NCT03558997

STATISTICAL ANALYSIS PLAN
VERSION: 1.0

Clinical Study Protocol 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

Compound:	Dupilumab (REGN668)
Protocol Number:	R668-ALG-16115
Clinical Phase:	Phase 2a
Sponsor:	Regeneron Pharmaceuticals, Inc.
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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AD	Atopic dermatitis
ADA	Anti-Drug Antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT (SGOT)	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST (SGPT)	Aspartate aminotransferase
AUC	Area under curve
BAU	Bioequivalent allergy unit
BUN	Blood urea nitrogen
CRF	Case report form
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
HIV	Human Immunodeficiency Virus
HLT	High Level Term
ICF	Informed consent form
ICH	International conference on harmonization
IL	Interleukin
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4

LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
NAb	Neutralizing Antibody
NAC	Nasal allergen challenge
PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
PNIF	Peak nasal inspiratory flow
PT	Preferred term
Q2W	Once every 2 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
sIgE	Specific immunoglobulin E
sIgG4	Specific immunoglobulin G4
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SC	Subcutaneous
SCIT	Subcutaneous immunotherapy
SD	Standard deviation

SE	Standard error
SOC	System organ class
SPT	Skin prick test
TARC	Thymus and activation-regulated chemokine
TEAE	Treatment emergent adverse event
Th2	Type-2 T helper cells
TNSS	Total nasal symptom score
TOSS	Total ocular symptom score
WHODD	World health organization drug dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for R668-ALG-16115 study.

1.1. Background/Rationale

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 G (IgG), including IgG4, decreased type 2 cytokines in tissues, decreased tissue migration of eosinophils and decreased mediator release from tissue mast cells, basophils and eosinophils.

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. 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 IgG/IgE ratio, in SCIT + dupilumab treated subjects as compared to subjects treated with SCIT alone.

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. 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.

This trial is a 4-arm, placebo-controlled, double-blind, randomized, parallel-group, proof-of-concept (phase 2a) study over a 16-week treatment period followed by an 8-week safety follow-up period in approximately 100 adult subjects with a history of Timothy Grass-induced allergic

rhinitis. Four treatment groups after 600mg loading dose are required to provide informative controls and minimize bias on clinical endpoints:

- dupilumab + SCIT
- SCIT
- dupilumab
- placebo.

In addition, this study will allow the evaluation of dupilumab monotherapy on clinical rhinitis symptoms and related biomarkers.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objective of the study is 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.

1.2.2. Secondary Objectives

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 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

1.2.3. 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, SCIT, dupilumab + SCIT, and placebo
- To assess changes in peak nasal inspiratory flow (PNIF) after NAC over 16 weeks of treatment with dupilumab, SCIT , dupilumab + SCIT, and placebo
- To assess total sneeze count after NAC over 16 weeks of treatment with dupilumab , SCIT, dupilumab + SCIT, and placebo
- To assess changes in serum TARC over 16 weeks of treatment with dupilumab, SCIT, dupilumab + SCIT, and placebo
- To assess changes in serum total IgE over 16 weeks of treatment with dupilumab , SCIT, dupilumab + SCIT, and placebo
- To assess changes in serum Timothy-grass-specific IgG and ratio of serum Timothy Grass-specific IgG to IgE over 16 weeks of treatment with dupilumab + SCIT as compared to SCIT
- To assess whether dupilumab as an adjunct to SCIT improves SCIT tolerability, defined as an increase in the proportion of subjects who achieve SCIT maintenance dose (4000 BAU), comparing 16 weeks of treatment with dupilumab + SCIT and 16 weeks of treatment withSCIT
- To assess whether dupilumab as an adjunct to SCIT improves SCIT tolerability, defined as an increase in the maximal tolerated SCIT dose, comparing 16 weeks of treatment with dupilumab + SCIT and 16 weeks of treatment withSCIT
- To evaluate the effects of treatment (dupilumab + SCIT vs SCIT) on local skin wheal size, measured approximately 15 minutes after each SCIT injection.

1.2.4. Modifications from the Statistical Section in the Final Protocol

The following other objectives are added into the SAP.

- To assess changes in serum Timothy-grass-specific IgG and ratio of serum Timothy Grass-specific IgG to IgE over 16 weeks of treatment with dupilumab + SCIT as compared to SCIT
- To assess whether dupilumab as an adjunct to SCIT improves SCIT tolerability, defined as an increase in the proportion of subjects who achieve SCIT maintenance dose (4000 BAU), comparing 16 weeks of treatment with dupilumab + SCIT and 16 weeks of treatment with SCIT.
- To assess whether dupilumab as an adjunct to SCIT improves SCIT tolerability, defined as an increase in the maximal tolerated SCIT dose, comparing 16 weeks of treatment with dupilumab + SCIT and 16 weeks of treatment with SCIT.
- To evaluate the effects of treatment (dupilumab + SCIT vs SCIT) on local skin wheal size, measured approximately 15 minutes after each SCIT injection.

- To assess change and percent in serum Timothy Grass sIgG subclasses other than Timothy Grass sIgG4 over 16 weeks of treatment with dupilumab + SCIT as compared to SCIT pending on available data

The following endpoints are added into the exploratory variables as well.

- Change and percent change from baseline (last pretreatment measurement) to week 17 in serum Timothy Grass sIgG for dupilumab + SCIT as compared to SCIT
- Change from baseline (last pretreatment measurement) to week 17 in log-transformed value of serum Timothy Grass sIgG to Timothy Grass sIgE ratio for dupilumab + SCIT as compared to SCIT
- Proportion of subjects who achieve SCIT maintenance dose (4000 BAU) during 16 weeks of treatment with dupilumab + SCIT as compared with SCIT
- Maximal tolerated SCIT dose during 16 weeks of treatment with dupilumab + SCIT as compared with SCIT
- Local skin wheal size at approximately 15 minutes after each SCIT injection during 16 weeks of treatment with dupilumab + SCIT as compared with SCIT
- Change and percent change from baseline (last pretreatment measurement) to week 17 in serum Timothy Grass sIgG subclasses other than Timothy Grass sIgG4 for dupilumab + SCIT as compared to SCIT pending on available data
- 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 average wheal sizes (diameter) over log-transformed allergen concentrations after the challenge (early phase reaction) for dupilumab + SCIT as compared to SCIT and for dupilumab as compared to placebo

The following endpoint is revised by removing the AUC over the course of hour 1 to hour 6 (late phase reaction) to fix the error in the protocol.

- 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 after the challenge (early phase reaction) for dupilumab + SCIT as compared to SCIT and for dupilumab as compared to placebo

1.2.5. Revision History for SAP Amendments

There is no SAP amendment.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

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 an 8-week post treatment follow-up period in subjects with a history of allergic rhinitis to grass pollen.

Within 2 weeks after NAC (visit 3), a total of approximately 100 adult subjects with a history of allergic rhinitis to grass pollen who successfully complete screening procedures will be randomized 1:1:1:1 at Randomization (visit 4) into the 4 treatment arms (n=25 in each arm) as defined in Section 1.1.

2.2. Sample Size and Power Considerations

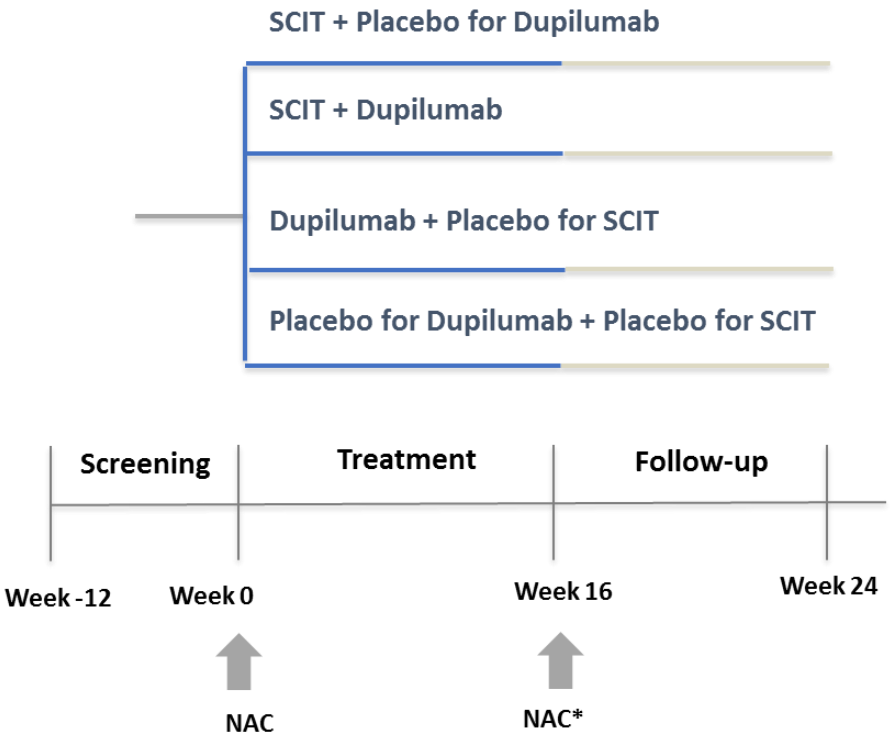
Approximately 100 patients are planned to be randomized. It is estimated that with 25 subjects per group, the study will have 80% power to detect a difference of 29% between dupilumab plus SCIT and placebo plus SCIT with respect to percent change from baseline in TNSS AUC (0-1h) at week 17, assuming that the mean percent changes from baseline values are -55% and -26% for dupilumab plus SCIT and placebo plus SCIT, respectively, and a common standard deviation (SD) of 35%. 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 (0-1h) at 1 year. A similar magnitude of improvement by adding dupilumab onto SCIT is assumed for the sample size calculation.

2.3. Study Plan

The study will consist of the following 3 periods: screening of up to 12 weeks, treatment period of 16 weeks, and follow-up of 8 weeks as presented below Figure 1 :

Figure 1: Study Flow Diagram



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

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. 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. At screening visit 3/Entry visit, a NAC and skin testing for early and late phase reactions will be performed. Grass allergic subjects will be eligible for enrollment based on having a TNSS ≤2 prior to the screening NAC (visit 3), peak TNSS ≥7 within the first hour during the up-titration phase. In addition, 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.

Dupilumab will be administered SC, as a 600 mg loading dose and then 300 mg Q2W. Placebo matching dupilumab is prepared in the same formulation without the addition of protein (ie, active substance, anti-IL-4Rα monoclonal antibody). Dupilumab dosing starts prior to SCIT dosing as shown in Table 1. Dupilumab/placebo are never to be given on the same day as SCIT/ placebo.

Table 1: 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]
Week 2	X[4]	X[4]
Week 3		X[4]
Week 4	X[4]	X[4]
Week 5		X[4]
Week 6	X[4]	X[4]
Week 7		X[4]
Week 8	X[4]	X[4]
Week 9		
Week 10	X[4]	X[4]
Week 11		
Week 12	X[4]	
Week 13		X[4]
Week 14	X[4]	
Week 15		
Week 16	X[4]	X[4]
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 2 .
[4] During week 2, week 4, week 6, week 10, and week 6, 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 aprat) AND SCIT/placebo and dupilumab/placebo are to be given in a different anatomical location. For SCIT/placebo visits, subjects are to be premedicated with an antihistamine.

SCIT will be up-dosed for 8 weeks to a maximum of 4,000 BAU dose, followed by an 8-week maintenance dose.

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.

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

Table 2: 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

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.

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 as noted in Section 10.2.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), the following population of analysis will be used for all statistical analysis.

3.1. The Full Analysis Set (FAS)

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

FAS is the primary analysis set for efficacy endpoints.

3.2. The Per Protocol Set (PPS)

The per-protocol set (PPS) includes all patients 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. Final determination of the PPS will be made before data base lock.

The primary endpoint will be evaluated on the PPS in addition to FAS.

3.3. The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized patients who receive at least one injection of study drug, it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be summarized based on the SAF.

The actual treatment group as treated is defined by the following rules:

1. To determine whether a patient received dupilumab or placebo
    - For a patient randomized to receive dupilumab, if the patient received all placebo injections, the actual treatment will be assigned as placebo.
    - For a patient randomized to receive dupilumab, if the patient received at least one dupilumab injection, the actual treatment will be same as the planned treatment.
    - For patients randomized to receive placebo but accidentally received dupilumab injections, the actual treatment will be assigned as dupilumab.
2. To determine whether a patient received SCIT or placebo SCIT
    - For a patient randomized to receive SCIT, if the patient received all placebo SCIT injections, the actual treatment will be assigned as placebo SCIT.
    - For a patient randomized to receive SCIT, if the patient received at least one SCIT injection, the actual treatment will be same as the planned treatment.
    - For patients randomized to receive placebo SCIT but accidentally received SCIT injections, the actual treatment will be assigned as SCIT.

For safety summaries, three analysis periods are defined as follows.

- Treatment period is defined as:
  - Day 1 to the Week 17 NAC visit for those patients who completed Week 17 visit with Week 17 visit date present
  - Day 1 to the last dose date plus 14 days for the patients who did not complete Week 17 visit or had missing or incomplete Week 17 visit date
- Follow-up period is defined as:
  - The date after the Week 17 visit date (or last dose date plus14 days if the date of Week 17 visit is unavailable) to the date of the end of study visit Week 24
- Overall study period is defined as:
  - Day 1 to the date of the end of study visit Week 24

The SAF will be the basis for the analyses for the treatment period and overall study period; however, for the analyses for the follow-up period, only a subset of SAF will be included, which is defined as the patients who enter the follow-up period and have at least one visit after week 17 NAC visit.

3.4. The Pharmacokinetic Analysis Set (PKAS)

The pharmacokinetic analysis set includes all randomized patients who received any dupilumab and who had at least one non-missing dupilumab drug concentration result following the first dose of dupilumab. Patients will be analyzed according to the treatment actually received.

3.5. The Immunogenicity Analysis Sets

The ADA analysis set (AAS) will consist of all patients who received any study drug and who had at least one non-missing ADA result from the dupilumab ADA assay after first dose of the study drug. Patients will be analyzed according to the treatment actually received.

The neutralizing antibody (NAb) Analysis Set (NAS) will consist of all patients who received any study drug and who had at least one non-missing NAb result from dupilumab neutralizing antibody assay or who had all samples negative in the dupilumab ADA assay after first dose of the study drug. Patients will be analyzed according to the treatment actually received.

3.6. Subgroups

Subgroups are defined as the following.

- Age group ($\geq$18 to <40, $\geq$40 to $\leq$55)
- Sex (Male, Female)
- Race (White, Other)
- Baseline weight group (<60 kg, $\geq$60-<100 kg, $\geq$100 kg)
- Baseline BMI group (<15 kg/m^2, $\geq$15-<25 kg/m^2, $\geq$25-<30 kg/m^2, $\geq$30 kg/m^2)

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline characteristics variables will be summarized:

- Demographic variables: Age at screening (year), age (year) group (≥18-<40, ≥40-≤55), sex, ethnicity, race, baseline weight (kg) with grouping (<60; ≥60-<100, ≥100), height (m), BMI (kg/m^2) with grouping (<15, ≥15-<25, ≥25-<30, ≥30)
- Baseline characteristics:
    - baseline TNSS AUC post NAC over the first hour after the challenge (0-1 hr post peak TNSS)
    - baseline peak TNSS
    - baseline TOSS AUC post NAC over the first hour of the challenge (0-1 hr post peak TNSS)
    - baseline Skin Prick Test with Serial Allergen Titration, as measured by AUC of the wheal sizes (diameter) over allergen concentrations (early phase reaction)
    - baseline Skin Prick Test with Serial Allergen Titration, as measured by AUC of the wheal sizes (diameter) over log-transformed allergen concentrations (early phase reaction)
    - baseline wheal size (diameter) induced by skin Timothy Grass intradermal injection 6 hrs after the challenge (late phase reaction)
    - baseline 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)
    - baseline sneeze count AUC over the course of 0 hour to hour after the challenge (early phase reaction)
    - baseline serum TARC
    - baseline serum total IgE
    - baseline serum Timothy Grass sIgE
    - baseline serum Timothy Grass sIgG4
    - baseline serum Timothy Grass sIgG
    - baseline subclasses of Timothy Grass sIgG other than sIgG4 (pending on available data)
    - baseline log-transformed value of serum Timothy Grass sIgG4 to Timothy Grass sIgE ratio
    - baseline log-transformed value of serum Timothy Grass sIgG to Timothy Grass sIgE ratio

4.2. Medical History

Medical history will be coded to a Preferred Term (PT), High Level Term (HLT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA at the coding CRO.

4.3. Prior/Concomitant Medications and Procedures

Medications/Procedures will be recorded from the day of informed consent until the end of study visit. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD) at the coding CRO. Patients will be counted once in all ATC categories linked to the medication.

Procedures will be coded to a Preferred Term (PT), High Level Term (HLT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA at the coding CRO.

Prior medications/procedures: medications taken or procedures performed prior to administration of the first study drug.

Concomitant medications/procedures: medications taken or procedures performed following the first dose of study drug through the end of study visit.

- Concomitant medications/procedures during the treatment period are medications/procedures taken after the first dose up to the date of last injection plus 14 days. Medications/procedures taken during the treatment period and continued afterwards into follow-up period will be counted only once as concomitant medications/procedures during the treatment period.
- Concomitant medications/procedures during the Follow-up period are medications/procedures taken after the end of treatment period to end of study.

4.4. Rescue Medication/or Prohibited Medication During Study

Prohibited concomitant medications/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.

Prohibited medications are not to be used after randomization except as rescue treatments. 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).

Concomitant treatments for allergies including allowed and rescue treatments (i.e., both medications and procedures):

If medically 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.

Blinded adjudication of rescue treatments will be implemented before database locks by considering the type of medication or procedure, indication, timing, frequency and the potential impact of the use of the prohibited medication or procedure. The rescue treatments will be adjudicated by the clinical study director and the adjudication procedure will be documented.

4.5. Efficacy Variables

4.5.1. Primary Efficacy Variable (s)

The primary endpoint in the study is:

- 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 SCIT

The algorithm for calculating the area under curve (AUC) is provided in Section 6.2.

Total Nasal Symptom Score (TNSS)

The Total Nasal Symptom Score (measured on a 0 to 12 scale) is a patient-reported composite symptom assessment of 4 symptoms graded on a 0 (none) to 3 (severe) scale: rhinorrhea, nasal congestion, nasal itching, and sneezing. The TNSS will be performed at Screening Visit 2 and each NAC visit (Screening Visit 3 and Visit 16). At the end of treatment (EOT) NAC (week 17), subjects will be observed for approximately 10 minutes and a resting/baseline TNSS $\leq$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. 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) $\geq$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) $\geq$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.

4.5.2. Secondary Efficacy Variables

The secondary endpoints are:

- 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
- 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 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
- Change and percent change from baseline (last pretreatment measurement) to week 17 in serum Timothy Grass sIgG4 for dupilumab + SCIT as compared to SCIT
- Change and percent change from baseline (last pretreatment measurement) to week 17 in serum Timothy Grass sIgE for dupilumab + SCIT as compared to SCIT
- 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

4.5.3. Exploratory Variables

Exploratory endpoints include:

- Change and percent change from baseline in the peak TNSS at week 17 for dupilumab + SCIT as compared to SCIT and for dupilumab 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 and for dupilumab 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 average wheal sizes (diameter) over allergen concentrations after the challenge (early phase reaction) for dupilumab + SCIT as compared to SCIT and for dupilumab 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 average wheal sizes (diameter) over log-transformed concentrations after the challenge (early phase reaction) for dupilumab + SCIT as compared to SCIT and for dupilumab as compared to placebo
- 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) for dupilumab + SCIT as compared to SCIT and for dupilumab as compared to placebo
- 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) for dupilumab + SCIT as compared to SCIT and for dupilumab as compared to placebo
- 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 after the challenge (early phase reaction) for dupilumab + SCIT as compared to SCIT and for dupilumab as compared to placebo

- Change and percent change from baseline (last pretreatment measurement) to week 17 in serum TARC for dupilumab + SCIT as compared to SCIT
- Change and percent change from baseline (last pretreatment measurement) to week 17 in serum total IgE for dupilumab + SCIT as compared to SCIT
- Change and percent change from baseline (last pretreatment measurement) to week 17 in serum Timothy Grass sIgG for dupilumab + SCIT as compared to SCIT
- Change from baseline (last pretreatment measurement) to week 17 in log-transformed value of serum Timothy Grass sIgG to Timothy Grass sIgE ratio for dupilumab + SCIT as compared to SCIT
- Proportion of subjects who achieve SCIT maintenance dose (4000 BAU) during 16 weeks of treatment with dupilumab + SCIT as compared with SCIT
- Maximal tolerated SCIT dose during 16 weeks of treatment with dupilumab + SCIT as compared with SCIT
- Local skin wheal size at approximately 15 minutes after each SCIT injection during 16 weeks of treatment with dupilumab + SCIT as compared with SCIT
- Change and percent change from baseline (last pretreatment measurement) to week 17 in serum Timothy Grass sIgG subclasses other than Timothy Grass sIgG4 for dupilumab + SCIT as compared to SCIT pending on data availability

Peak TNSS

The peak TNSS should be the highest TNSS value between 0 hour and hour 1 inclusive.

Total Ocular Symptom Score (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]. The TOSS score will be recorded during the NAC assessments (Screening Visit 3 and Visit 16). 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.

Peak nasal inspiratory flow (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 and at 6 hours. The PNIF will be performed at each NAC visit (Screening Visit 3 and Visit 16).

Sneeze Count

Sneezes will be counted 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 and at 6 hours as noted. The sneezes count will be performed at each NAC visit (Screening Visit 3 and Visit 16).

Skin Prick Test (SPT) with Serial Allergen Titration

The SPT with serial allergen titration assesses the early phase reaction at 0-60 minutes. The skin prick test with serial allergen titration procedure will be performed two times during the study: at visit 3 (on the day of the screening NAC) and at the EOT NAC visit (visit16). The procedure should be performed over a 30 minute time period (15 min placement of skin pricks, 15 minutes (+/- 2 minutes) after placement to evaluate responses) during the last 2 hours of the NAC day when the subject is otherwise undergoing hourly assessments.

The test will be performed in duplicate by titration of Timothy grass extract at six doses ranging from 14-10000 BAU. Duplicate probes with a negative control solution and a positive histamine control will be administered simultaneously with Timothy grass extract probes. A mean wheal diameter 3 mm greater than the negative control is considered a positive test result. Skin responses to the skin prick test with serial allergen titration will be measured 15 minutes after placement (+/- 2 minutes). Mean wheal diameters will be calculated by adding the longest diameter to the longest orthogonal diameter and dividing by 2. For each of the duplicate skin prick tests, the longest and longest orthogonal diameters should be recorded, and the mean diameter of each wheal calculated to two decimal places. The mean wheal diameters from the duplicate skin pricks will then be averaged and recorded.

The formula used to calculate the average wheal diameter AUC over allergen concentrations is similar as the one inside Section 6.2, where t_i is c_i, the concentration (in BAU/ml) for which D_i is measured. D_i is the average wheal diameter obtained at concentration c_i, $c_0 = 14$, $c_1 = 41$, $c_2 = 123$, $c_3 = 370$, $c_4 = 1111$, $c_5 = 3333$, $c_6 = 10000$. The formula used to calculate the average wheal diameter AUC over log-transformed allergen concentrations is similar to above, however, c_i is the log-transformed concentration.

The change from baseline, percent change from baseline values for the mean wheal diameters from measurement 1 and 2 for skin prick test of negative control, positive histamine control, and each concentration level of Timothy grass allergen will be also summarized.

Intradermal Allergen Injection

The intradermal allergen injection assesses late phase reaction from 6-24 hours. The intradermal allergen injection procedure will be performed two times during the study: at visit 3 (on the day of the screening NAC) and at the EOT NAC visit (visit16). The intradermal allergen injection procedure will be performed on the extensor and volar aspect of the forearm. The intradermal allergen injection will be performed at the beginning of the NAC day, before the NAC begins, as described below. The skin response to the intradermal allergen will be evaluated at approximately 6 hours after placement- at the end of the NAC day. The mean wheal diameter measured at 15 minutes and 6 hours after injection for the Timothy grass allergen extract of 14, 41, 123 BAU/ml will be collected.

The maximum mean wheal diameters 6 hours after injection at the EOT NAC visit (visit 16) versus the maximum mean wheal diameters 6 hours after injection at the screening NAC visit (Visit 3) up to the largest concentration level at EOT NAC visit will be identified. The change and percent change between these two values will be calculated and summarized. If the

maximum mean wheal diameters are not at the same Timothy grass allergen concentration at Visit 3 and EOT/Visit 16, the assessment at the smaller one of the two concentrations will be used in the change and percent change analysis. That is, the wheal diameters of Visit 3 and EOT/Visit 16 for the change and percent change calculation should be based on the same concentration.

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the 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, and/or SAEs, should be reported as AEs and SAEs.

All adverse events are to be coded to a "Preferred Term (PT)", "High Level Term (HLT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA, latest version).

An **Adverse Event** is any untoward medical occurrence in a patient 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.

AEs also include: any worsening (i.e., 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; abnormal laboratory findings considered by the investigator to be clinically significant; and any untoward medical occurrence.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/ incapacity; is a congenital anomaly/ birth defect; or is an important medical event.

The criteria for determining whether an abnormal laboratory, vital sign or ECG finding should be reported as an AE are as follows:

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

The pre-treatment period is defined as the period from the patient providing informed consent up to the first dose of study drug. The pre-treatment AEs are AEs that developed or worsened in severity during pre-treatment period.

The treatment emergent period is defined as the period from the administration of first study dose to the EOS visit. The treatment-emergent period consists of the treatment period and follow-up period. The definitions of the treatment period and the follow-up period are described inside Section 3.3. Treatment-emergent AEs (TEAEs) are AEs that developed or worsened in severity compared to the baseline during the treatment emergent period. As only the worsening pre-existing AEs and new AEs reported during the treatment and follow-up period will be collected in the study, all AEs collected during the treatment and follow-up period are considered as TEAEs.

4.6.2. Adverse Events of Special Interest

In this study, the adverse event of special interest (AESI) category includes:

- 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)
- Keratitis (any event regardless of severity or seriousness)

Section 10.4 provides a list of AESIs search criteria.

4.6.3. Laboratory Safety Variables

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory.

Samples for laboratory testing will be collected according to visit schedule (Section 10.2). Tests will include:

Serum Chemistry

Sodium	Total protein, serum	Total bilirubin[1]
Potassium	Creatinine	Total cholesterol[2]
Chloride	Blood urea nitrogen (BUN)	Triglycerides
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)[3]

Glucose	Alkaline phosphatase
Albumin	Lactate dehydrogenase (LDH)

[1] Direct and indirect bilirubin will be measured when the total bilirubin is above the ULN
[2] Low-density lipoprotein and high-density lipoprotein
[3] CPK isoenzymes will be measured when CPK >5× the ULN

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

Serum and urine pregnancy testing will be performed for all female patients of childbearing potential at time points according to Section 10.2. The following tests will be performed at screening: HIV Ab, HBsAg, HBsAb, HBcAb, Hepatitis C antibody.

4.6.4. Vital Signs

The following vital signs parameters will be collected:

- Respiratory rate (bpm)
- Pulse (beats/min)

- Sitting systolic and diastolic blood pressures (mmHg)
- Body temperature (ºC)

Vital signs will be collected predose at the time points according to Section 10.2.

4.6.5. Body Weight and Height

Body weight and height will be measured at time points according to Section 10.2.

4.6.6. Physical Examination Variables

The physical examination variable values are dichotomized to normal and abnormal. A thorough and complete physical examination will be performed at time points according to visit schedule (Section 10.2).

4.6.7. 12-Lead Electrocardiography (ECG) Variables

Standard 12-Lead ECG parameters include: Ventricular HR, PR interval, QRS interval, corrected QT interval (QTc Fridericia [QTcF] **=QT/[RR0.33] and QTc** Bazett **[QTcB]=QT/[RR0.5]**) ECG status: normal, abnormal not clinical significant or abnormal clinical significant. Electrocardiograms should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at time points according to Section 10.2.

4.6.8. 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.

4.6.9. 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 at Screening Visit 2 and each NAC visit (Screening Visit 3 and Visit 16). Peak expiratory flow must be >80% predicted to perform the NAC in any subject with a history of asthma.

4.7. Pharmacokinetic (PK) Variables

Serum samples for measuring functional dupilumab concentrations will be collected at time points according to Section 10.2. PK variables consist of functional dupilumab concentration and time (both actual and nominal).

4.8. Immunogenicity Variable

The immunogenicity variables are ADA status, titer, neutralizing antibody (NAb) status, and time-point/visit. Serum samples for anti-dupilumab antibody will be collected at time points according to schedule (Section 10.2). Samples positive in the dupilumab ADA assay will be

further characterized for ADA titers and for the presence of neutralizing antibody (NAb) against dupilumab.

4.9. Biomarkers Variables

Biomarker samples will be collected at time points according to according to Section 10.2. Biomarker measurements (TARC, total IgE, Timothy Grass specific IgE, Timothy Grass specific IgG4, Timothy Grass specific IgG) 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.

5. STATISTICAL METHODS

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

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

All data will be summarized by the following 4 treatment groups defined in Section 1.1.

5.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group for FAS. Listing of demographics and baseline characteristics will be presented.

5.2. Medical History

Medical history will be summarized by primary SOC and PT for each treatment group. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treatment groups. Medical history will be listed.

5.3. Prior/Concomitant Medications/Procedures

Number and proportion of patients taking prior/concomitant medications, prohibited medications and rescue medications will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC level 4, based on the overall incidence for the combined treatment groups. Patients will be counted only once for each medication class (ATC level 2 and 4) linked to the medication.

Number and proportion of patients taking prior/concomitant procedures will be summarized, sorted by decreasing frequency of SOC and PT based on the overall incidence for the combined treatment groups. Patients will be counted only once for each SOC and PT linked to the procedure.

Concomitant medications used to treat SCIT related adverse events will be tabulated separately.

Prior medications or procedures started before screening visit and started between screening visit and first injection date will be summarized separately.

Listing of medications and procedures will be provided.

5.4. Rescue/ Prohibited Medications

Number and proportion of patients taking prohibited procedures and rescue procedures will be summarized, sorted by decreasing frequency of SOC and PT based on the overall incidence for the combined treatment groups. Patients will be counted only once for each SOC and PT linked to the procedure.

Concomitant treatments for allergies including allowed and rescue treatments (i.e., both medications and procedures) will be analyzed similarly.

5.5. Subject Disposition

The following summaries by table will be provided:

- The total number of screened patients
- The total number of randomized patients: received a randomization number
- The total number of patients in each analysis set
- The total number of patients who completed the study and discontinued the study with the reason of discontinuation
- The total number of patients who completed the study treatment and discontinued the study treatment with the reason of discontinuation

The following listings will be provided:

- Listing of patient disposition including: date of randomization, date of the last visit, received dose, completed study drug or discontinued by reason, completed study or discontinued by reason
- A listing of patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from the study or treatment, along with reasons for discontinuation
- Summary table with listing of protocol deviations will be provided

Time to the discontinuation will be assessed by Kaplan-Meier estimates (K-M plot) for each treatment group.

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Measurement of Compliance

The compliance with study treatment will be calculated separately for dupilumab injection and SCIT injection as follows:

Treatment Compliance = (Number of study drug injections during exposure period) / (Number of planned study drug injections during exposure period) x 100%, where the study drug injections can be dupilumab (or placebo dupilumab) injection, or SCIT (or placebo SCIT) injection.

For treatment compliance calculation of dupilumab injection, the two injections taken at the randomization visit 4 will be counted as 1 injection.

For treatment compliance calculation of SCIT injection, all the injections taken at the same visit will be counted as one single injection. Because due to the judgement of investigators to avoid patients having intolerable allergic symptoms, patients may not receive all the planned SCIT injections for a visit according to protocol.

Summary of study drug administration will include the number of study drug doses administered and treatment compliance. The treatment compliance will be presented by the following specific ranges for each treatment group: <80%, and ≥80%.

Listing of dose administration: including date/time, study day, number of injections, locations of injections, dosing information, and whether or not the total dose is administered for each dose will be presented.

5.6.2. Exposure to Investigational Product

The duration of treatment exposure during the study in day is calculated as:

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

The calculations are regardless of temporary dosing interruption. The duration of exposure during the study will be summarized by treatment group using number of patients, means, SD, minimums, medians, and maximums.

In addition, the duration of exposure will be summarized categorically by counts and percentages for each of the following categories and cumulatively by these categories as well:
≥ 14 days, ≥ 28 days, ≥ 42 days, ≥ 56 days, ≥ 70 days, ≥ 84 days, ≥ 98 days, ≥ 112 days and ≥ 126 days.

The duration of observation period during the study in day is calculated as:

(Date of the last visit – date of the first study drug injection) +1 day.

The number (%) of patients with observation periods will be presented by specific time periods. The time periods of interest are specified as: < 8 days, ≥ 8 days, ≥ 15 days, ≥ 22 days, ≥ 29 days, ≥36 days, ≥43 days, ≥50 days, ≥ 57 days, ≥ 71 days, ≥92 days, ≥113 days, ≥120 days, ≥141 days, and ≥169 days.

5.7. Analyses of Efficacy Variables

For all efficacy variables, unless specified, the analysis will be comparisons of

- dupilumab + SCIT versus SCIT
- dupilumab versus placebo
- dupilumab + SCIT versus dupilumab for percent change and change in TNSS AUC only

The efficacy analyses will be based on the FAS Population. All statistical tests will be 2-sided at the 5% significance level. All confidence intervals (CIs) will be 2-sided 95% CIs.

5.7.1. Analysis of Primary Efficacy Variable

The primary endpoint will be analyzed by using the analysis of covariance (ANCOVA) model as the primary analysis method. The model will include treatment group being the main factor and baseline value as the covariate. The missing AUC value at a visit directly when a patient does not have any TNSS score collected at the visit, will be imputed by multiple imputation (MI) methods 40 times to generate 40 complete data sets by using the Statistical Analysis System (SAS) procedure MI following the 2 steps below:

Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure using seed number 16115. The monotone missing pattern means that if a patient has missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the patient.

Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with seed number 51161 and adjustment for covariates including treatment groups and relevant baseline.

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. The least-squares (LS) mean for each treatment group with its corresponding standard error (SE), the LS mean difference between treatment group and its corresponding SE and 95% CI, and the p-value corresponding to the between-treatment-group difference will be reported.

In case of missing TNSS scores at one or more time points at a visit, all available TNSS scores collected at the visit will be used to calculate the AUC at the visit. The missing TNSS score at timepoints will not be imputed. The algorithm for calculation of AUC is provided in Section 6.2.

Sensitivity analyses:

- Post-baseline Last Observation Carried Forward (LOCF) approach will be used to impute the primary efficacy data at week 17, then the imputed data will be analyzed using ANCOVA model.
- All observed data without imputation will be included for analysis using ANCOVA model.

The primary efficacy analyses will be performed on FAS, as well as on PPS as a supportive analysis.

Subgroup analysis:

Subgroup analysis for the primary endpoint based on FAS will be performed. Descriptive statistics will be displayed for each subgroup for each treatment group.

5.7.2. Analyses of Secondary and Exploratory Efficacy Variables

The change and percent change from baseline in continuous secondary and exploratory efficacy endpoints will be analyzed using the same approach as that used for the analysis of the primary endpoint, unless specified otherwise.

The biomarker related continuous endpoint will be analyzed using a rank based ANCOVA model with treatment and relevant baseline as covariates. Post-baseline LOCF method will be used to impute the missing data. The comparison will be performed between dupilumab +SCIT vs SCIT.

The proportion of subjects who achieve SCIT maintenance dose (4000 BAU) during 16 weeks of treatment will be compared by Chi-square test between dupilumab + SCIT and placebo for dupilumab +SCIT groups. The maximal tolerated SCIT dose during 16 weeks of treatment and the local skin wheal size at approximately 15 minutes after each SCIT injection during 16 weeks of treatment will be summarized descriptively. If the wheel size is too small to measure after the SCIT injection, the diameter is set to zero.

5.7.3. Adjustment for Multiple Comparison

There is no control for multiplicity.

5.8. Analysis of Safety Data

The summary of safety and tolerability will be performed based on SAF and presented for each treatment group.

The safety analysis will be based on the reported AEs, clinical laboratory evaluations, physical examination, vital signs and 12-lead ECG.

Thresholds for treatment-emergent Potentially Clinically Significant Values (PCSVs) in laboratory variables and vital signs are defined in Section 10.3. Treatment-emergent PCSV is any PCSV developed or worsened in severity compared to the baseline during the treatment and follow-up period.

The time interval to detect any event or abnormality is between the first injection of study medication and EOS.

5.8.1. Adverse Events

Listing of TEAEs, serious TEAEs, and TEAEs resulting in death and study drug discontinuation will be generated.

Number and proportions of patients reporting TEAEs will be summarized for overall during the study sorted by decreasing frequency of SOC and PT based on the overall incidence for the combined treatment groups.

Summaries of TEAEs will include:

- TEAEs
  - TEAEs by SOC/PT
  - TEAEs by SOC/HLT/PT
  - TEAEs by PT
  - Common TEAEs by SOC/PT (incidence with PT ≥2%)
  - TEAEs by severity by SOC/PT
  - Severe TEAEs by SOC/PT
  - Severe TEAEs related to dupilumab or placebo for dupilumab as assessed by the investigator by SOC/PT
  - Severe TEAEs related to SCIT or placebo for SCIT as assessed by the investigator by SOC/PT
  - Severe TEAEs related to study procedure as assessed by the investigator by SOC/PT
- Serious TEAEs by SOC/PT

  - Serious TEAEs by SOC/PT
  - Serious TEAEs by SOC/HLT/PT
  - Serious TEAEs related to dupilumab or placebo for dupilumab as assessed by the investigator by SOC/PT
  - Serious TEAEs related to SCIT or placebo for SCIT as assessed by the investigator by SOC/PT
  - Serious TEAEs related to study procedure as assessed by the investigator by SOC/PT
- TEAEs leading to permanent discontinuation from study treatment by SOC/PT
- Death by SOC/PT

In addition, separate summary will be provided for the TEAE caused by SCIT or placebo SCIT injection.

Number of patients with dupilumab/placebo and SCIT/placebo reactions will be summarized as follows.

- Dupilumab/placebo for dupilumab injection reaction:
  - by preferred ISR term
  - by adverse event preferred term.
- SCIT/Placebo for SCIT injection reactions
  - by preferred ISR term for early local, late phase, and overall study
  - by adverse event preferred term for early local, late phase, and overall study
- SCIT/placebo for SCIT reactions
  - by reaction type and toxicity grade
  - by adverse event preferred term.

Number and proportion of patients reporting pre-treatment adverse events will be tabulated by SOC and PT.

Subgroup analysis

Subgroup analysis will be performed for TEAE except injection reactions.

5.8.2. Analysis of Adverse Events of Special Interest

The adverse events of special interest (AESI) will be summarized by AESI category (see Section 10.4) and HLT/PT.

In addition, separate summary will be provided for the AESI caused by SCIT or placebo SCIT injection.

5.8.3. Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry, hematology and urinalysis results, and will be converted to standard international units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory result and change from baseline by visit
- The number (n) and percentage (%) of patients with abnormal lab value during study whose baseline values are normal (overall and per each lab parameter)
- The number (n) and percentage (%) of patients with treatment-emergent PCSVs
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listing of all laboratory parameters normal range, abnormal flag and treatment-emergent PCSV by patient and visit will be provided.

5.8.4. Analysis of Vital Signs

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variables and change from baseline by visit
- The number (n) and percentage (%) of patients with treatment-emergent PCSV
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listings of vital sign will be provided with flags indicating the treatment-emergent PCSVs.

5.8.5. Physical Exams

The number (n) and percentage (%) of patients with abnormal physical exams will be summarized at baseline, end of treatment period and end of study by treatment group. A summary of treatment-emergent abnormal findings will be provided.

5.8.6. Analysis of 12-Lead ECG

Summaries of 12-lead ECG parameters by treatment group will include:

- Each ECG parameter and change from baseline
- The number (n) and percentage (%) of subjects with PCSV, depending on data
- ECG status (i.e. normal, abnormal) summarized by a shift table

Listings of ECG will be provided with flags indicating PCSVs.

5.9. Analysis of Pharmacokinetic Data

The following analyses will be conducted:

- Descriptive statistics of functional dupilumab concentrations in serum at each sampling time by dose

- Graphical presentations of median and mean (+/- SD) functional dupilumab concentration in serum vs nominal time profiles
- Graphical presentations of individual functional dupilumab concentration in serum vs actual sampling time profiles
- Assessment of the impact of anti-drug antibodies on functional dupilumab concentrations in serum

No formal statisitical analysis will be performed. For the descriptive statistical analysis, concentrations below the lower limit of quantitation (LLOQ) will be set to zero. When plotted on semi-log scale, concentrations are imputed as LLOQ/2. Mean data are presented by nominal time. Individual concentrations are presented by actual time.

5.10. Analysis of Immunogenicity Data

5.10.1. Analysis of ADA Data

Immunogenicity will be characterized by the ADA responses observed in patients in the ADA analysis set:

- Pre-existing immunoreactivity, defined as either an ADA positive response in the dupilumab ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 4-fold over baseline titer levels
- Treatment-emergent response, defined as a positive response in the dupilumab ADA assay post first dose when baseline results are negative or missing
- Treatment-boosted response, defined as a positive response in the dupilumab ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive
- Maximum Titer Values (Titer value category)
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

The following summaries will be provided:

- Number (%) of ADA-negative patients (pre-existing immunoreactivity or negative in the dupilumab ADA assay at all time points)
- Number (%) of treatment-emergent ADA-positive patients
- Number (%) of treatment-boosted ADA-positive patients

Listing of all ADA titer levels will be provided for treatment-emergent and treatment-boosted ADA response patients.

5.10.2. Analysis of Neutralizing Antibodies (NAb) Data

The absolute occurrence (n) and percent of patients (%) with NAb positive or negative status will be provided by treatment group for patients in the NAb analysis set.

5.11. Analysis of Immunogenicity with Exposure, Safety and Efficacy

5.11.1. Immunogenicity and Exposure

Associations between ADA and systemic exposure to dupilumab will be explored. Plots of dupilumab concentration may be provided for analyzing the potential impact of treatment-emergent ADA responses and titer (high, moderate or low) on PK.

5.11.2. Immunogenicity and Safety and Efficacy

Association between ADA and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow])

Association between ADA and primary efficacy endpoints may be explored (e.g. scatter plot or spaghetti plot).

The above mentioned safety and efficacy analyses will be conducted using the following ADA response categories:

- ADA positive patients, that is patients with treatment-emergent or treatment-boosted response,
- ADA negative patients, that is patients with pre-existing immunoreactivity or negative in the ADA assay at all time points
- NAb positive patients, that is patients who were positive in the NAb assay at any time point analyzed.
- Maximum post-baseline titer level in treatment emergent or treatment boosted ADA positive patients:
  - High,
  - Moderate,
  - Low

5.12. Analysis of Biomarker Data

All biomarker analyses will be performed on the FAS using all observed data. Descriptive statistics for the observed values, change from baseline and percent change from baseline values by treatment and visit will be provided for the biomarker variables.

The Wilcoxon signed-rank test will be used to test if the change or percentage change from baseline value is significantly different from zero. P-value will be reported.

Exploratory analyses for the difference between dupilumab groups and placebo on the change from baseline and percent change from baseline values will be performed using a rank-based ANCOVA model with treatment group and the relevant baseline values as covariate. Missing value will be imputed by LOCF method for visits between post-baseline to week 17. After week 17, no imputation will be made. P-value for difference between dupilumab +SCIT and SCIT will be provided.

Correlation of baseline serum Timothy Grass sIgE, Timothy Grass specific IgG, sIgG4, TARC and total IgE, absolute change or percent change at weeks 4, 8, and 17 from baseline in these biomarkers; with the following clinical endpoints will be explored using the Spearman's rho test. Both Spearman correlation coefficients and p-value will be reported. Correlation of baseline serum Timothy Grass sIgE, Timothy Grass specific IgG, sIgG4, TARC and total IgE with the following clinical endpoints will also be analyzed by the ANCOVA model with the clinical endpoint as the dependent variable and the baseline biomarker as the covariate, treatment group, and treatment group by baseline biomarker interaction as the factors. The missing values will be imputed using post-baseline LOCF. Similar correlation analysis will be performed for the subclasses of Timothy Grass sIgG other than sIgG4 pending on available data.

- Change and percent change from baseline in TNSS AUC post NAC over the first hour after the challenge (0-1 hr post peak TNSS) at week 17
- Change and percent change from baseline in TOSS AUC post NAC over the first hour after the challenge (0-1 hr post peak TNSS) at week 17
- 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 average wheal sizes (diameter) 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)

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment of the study for all measurements will be the latest available valid measurement taken prior to the first administration of study drug. If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization. The baseline of TNSS is defined in Section 4.5.1.

The following rules specify the determination of baseline by both date/time information:

- For the AE, lab, PK and ADA data, both date and time of the measurement will be used to determine baseline by comparing with the first injection date and time.
- For other data except AE, lab, PK or ADA, only date of the measurement will be used to determine baseline by comparing with the first injection date.

For the rescreened patients, all data from the same patient will be used to derive baseline regardless if the data is from the screen-failure subject ID or enrolled subject ID.

6.2. Data Handling Convention for Efficacy Variables

Algorithm for calculation of area under curve (AUC)

The AUC will be calculated using trapezoid rule. For example, the AUC within 1 hour will be calculated using formula

$$AUC_{[0-1h]} = [\sum_{i=1}^{5}(t_i - t_{i-1}) * (D_i + D_{i-1})/2]/(t_5 - t_0)$$

Where

- D_i is the TNSS value obtained at time t_i
- t_i is the time (in hours) for which D_i is measured, such as $t_0 = 0$;$t_1 = 1/12$ hour for 5 minutes, $t_2 = 0.25$ hour for 15 minutes, $t_3 = 0.5$ hour for 30 minutes, $t_4 = 0.75$ hour for 45 minutes and $t_5 = 1$ for 1 hour.

In case of missing TNSS scores at one or more time points at a visit, all available TNSS scores collected at the visit will be used to calculate the AUC at the visit. The missing TNSS score at timepoints will not be imputed.

For example, if there is one missing timepoint value within 1 hour, then the AUC within 1 hour at the visit will be calculated using the 5 available TNSS scores. These 5 scores will be numbered as $D_0, D_1, D_2, D_3, D4$, *at timepoints* t_0, t_1, t_2, t_2, t_4, the AUC will be calculated as

$$AUC_{[0-1h]} = [\sum_{i=1}^{4}(t_i - t_{i-1}) * (D_i + D_{i-1})/2]/(t_4 - t_0)$$

Data Handling Convention for Missing Data

Rules for handling missing data for primary and secondary efficacy variables are described in Section 5.7.1 and Section 5.7.2.

Adverse event

If the intensity of a TEAE is missing, it will be classified as "severe" in the frequency tables by intensity of TEAE. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as "related" in the frequency tables by relation to the investigational product.

Adverse event start date

AE start date will be used for AE classification and analysis of AESIs. If AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed and an imputation flag will indicate which date component is missing.

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and the AE start month is the same as the first dose month) then impute AE start day using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Otherwise impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. Imputation flag is 'D'.

If AE start month is missing, and AE start year is not missing: If AE start year is less than the first dose year, use the informed consent day and month. If AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use AE end date instead. If AE start year is after the first dose year, use 01 January. Imputation flag is 'M'.

If AE start year is missing: Impute AE start date using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Imputation flag is 'Y'.

Adverse event end date

The general recommendation is not to impute AE end date. However, since AE end date will be used for AE starting date imputation, In order to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in CRF will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing: Impute AE end date using the last day of the month. If this leads to a date after end of study follow up date, use end of follow up date instead.

If AE end month is missing, and AE end year is not missing: Impute AE end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the end of follow up date instead.

If AE end year is missing: Impute AE end date using the end of follow up date.

Medication start and end date missing

To determine whether a medication is prior medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be calculated in medication listings.

Prior medication start date

If start day is missing, and start month and year are not missing: Impute the start day using the first day of the month. Imputation flag is 'D';

If start month is missing, and start year is not missing: Impute the day and month using 01 January. Imputation flag is 'M'.

If start year is missing: Impute start date using 2 years before inform consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However in order to simplify the programming flow, the imputation is proposed to in line with the protocol which specifies to collect up to 2 years prior medication. Since the start date of prior medication will not be used in any analysis, the rule will not impact the analysis result.

Prior medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'M'.

If end year is missing: Impute end date using the first dose intake date –1. Imputation flag is 'Y'.

Concomitant medication start date

The imputation rule for concomitant medication start date is the same as AE start date.

Concomitant medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date after end of study follow up date, use end of follow up date instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the end of follow up date instead. Imputation flag is 'M'.

If end year is missing: Impute date using the end of follow up date. Imputation flag is 'Y'.

Medication coding

Medications whose ATC level 4 cannot be coded will be summarized by setting ATC4=ATC2 in the table programs. However, these uncoded ATC level 4 records still need to be confirmed with study DM and study MD.

PCSV

Patients who had post-baseline PCSV but missing baseline value will be regarded as having treatment emergent PCSV.

6.3. Visit Windows

Data analyzed by-visit-analysis (including efficacy, laboratory data, visit sign, and ECG) will be summarized by the study scheduled visits described in the study protocol and SAP, "Schedule of Event". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination (ET) visit and end of treatment (EOT)/end of study (EOS) have the potential to be summarized. No analysis visit windows will be applied for the study scheduled visits.

The following analysis visit windows will be used to map the unscheduled visits, ET and EOT/EOS visits, based on the study day:

Visit	Target Day	Analysis Time Window Based on Study day*
Screening	<1	<1
Baseline	1	1
Week 1	8	[2,11]
Week 2	15	[12,18]
Week 3	22	[19,25]
Week 4	29	[26, 32]
Week 5	36	[33, 39]
Week 6	43	[40, 46]
Week 7	50	[47, 53]
Week 8	57	[54, 64]
Week 10	71	[65, 81]
Week 13	92	[82, 102]
Week 16	113	[103, 116]
Week 17	120	[117, 130]
Week 20	141	[131, 155]
Week 24	169	>=156

*Study day is calculated relative to the date of first study drug injection.

In general, the following order will be used to select the record for analysis at given visit:

1. Scheduled visit
2. Early termination (ET) or end of study (EOS), whichever comes first if scheduled visit not available
3. Unscheduled visit if both scheduled visit and ET/EOT/EOS are not available

For the multiple measurements of the same test in the same window, the following rules will be used to pick up the analysis value:

- If multiple valid values of a variable within an analysis visit window, the closest from the target study day will be selected.
- If the difference is a tie, the value after the targeted study day will be used.
- If multiple available values of a variable exist within a same day, then the first value of the day will be selected.

6.4. Unscheduled Assessments

Both scheduled and unscheduled measurements will be considered for determining abnormal/PCSV values from laboratory, vital sign or ECG as well as the baseline values.

7. INTERIM ANALYSIS

There is no interim analysis.

8. SOFTWARE

All analyses will be done using SAS Version 9.4 or above.

9. REFERENCES

ICH. (1996, July 30). ICH Harmonized tripartite guideline: Structure and content of clinical study reports (E3). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

ICH. (1997, July 17). ICH Harmonized tripartite guideline: General considerations for clinical trials (E8). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

10. APPENDIX

10.1. Summary of Statistical Analyses

Efficacy Analysis:

Parameter(s)	Endpoints	Primary Statistical Method	Supportive/Sensitivity Statistical Method	Subgroup Analysis
TNSS	percent change and absolute change from baseline in AUC for TNSS (0-1 hr post peak TNSS) at week 17	ANCOVA model, missing data imputed by Multiple Imputation (MI)	Yes	Yes
TOSS	percent change and absolute change from baseline in AUC for TOSS (0-1 hr post peak TNSS) at week 17	ANCOVA model, missing data imputed by Multiple Imputation (MI)	No	No
Skin Prick Test with Serial Allergen Titration	percent change and absolute change from baseline in AUC for wheal sizes (diameter) (0-1 hr post peak TNSS) at week 17	ANCOVA model, missing data imputed by Multiple Imputation (MI)	No	No
skin Timothy Grass intradermal injection	percent change and absolute change from baseline in wheal size (diameter) induced by skin Timothy Grass intradermal injection 6 hrs after the challenge) at week 17	ANCOVA model, missing data imputed by Multiple Imputation (MI)	No	No

Parameter(s)	Endpoints	Primary Statistical Method	Supportive/Sensitivity Statistical Method	Subgroup Analysis
PNIF	percent change and absolute change from baseline in PNIF AUC (0-1 hr post peak TNSS, and 1-6hr post peak TNSS) at week 17	ANCOVA model, missing data imputed by Multiple Imputation (MI)	No	No
sneeze count	percent change and absolute change from baseline in sneeze count AUC (0-1 hr post peak TNSS, and 1-6hr post peak TNSS) at week 17	ANCOVA model, missing data imputed by Multiple Imputation (MI)	No	No

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics	No	Yes for selected AE summary	No
Laboratory Measures	SAF	Descriptive Statistics	No	No	No
Vital sign	SAF	Descriptive Statistics	No	No	No
ECG	SAF	Descriptive Statistics	No	No	No

10.2. Schedule of Time and Events

Schedule of Events – Screening, Baseline and Treatment Periods

	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																			

Study Procedure	Screening Period				Treatment Period															
	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]**	
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		

Study Procedure	Screening Period				Treatment Period																
	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]	
Training for Self-injection (dupilumab/PBO)				X																
Dupilumab/PBO distribution				X		X						X		X				X		
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

	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]**	
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

	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]**	
Laboratory Testing																				
HIV Ab, HBsAg, HBcAb, Hep C Ab,		X																X		
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

	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]**	
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

	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]**	
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
Serum Timothy Grass sIgG4[11]			X	X		X		X		X		X		X		X	X		X	X
Drug Concentration and ADA:																				

	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]**	
Functional dupilumab PK[11, 12]			X						X			X		X		X	X		X	X
Anti-drug antibody[11, 12] (ADA)			X													X			X	X

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 2.
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 the protocol 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.

10.3. Analyses of Efficacy Variables Criteria for Potentially Clinically Significant Values (PCSV) for Adult Patients

Parameter	Treatment Emergent PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN*	Enzyme activity must be expressed in ULN, not in IU/L.
	>5 and ≤ 10 ULN and baseline ≤ 5 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007.
	>10 and ≤ 20 ULN and baseline ≤ 10 ULN	Each category is calculated independently.
	>20 ULN and baseline ≤ 20 ULN	* At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN*	Enzyme activity must be expressed in ULN, not in IU/L.
	>5 and ≤ 10 ULN and baseline ≤ 5 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007.
	>10 and ≤ 20 ULN and baseline ≤ 10 ULN	Each category is calculated independently.
	>20 ULN and baseline ≤ 20 ULN	* At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L.
		Concept paper on DILI – FDA draft Guidance Oct 2007.

Parameter	Treatment Emergent PCSV	Comments
Total Bilirubin*	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
Conjugated Bilirubin	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin >1.5 ULN) and (Direct Bilirubin <=35% Total Bilirubin or Total Bilirubin <=1.5 ULN) at baseline	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	(ALT>3 ULN and TBILI>2 ULN) and baseline (ALT <=3 ULN **or** TBILI <=2 ULN)	Concept paper on DILI – FDA draft Guidance Oct 2007.
CPK*	>3 and ≤ 10 ULN and baseline ≤ 3ULN* >10 ULN and baseline ≤ 10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L >=30% change from baseline and <100% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria

Parameter	Treatment Emergent PCSV	Comments
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L and <=408 µmol/L at baseline <120 µmol/L and >= 120 µmol/L at baseline	Harrison- Principles of internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria
Chloride Hypochloremia Hyperchloremia	 <80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	Two independent criteria
Sodium Hyponatremia Hypernatremia	 ≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	Two independent criteria
Potassium Hypokalemia Hyperkalemia	 <3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	FDA Feb 2005. Two independent criteria
Total Cholesterol	≥7.74 mmol/L and < 7.74 mmol/L at baseline	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L and < 4.6 mmol/L at baseline	Threshold for therapeutic intervention.
Glucose Hypoglycaemia Hyperglycaemia	 (≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or >=LLN) at baseline ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and < 11.1 mmol/L (unfasted); <7 mmol/L (fasted) at baseline	 ADA May 2005. ADA Jan 2008.
HbA1c	>8% and <= 8% at baseline	
Albumin	≤25 g/L and >25 g/L at baseline	

Parameter	Treatment Emergent PCSV	Comments
CRP	>2 ULN or >10 mg/L (if ULN not provided) and <=2 ULN or <=10 mg/L (if ULN not provided) at baseline	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black); <2.0 Giga/L and >=2.0 Giga/L at baseline (Black) ≥16.0 Giga/L and < 16 Giga/L at baseline	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L and <= 4.0 Giga/L at baseline	
Neutrophils	<1.5 Giga/L and >=1.5 Giga/L at baseline (Non-Black); <1.0 Giga/L and >=1.0 Giga/L at baseline (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L <= 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L <= 0.1 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female. ≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).

Parameter	Treatment Emergent PCSV	Comments
Hematocrit	≤0.37 v/v and > 0.37 v/v at baseline for Male ; ≤0.32 v/v and > 0.32 v/v at baseline for Female ≥0.55 v/v and < 0.55 v/v at baseline for Male ; ≥0.5 v/v and < 0.5 v/v at baseline for Female	Two Criteria are independent
RBC	Female <3 Tera/L and baseline ≥3 Tera/L ≥6 Tera/L and baseline < 6 Tera/L Male <4 Tera/L and baseline ≥4 Tera/L ≥7 Tera/L and baseline < 7 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L and >=100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria
Urinalysis		
pH	≤4.6 and > 4.6 at baseline ≥8 and < 8 at baseline	Two independent criteria
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.

Parameter	Treatment Emergent PCSV	Comments
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: CPMP 1997 guideline.
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms & < 120 ms at baseline	
QTc Borderline Prolonged* Additional	<u>Absolute values (ms)</u> Borderline: 431-450 ms and < 431ms at baseline for Male; 451-470 ms and < 451 ms at baseline for Female Prolonged: >450 to <500 ms and <= 450 ms at baseline for Male; >470 to <500 ms and <= 470 ms at baseline for Female ≥500 ms and < 500 ms at baseline <u>Increase from baseline</u> Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula. *QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings. 5 independent criteria

10.4. Search Criteria for TEAE of Special Interest/TEAE Syndrome

AESI	Search Criteria
Anaphylactic reactions	For SMQ "anaphylactic reaction" An **algorithmic approach** will be used. A case must include either: 1. A narrow term (a term from Category **A**); 2. Patient with both a term from Category **B** AND a term from Category **C**; 3. Patient with a term from Category **D** AND { a term from Category **B** - OR a term from Category **C** } For bullets 2 and 3, the search terms that are included under the SMQ for a particular event need to have the same start date (for e.g. if search shows cough (category B term) occurring at day 3 and urticaria (category C term) occurring at day 7, this event is not adjudicated as anaphylactic reaction as this is inconsistent with the clinical presentation of anaphylaxis as an acute event with simultaneous involvement of 2 or more body systems. For SCIT anaphylactic reactions, only those with toxicity grade 3 will be included into this category. Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock
Systemic or severe hypersensitivity reactions	Hypersensitivity: Narrow SMQ for hypersensitivity For systemic hypersensitivity, events in which 2 or more body systems are involved (as defined by System Organ Class) would be considered for adjudication based on further medical judgement For severe hypersensitivity, an additional search will be done; - HLT = Injection site reactions - Severity = "severe" The SCIT anaphylactic reactions will also be counted in this category regardless of toxicity grade. Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock
Malignancy	• SMQ "Malignant tumours" • SMQ "Tumours of unspecified malignancy"
Helminthic infections[2]	-HLT = Cestode infections -HLT = Helminthic infections NEC -HLT = Nematode infections -HLT = Trematode infection

Suicidal behavior	Include the following PTs • Completed suicide • Suicidal ideation • Suicide attempt • Depression suicidal • Suicidal behavior
Any type of conjunctivitis or blepharitis (severe or serious)	broad CMQ conjunctivitis (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Ocular hyperaemia, Conjunctival hyperaemia, Xerophthalmia) Blepharitis PTs (Blepharitis, blepharitis allergic) **AND** Serious AE= "Yes" OR Severity= "severe" Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock.
Keratitis	Any of the following PTs: a. Keratitis b. Allergic keratitis c. Ulcerative keratitis d. Atopic keratoconjunctivitis e. Herpes ophthalmic f. − Ophthalmic herpes simplex Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock.

The search criteria are meant to assist the process of identification of TEAE of Special Interest/TEAE Syndrome. However, since these criteria might not be exhaustive in some cases or may not be specific in other cases. Hence an additional blinded review of all PTs in the database may be performed by the Medical monitor, based on medical judgement, to identify any TEAE of Special Interest/TEAE Syndrome that might have been missed by the criteria or to identify any TEAE may been inaccurately assigned as AESI by the algorithmic search.

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