redacted]	X																			
Medical History	X																			
Demographics	X																			
Randomization (R)				X																
SPT for Timothy Grass	X																			
Serum Timothy Grass sIgE	X																			
Treatment:																				
Dupilumab/ PBO loading[2]				X																
Dupilumab 300 mg q 2 weeks dosing[2, 3]						X	←----------X----------→											X		
Visit for SCIT Injections[4, 5,]					X	X[5]	X	X[5]	X	X[5]	X	X	X[5]	X	X[5]			X		
Premedicate with loratadine 10 mg orally[6]					X	X	X	X	X	X	X	X	X	X	X			X		
Training for Self-injection (dupilumab/PBO)				X																
Dupilumab/PBO distribution				X		X						X		X				X		

	Screening Period				Treatment Period															
Study Procedure	**V1**	**V2**	**NAC V3**	**R[1] V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**EOT NAC V16**	**V17**	**Unscheduled Visit (if applicable)[13]**	**EOS V18**	**ET**
Week (W)					**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**13**	**16**	**17**	**20**		**24**	
Study Day	**+1 to -84**			**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**71**	**92**	**113**	**120**	**141**		**169**	
Window in Weeks	**±1**				**-1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**		**±3[18]**	
Dupilumab/PBO diary review/ Accountability[7]						←----------X----------→												X		X
Subject Dosing Diary[8]				X		X		X		X		X	X	X				X		X
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:																				
TNSS		X	X											X		X				X
TOSS			X													X				X
PNIF			X													X				X
Intradermal skin challenge testing (LPR)			X													X				X
Skin Prick Test with Serial Allergen Titration (EPR)			X													X				X
Safety:																				
Weight	X		X													X		X		X
Height	X																			
Vital Signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X		X													X		X	X	X
Spirometry		X																X		
ECG		X														X		X	X	X
Peak expiratory flow[9]		X	X													X		X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing																				
HIV Ab, HBsAg, HBcAb, Hep C Ab,		X																X		

	Screening Period				Treatment Period															
Study Procedure	**V1**	**V2**	**NAC V3**	**R[1] V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**EOT NAC V16**	**V17**	**Unscheduled Visit (if applicable)[13]**	**EOS V18**	**ET**
Week (W)					**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**13**	**16**	**17**	**20**		**24**	
Study Day	**+1 to -84**			**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**71**	**92**	**113**	**120**	**141**		**169**	
Window in Weeks	**±1**				**-1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**		**±3[18]**	
Hematology, Chemistry		X						X				X		X		X	X	X	X	X
Urinalysis		X						X				X		X		X	X	X	X	X
Pregnancy Test if indicated [in WOCBP]		X[14]		X[15]				X[15]				X[15]		X[15]		X[15]	X[15]	X[15]	X[14]	X[14]
Nasal mucosal brushing[10]		X[16]	X											X[17]		X				X
Nasal fluid collection			X													X				X
Future Biomedical Research:																				
Research serum[11, 12]			X	X		X		X		X		X		X		X			X	X
Research plasma[11, 12]			X	X		X		X		X		X		X		X			X	X
[redacted]			X																	
Biomarker:																				
Blood for basophil sensitivity assays, Th2A profiling and PBMC banking[11]			X													X				X
SerumTARC[11]			X	X				X				X		X		X	X		X	X
Serum total IgE[11]			X	X		X		X		X		X		X		X	X		X	X
Serum Timothy Grass sIgE[11]			X	X		X		X		X		X		X		X	X		X	X

	Screening Period				Treatment Period															
Study Procedure	**V1**	**V2**	**NAC V3**	**R[1] V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**EOT NAC V16**	**V17**	**Unscheduled Visit (if applicable)[13]**	**EOS V18**	**ET**
Week (W)					**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**13**	**16**	**17**	**20**		**24**	
Study Day	**+1 to -84**			**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**71**	**92**	**113**	**120**	**141**		**169**	
Window in Weeks	**±1**				**-1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**		**±3[18]**	
Serum Timothy Grass sIgG4[11]			X	X		X		X		X		X		X		X	X		X	X
Drug Concentration and ADA:																				
Functional dupilumab PK[11, 12]			X						X			X		X		X	X		X	X
Anti-drug antibody[11, 12] (ADA)			X													X			X	X

8.1.1. Footnotes for the Schedule of Events Table

1. Randomization (V4) must occur within 2 weeks of NAC (V3)
2. Dupilumab or placebo for dupilumab loading dose is given day of randomization. Subsequent dupilumab/placebo dosing is given Q2W.
3. Dupilumab/placebo dosing must be given ±3 days of the visit window.
4. SCIT/placebo should be given 1 to 7 days following dupilumab/placebo loading dose. Subsequent SCIT/placebo dosing follows dosing regimen as depicted in Table 1.
5. During week 2, week 4, week 6, week 10, and week 16, when both dupilumab/placebo and SCIT/placebo are given in the same week, SCIT/placebo and dupilumab/placebo are NOT to be given on the same day (can be 1 day to 7 days apart) AND SCIT/placebo and dupilumab/placebo are to be given in a different anatomical location.
6. For SCIT/placebo visits, subjects are to be premedicated with an antihistamine as described in Section 5.1.1.2
7. Starting at visit 4, study drug will be dispensed to the subject for the dose that will be administered before the next dupilumab/placebo distribution visit. Subjects will return the original kit box at each dupilumab/placebo distribution visit for accountability
8. For subjects who choose to self-administer study drug, counsel subject on proper dosing diary completion/reporting of each dose of study drug that is administered outside of the study site
9. Peak expiratory flow will be measured prior to NAC in any subject with a history of asthma. Peak expiratory flow must be >80% predicted to perform the NAC in any subject with a history of asthma (please refer to the peak flow meter chart in the Study Operations Manual as a reference of predicted peak expiratory flow values)
10. Collected 6 hours post NAC
11. Collected pre-NAC
12. Serum samples to be collected for ADA and PK assessments, prior to dosing of dupilumab at timepoints indicated in the Schedule of events
13. Assessments and procedures at the unscheduled visit are to be performed at the discretion of the principal investigator
14. Serum pregnancy test
15. Urine pregnancy test
16. Baseline nasal brushing and nasal brushing on study drug (which is performed at least 28 days before the final NAC) will not be performed if they interfere with the subject's timely completion of the study (prior to the onset of the subsequent allergy season) as outlined in the Study Operations Manual
17. Should be performed approximately 28 days before the final NAC

18. The visit should be conducted as close as possible to the designated study schedule date and the window for the days used only as needed.

8.1.2. Early Termination Visit

Subjects who are withdrawn from the study treatment before the primary endpoint visit (week 17) will be asked to return to the study site once for an early termination visit consisting of the end of treatment assessments described in Table 3, which includes an end of treatment NAC. Subjects should return as soon as possible for the end of treatment assessment, so that the NAC assessment may be performed while study drug(s) (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) were recently administered. Subjects who are withdrawn from the study treatment after the primary endpoint visit will be asked to return to the study site for early termination assessments, including NAC.

8.1.3. Unscheduled Visits

All attempts should be made to keep subjects on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

8.2. Study Procedures

8.2.1. Efficacy Procedures

A variety of parameters will be collected during the study to assess efficacy/effectiveness of dupilumab monotherapy, SCIT monotherapy, dupilumab + SCIT, and placebo.

Questionnaires and subject-reported assessments should be administered prior to obtaining investigator assessments, safety and laboratory assessments, and study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) administration.

Please see Study Operations Manual for detailed instructions on the procedures and the administration and use of all subject-reported instruments.

8.2.1.1. NAC and NAC assessments: TNSS, TOSS, PNIF, and Total Sneezes

The NAC and NAC assessments will be administered by study site personnel as noted in Table 3.

At the week 17 NAC on study drugs (dupilumab or placebo for dupilumab and SCIT or placebo), subjects may not have taken anti-histamines for at least 5 days. If the subject reports having taken anti-histamines within 5 days of the final NAC, they can be rescheduled for the week 17 visit so long as they have not taken anti-histamines within 5 days of the visit.

TNSS

At the end of treatment NAC (week 17), subjects will be observed for approximately 10 minutes and a resting/baseline TNSS ≤2 must be achieved, signifying that the subject does not have active nasal symptoms at rest (due to viral infection, sinusitis, allergies, etc.), prior to NAC. TNSS (measured on a 0-12 scale) is a composite symptom assessment of congestion, itching, rhinorrhea (each graded on 0-3 scale, 3 being severe), and sneezing (2 being 3-4 sneezes and

3 being >5 sneezes. TNSS report will be included in the Study Operations Manual. If the subject has a resting/baseline TNSS≤2 and therefore has no appreciable nasal symptoms at rest, a NAC will be performed. The NAC will be performed using increasing doses of Timothy Grass extract every 10 minutes, with TNSS score recorded approximately every 10 minutes (up-titration symptom score), up until they reach the concentration of Timothy Grass extract that was used to achieve a Total Nasal Symptom Score (TNSS) ≥7 at their baseline NAC visit. This TNSS score will be recorded. After recording the TNSS attained using concentration of Timothy Grass extract that was used to achieve a Total Nasal Symptom Score (TNSS) ≥7 at their baseline NAC visit, the subject will be observed for the subsequent hour and the TNSS will be recorded at 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, and then hourly up to 6 hours.

TOSS

TOSS (measured on a 0-3 scale, 3 being severe) is a composite symptom assessment of ocular symptoms (Itchy, Red, tearing [eyes watering], and swelling [puffy eyes] (see TOSS report in Study Operations Manual). The TOSS score will be recorded during the NAC assessments. The TOSS score will be recorded approximately every 10 minutes (up-titration symptom score), up until they reach the concentration of Timothy Grass extract that was used to achieve a TNSS ≥7 at their baseline NAC visit. This TOSS score will be recorded. The subject will be observed for the subsequent hour and the TOSS score will be recorded at 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, and then hourly up to and at 6 hours as noted in Table 3.

PNIF

Peak nasal inspiratory flow (measured in nasal patency, L/min) will be measured and recorded approximately every 10 minutes during the uptitration phase of the NAC and will be measured and recorded during the subsequent hour after peak TNSS is achieved (at 5 minutes, 15 minutes, 30 minutes, 45 minutes, and 1 hour) and hourly up to an at 6 hours as noted in Table 3.

Total Sneezes

Total sneezes will be counted and recorded during the uptitration phase and during the hour after peak TNSS is achieved.

8.2.1.2. Skin Prick Test with Serial Allergen Titration

The SPT with serial allergen titration assesses the early phase reaction at 0-60 minutes. It will be performed as noted in Table 3.

8.2.1.3. Intradermal Allergen Injection

The intradermal allergen injection assesses late phase reaction from 6-24 hours. It will be performed as noted in Table 3.

8.2.1.4. Nasal Brushing

Nasal Brushings at Baseline and at Approximately 12 Weeks on Study Drugs.

The nasal brushing procedure will be performed at baseline, approximately 28 days prior to the initial NAC visit. The baseline nasal brushing must occur while TNSS ≤2 and it must be at least 28 days prior to the screening visit 3/Entry visit, so that the nasal mucosa may re-epithelialize and return to a resting state prior to NAC. If the subject reports nasal symptoms and has a TNSS>2 at Screening visit 2, they can be rescheduled for screening visit 2 when they are no longer symptomatic- for re-evaluation by TNSS. The baseline nasal brushing should not be performed if the 28 day waiting period until the NAC will compromise the subject's ability to complete the 16 week treatment period and final 17 week NAC prior to the subsequent allergy season (eg, subjects cannot have any expected seasonal or environmental allergic symptoms at the week 17 NAC visit). If however, the full 16 week treatment period and 17 week NAC visit is expected to be completed prior to the subsequent allergy season, subjects should undergo baseline nasal brushing. Forgoing the baseline nasal brushing in this case will not be considered a protocol deviation, but the event will be recorded and justified. It is expected that subjects who are enrolled in the final month of the enrollment period, as described in the Study Operations Manual, will not undergo the baseline nasal brushing.

Nasal Brushings after NAC: At Screening Visit 3/Entry Visit Prior to Randomization and at Week 17 Visit on Study Drug Must be Performed on All Subjects.

The required nasal brushings will occur 6 hours after NAC at screening visit 3/Entry visit and will occur 6 hours after NAC at the week 17 visit on study drug.

8.2.1.5. Nasal Fluid Collection

Nasal fluid is collected during the 2 NAC study visits to determine the levels of cytokines and chemokines produced in response to NAC. Nasal fluid is collected (1) at the initial NAC visit: at baseline prior to NAC and over the course of 6 hours after NAC and (2) at the 17 week (on study drug) NAC visit at baseline prior to NAC and over the course of 6 hours after NAC.

8.2.2. Safety Procedures

8.2.2.1. Vital Signs

Vital signs, including temperature, sitting blood pressure, pulse, and respiration will be collected predose at time points according to Table 3.

8.2.2.2. Physical Examination

A thorough and complete physical examination will be performed at time points according to Table 3. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the subject's medical history.

8.2.2.3. Electrocardiogram

A standard 12-lead ECG will be performed at time points according to Table 3. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT (identify QTcB or QTcF) intervals will be recorded. The ECG strips or reports will be retained with the source.

8.2.2.4. Spirometry

Spirometry will be performed in all subjects. If subjects have asthma and use short acting medications, the following instructions must be followed: after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, FEV1, forced vital capacity (FVC) and forced expiratory flow at 25% to 75% of forced vital capacity (FEF 25-75) will be determined at screening visit 2.

8.2.2.5. Peak Expiratory Flow

Peak expiratory flow will be measured using a peak flow meter (L/min) in any subject with a history of asthma prior to NAC on the day of the NAC. Peak expiratory flow must be >80% predicted to perform the NAC in any subject with a history of asthma. Detailed instructions for peak expiratory flow are included in the Study Operations Manual.

8.2.2.6. Laboratory Testing

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at visits according to Table 3. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Total cholesterol*
Chloride	Blood urea nitrogen (BUN)	Triglycerides
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

*(low-density lipoprotein [LDL] and high-density lipoprotein [HDL])

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Other Laboratory Tests

HIV Ab, HBsAg, HBcAb, and Hep C Ab will be performed at screening visit 2.

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 9.4.5.

8.2.3. Drug Concentration and Measurements

Samples for drug concentration will be collected at time points listed in Table 3.

[redacted].

8.2.4. Anti-Drug Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Table 3.

[redacted].

8.2.5. Pharmacodynamic and Biomarker Procedures

8.2.5.1. Biomarker Sample collections

Biomarker samples will be collected at time points according to Table 2. Biomarker measurements (TARC, total IgE, Timothy Grass specific IgE, Timothy Grass specific IgG4) will be performed in serum or plasma to determine effects on biomarkers of relevant physiological and pathogenic processes.

Biomarker results will be used to better understand the pathophysiology of Timothy Grass allergy, mechanism of action of dupilumab and possible toxicities. In addition to the circulating biomarkers above, transcriptome sequencing of nasal mucosa after NAC, cytokine/chemokine measurements in nasal secretions, basophil allergen sensitivity and Th2A assays will be performed.

[redacted]

[redacted]

9. SAFETY DEFINITIONS, REPORTING, AND MONITORING

9.1. Obligations of Investigator

The investigator must promptly report to the Institutional Review Board (IRB)/Ethics Committee (EC) all unanticipated problems involving risks to subjects, according to local regulations. This may include death from any cause and all serious adverse events (SAEs) related to the use of the study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT). It is recommended that all SAEs be reported to the IRB/EC, according to local regulations.

9.2. Obligations of Sponsor

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, IECs/IRBs as appropriate, and to the investigators (in a blinded manner).

Any AE not listed as an expected event in the Reference Safety Information section of the Investigator's Brochure will be considered as unexpected. Any worsening of or new onset of allergy symptoms related to the nasal allergen challenge which occur during the screening period prior to study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) administration will be considered expected (Section 9.4.1).

In addition, the sponsor will report all other SAEs to the health authorities, according to local regulations.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the clinical study report to health authorities and IECs/IRB as appropriate.

9.3. Definitions

9.3.1. Adverse Event

An AE is any untoward medical occurrence in a subject administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

9.3.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a subject is a passenger).
- Is **life-threatening** – in the view of the investigator, the subject is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

9.4. Recording and Reporting Adverse Events

9.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of study, with the exception of symptoms that occur in response to the NAC on the day of the NAC. Allergic symptoms that occur in response to the NAC are not to be reported as AEs, as they will be recorded as outcome measures. However, AEs that occur in

response to the NAC that are outside of expected symptoms which are recorded in response to the NAC, or SAEs, should be reported as AEs and SAEs. Information on follow-up for AEs is provided in Section 9.4.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 9.4.5.

9.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drugs (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT) or procedures, must be reported to the sponsor (or designee) within 24 hours.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

In the event the investigator is informed of an SAE after the subject completes the study, the following will apply:

- SAE with an onset within 30 days of the end of study or within 30 days of last study drug administration if the subject early terminated from the study - the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of study/early termination visit - only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

9.4.3. Other Events that Require Accelerated Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Symptomatic Overdose of Study Drug: Accidental or intentional overdose of at least 2 times the intended dose of study drugs within the intended therapeutic window, if associated with an AE,

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female study subject during the study or within 12 weeks of the last dose of study drugs. Any complication of pregnancy affecting a female study subject and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

Adverse Events of Special Interest (AESIs): All AESI, serious and nonserious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 9.4.2. Adverse events of special interest for this study include the following: anaphylactic reactions, systemic or severe hypersensitivity reactions, malignancy (except in-situ carcinoma of the cervix, non-metastatic squamous or basal cell carcinoma of the skin), helminthic infections, suicide-related events, any type of conjunctivitis or blepharitis (severe or serious or lasting ≥4 weeks), keratitis.

Refer to the study manual for the procedures to be followed.

9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a subject's withdrawal from the study must be reported to the sponsor's Medical/Study Director within 30 days.

9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy

Contact the Medical/Study Director in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 9.5.1.

9.4.6. Follow-up

Adverse event information will be collected until the subject's last study visit.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

The severity of AEs will be graded according to the following scale:

- **Mild:** Does not interfere in a significant manner with the patient normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms but may be given because of personality of the patient.
- **Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.
- **Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health. Treatment for symptom may be given and/or patient hospitalized.

The severity of AEs related to SCIT or SCIT-placebo for SCIT-related-allergic or anaphylactic reactions (including AESIs) will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.3, criteria for grading allergic reactions and anaphylaxis (Cox, 2010) (Appendix 1). Not all AEs but only the SCIT or SCIT-placebo-related-allergic or anaphylactic reactions (including AESIs) will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE).

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Injection Site Reactions due to study drug (dupilumab or placebo for dupilumab and SCIT or placebo for SCIT)

The severity of injection site reactions will be graded according to the following scale (semi-colon indicates "or" within description of grade):

- **Mild**: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity
- **Moderate**: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity
- **Severe**: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires ER visit or hospitalization; necrosis or exfoliative dermatitis

9.5.2. Evaluation of Causality

Relationship of Adverse Events to Dupilumab or placebo for dupilumab:

The relationship of AEs to study drug (dupilumab or placebo for dupilumab) will be assessed by the blinded investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by dupilumab or placebo for dupilumab?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug (dupilumab or placebo for dupilumab)

Related: There is a reasonable possibility that the event may have been caused by the study drug (dupilumab or placebo for dupilumab)

The investigator should justify the causality assessment of each SAE.

A list of factors to consider when assessing the relationship of AEs to dupilumab or placebo for dupilumab is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the event may have been caused by dupilumab or placebo for dupilumab?

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the subject's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of study drug (dupilumab or placebo for dupilumab)
- do not reappear or worsen when dosing with study drug (dupilumab or placebo for dupilumab) is resumed

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the subject's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of study drug (dupilumab or placebo for dupilumab)
- resolve or improve after discontinuation of study drug (dupilumab or placebo for dupilumab)
- reappear or worsen when dosing with study drug (dupilumab or placebo for dupilumab)
- are known or suspected to be a response to the study drug (dupilumab or placebo for dupilumab) based upon preclinical data or prior clinical data

Relationship of Adverse Events to SCIT or placebo for SCIT:

The relationship of AEs to SCIT or placebo for SCIT will be assessed by the blinded investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by SCIT or placebo for SCIT?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by SCIT or placebo for SCIT

Related: There is a reasonable possibility that the event may have been caused by SCIT or placebo for SCIT

The sponsor will request prespecified information about the SCIT or placebo for SCIT-related AEs; instructions to record this information is in the Study Operations Manual.

The sponsor will request information to justify the causality assessment of SAEs, as needed.

A list of factors to consider in assessing the relationship of AEs to SCIT or placebo for SCIT is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the event may have been caused by SCIT or placebo for SCIT?

No:

- due to patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following SCIT or placebo for SCIT
- do not reappear or worsen when SCIT or placebo for SCIT is resumed
- are not a suspected response to SCIT or placebo for SCIT based upon preclinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by patient's disease state or clinical condition
- follow a reasonable temporal sequence following SCIT or placebo for SCIT
- resolve or improve after discontinuation of SCIT or placebo for SCIT
- reappear or worsen when SCIT or placebo for SCIT treatment is resumed

Relationship of Adverse Events to Study Procedures

The relationship of AEs to study procedures will be assessed by the blinded investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study procedure?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study procedure.

Related: There is a reasonable possibility that the event may have been caused by the study procedure.

The sponsor will request information to justify the causality assessment of SAEs, as needed.

A list of factors to consider in assessing the relationship of AEs to study procedures is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the event may have been caused by study procedures?

No:

- due to the subject's disease state or clinical condition
- do not follow a reasonable temporal sequence following study procedure.
- do not reappear or worsen when the study procedure is resumed
- are not a suspected response to the study procedure based upon preclinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the subject's disease state or clinical condition
- follow a reasonable temporal sequence following the study procedure.
- resolve or improve after discontinuation of study drug study procedure.
- reappear or worsen when the study procedure is resumed
- are known or suspected to be a response to study procedure based upon preclinical data or prior clinical data

9.6. Safety Monitoring

The investigator will monitor the safety of study subject at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

9.7. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the reference safety information in the Investigator's Brochure, and has a reasonable suspected causal relationship to the study drug).

10. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in Section 4.

10.1. Statistical Hypothesis

The primary efficacy endpoint is the percent change from baseline in TNSS AUC (0-1 hr) at week 17. The comparison between dupilumab + SCIT as compared to placebo + SCIT monotherapy will be made.

Let μD (and μP) be the true mean percent change from baseline in in TNSS AUC (0-1 hr) for Dupilumab + SCIT and Placebo + SCIT, respectively. The following hypothesis for the superiority testing will be tested at the 5% 2 sided significance level:

H0: $\mu D = \mu P$, ie, the mean percent change from baseline to week 17 is the same between Dupilumab + SCIT and Placebo + SCIT

against the alternative

Ha: $\mu D \neq \mu P$, ie, the mean percent changes from baseline to week 17 are different between Dupilumab + SCIT and Placebo + SCIT

10.2. Justification of Sample Size

It is estimated that with 25 subjects per group, the study will have 80% power to detect a difference of 29% between dupilumab plus SCIT and placebo plus SCIT monotherapy with respect to percent change from baseline in TNSS AUC (0-1 hr) at week 17, assuming that the mean percent changes from baseline values are -55% and -26% and a common standard deviation (SD) of 35% for dupilumab plus SCIT and placebo SCIT monotherapy, respectively. The significance level is set to 2-sided, 0.05 level.

The assumptions used for primary endpoint were based on the study result from the Scadding (2017) study. The Scadding study shows after 1 year treatment, the difference between SCIT and placebo is 34% for the percent change in TNSS AUC (0-1 hr) at 1 year. A similar magnitude of improvement by adding dupilumab onto SCIT is assumed for the sample size calculation.

10.3. Analysis Sets

10.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized subjects. Efficacy analyses will be based on the treatment allocated at randomization (as randomized).

The per protocol set (PPS) includes all subjects in the FAS except for those who are excluded because of major protocol violations. A major protocol violation is one that may affect the interpretation of study results.

All efficacy variables will be evaluated on the FAS; the primary endpoint will also be evaluated on the PPS. Analysis on the FAS will be considered to be primary.

10.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized subjects who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

10.3.3. Pharmacokinetic Analysis Sets

The pharmacokinetic (PK) analysis set includes all randomized subjects who received any study drug and who had at least 1 non-missing drug concentration result following the first dose of study drug.

10.3.4. Anti-Drug Antibody Analysis Sets

The ADA population includes all treated subjects who had received any amount of dupilumab study drug or dupilumab placebo and had at least 1 non-missing anti-drug antibody result following the first dose of dupilumab study drug or dupilumab placebo.

10.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of subjects reflected in the calculation (n), mean, median, first quartile (Q1), third quartile (Q3), SD, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

10.4.1. Subject Disposition

The following will be provided:

- The total number of screened subjects: met the inclusion criteria regarding the target indication and signed the ICF
- The total number of randomized subjects: received a randomization number
- The total number of subjects in each analysis set (eg, FAS, provided in Section 10.3.2)
- The total number of subjects who discontinued the study, and the reasons for discontinuation
- A listing of subjects treated but not randomized, subjects randomized but not treated, and subjects randomized but not treated as randomized
- A listing of subjects prematurely discontinued from treatment, along with reasons for discontinuation

10.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all subjects combined.

10.4.3. Efficacy Analyses

10.4.3.1. Primary Efficacy Analysis

The primary endpoint will be analyzed by using the multiple imputation (MI) with analysis of covariance (ANCOVA) model. Missing data will be imputed 40 times to generate 40 complete data sets by using the Statistical Analysis System (SAS) procedure MI. Each of the 40 complete datasets will be analyzed using an ANCOVA model with treatment group being the main factor and baseline value as the covariate. The SAS MIANALYZE procedure will then be used to generate valid statistical inferences by combining results from the 40 analyses using Rubin's formula.

All observed data will be used for analysis. Sensitivity analysis such as ANCOVA model with last observation carry forward (LOCF) method will also be conducted. Additional details on sensitivity analyses will be provided in the SAP.

10.4.3.2. Secondary Efficacy Analysis

The continuous secondary efficacy endpoints will be analyzed using the same approach as that used for the analysis of the primary endpoint.

The biomarker related continuous endpoint will be analyzed using a rank based ANCOVA model with treatment and relevant baseline as covariates. LOCF method will be used to impute the missing data.

10.4.3.3. Multiplicity Considerations

There is no control for multiplicity on the secondary and exploratory endpoints.

10.4.3.4. First-Step Analysis

A first-step analysis may be performed when the last subject completes 16 weeks of the treatment period and performed the NAC at week 17 as specified in the protocol (Visit 16 visit or earlier for those subjects who are withdrawn prematurely from the study). No changes in the conduct of the study will be made based on this first-step analysis. The assessment of primary and secondary endpoints up to end of treatment NAC Visit 16 (week 17) as specified in Section 4.2.1and Section 4.2.2 and performed during the analysis will be the final analysis of the primary endpoints and secondary endpoints. If a decision is made to perform the first-step analysis, in order to maintain study integrity with respect to the post-treatment follow-up visits, safety visits and analyses, a dissemination plan will be written. This plan will clearly identify the team (including the statistician) that will perform the first-step analysis and all related activities, restrict other clinical team members and other Sponsor personnel from access to individual subject treatment allocation and site level analysis results, and ensure that the dedicated team will not participate in the data review or data decisions for the following post treatment analyses. However, the dedicated team can participate in the analysis following the final database lock.

10.4.4. Safety Analysis

10.4.4.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment period is defined as the day from first dose of study drug to end of study. The treatment-emergent period includes the 16-week treatment period and follow-up period

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the treatment emergent period.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of subjects with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 9.5.1 presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

10.4.4.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of subjects with a potentially clinically significant value (PCSV) at any postrandomization time point will be summarized for each clinical laboratory test.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

10.4.4.3. Treatment Exposure

The duration of exposure during the study will be presented by treatment group and calculated as:

(Date of last study drug injection – date of first study drug injection) + 14 days

The number (%) of subjects randomized and exposed to double-blind study drug will be presented by specific time periods for each treatment group. The time periods of interest will be specified in the SAP.

In addition, duration of exposure during the study will be summarized for each treatment group using number of subjects, means, SD, minimums, Q1, medians, Q3, and maximums.

A summary of the number of doses by treatment group will be provided.

10.4.4.4. Treatment Compliance

The compliance with study treatment will be calculated as follows:

> Treatment Compliance of study drug = (Number of study drug injections during exposure period)/ (Number of planned study drug injections during exposure period) × 100%

The treatment compliance will be presented by specific ranges for each treatment group. The ranges of interest will be specified in the SAP.

10.4.5. Pharmacokinetics

Descriptive statistics will be used to summarize the concentration data at each sampling time. No formal statistical analysis will be performed.

10.4.6. Analysis of Anti-Drug Antibody Data

Listings of treatment-emergent ADA and titers presented by subject, time point, and dose cohort will be provided. Incidence of treatment-emergent and treatment-boosted ADA will be assessed as absolute occurrence (N) and percent of subjects (%), grouped by study cohorts and ADA titer level.

Assessment of association of treatment -emergent and treatment boosted ADA with potential impact of ADA response on PK, safety and efficacy may be evaluated.

10.4.7. Analysis of Pharmacodynamic and Exploratory Biomarker Data

The exploratory biomarker data will be summarized by descriptive statistics.

10.5. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- The baseline assessment will be the latest, valid pre-first-dose assessment available

General rules for handling missing data:

- Rules for handling missing data for assessment (other than efficacy)
- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.
- No imputations for missing laboratory data, ECG data, vital sign data, or physical examination data will be made.

Visit windows:

- Assessments taken outside of protocol allowable windows will be displayed according to the case report form (CRF) assessment recorded by the investigator.

Unscheduled assessments:

- Extra assessments (laboratory data or vital signs associated with nonprotocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

10.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 16.1.

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at Regeneron.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with both paper and an electronic data capture (EDC) tool.

11.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database
- AWARE, Business Objects XI – pharmacovigilance activities (Sanofi)

12. STUDY MONITORING

12.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first subject, and periodically during the study.

The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of subjects are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements

12.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate subject records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (CRFs) within the EDC system by trained site personnel. All required CRFs must be completed for each and every subject enrolled in the study. After review of the clinical data for each subject, the investigator must provide an electronic signature. A copy of each subject CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

13. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately

- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC -approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each subject prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the subject in language that he/she can understand. The ICF should be signed and dated by the subject and by the investigator or authorized designee who reviewed the ICF with the subject.

- Subjects who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Subjects who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the subject's study record, and a copy of the signed ICF must be given to the subject.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study subjects must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the subject’s study record and a copy must be given to the subject.

14.2. Subjects Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study subject will be maintained. Subjects should be identified by a subject identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The subject's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

14.3. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the subjects (eg, advertising) before any subject may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the subject, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of subjects or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

15. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment

16. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

16.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

16.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any subject within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of subjects required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the subjects' interests.

17. STUDY DOCUMENTATION

17.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of subject final eCRFs that will be provided to the sponsor.

17.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

18. DATA QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are summarized.

Data Management

The sponsor is responsible for the data management of this study including quality checking of the data (Section 11.1).

Study Monitoring

The investigator must allow study-related monitoring, IRB/EC review, audits, and inspections from relevant health regulatory authorities, and provide direct access to source data documents (Section 12.1, Section 12.2, Section 13)

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of subjects are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements (Section 12.1).

All subject/patient data collected during the study will be recorded on paper or electronic CRF unless the data are transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for affirming that data entries in the CRF are accurate and correct by electronically signing a declaration that accompanies each set of subject final CRF (Section 12.3 and Section 17.1).

Study Documentation

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF (Section 12.2).

The investigator will retain all records and documents, including signed ICFs, pertaining to the conduct of this study for at least 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor (Section 17.2).

19. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

20. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

21. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

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23. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Study To Evaluate The Efficacy Of Dupilumab As An Adjunct For Subcutaneous Grass Immunotherapy To Reduce Provoked Allergic Rhinitis Symptoms Using The Nasal Allergen Challenge Model, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

(Signature of Investigator) (Date)

(Printed Name)

APPENDIX 1. TOXICITY GRADING SCALE FOR GRADING ALLERGIC REACTIONS AND ANAPHYLAXIS – COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE VERSION 4.0, PUBLISHED 28 MAY 2009; V4.03, 14 JUNE 2010)

The CTCAE descriptive terminology will be utilized for reporting AEs of allergic reactions and anaphylaxis. A grading (severity) scale is provided for each AE term.

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen					
Anaphylaxis	–	–	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the conduct of the study.

Study Title: A Study To Evaluate The Efficacy Of Dupilumab As An Adjunct For Subcutaneous Grass Immunotherapy To Reduce Provoked Allergic Rhinitis Symptoms Using The Nasal Allergen Challenge Model

Protocol Number: R668-ALG-16115

Protocol Version: R668-ALG-16115 Amendment 2

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00062320 v1.0

ESig Approval	[redacted] 12-Nov-2018 17:12:34 GMT+0000
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