REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: 1.0

Clinical Study Protocol Title:

A Study to Evaluate the Efficacy and Safety of Dupilumab Monotherapy in Pediatric Patients with Peanut Allergy

Compound:	Dupilumab (REGN668)
Protocol Number:	R668-ALG-1702 Amendment 2
Clinical Phase:	Phase 2
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
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Study Medical Director:	[redacted]
Version/Date:	Original Statistical Analysis Plan / March 3, 2021

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 Antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under curve
BUN	Blood urea nitrogen
CoFAR	Consortium of Food Allergy Research
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
DBPCFC	Double-blind, placebo-controlled food challenge
DLS	Dose limiting symptom
EC	Ethics Committee
EDC	Electronic data capture
EoE	Eosinophilic Esophagitis
FAQLQ	Food allergy quality of life questionnaire
FDA	Food and Drug Administration
FeNO	Fractional Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in 1 Second
GCP	Good Clinical Practice
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
Hep C Ab	Hepatitis C antibody
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IgE	Immunoglobulin E
IL-4	Interleukin 4
IL-4Rα	Interleukin 4 Receptor Alpha
IL-13	Interleukin 13
IM	Intramuscular
IL	Interleukin
IRB	Institutional Review Board

IV	Intravenous
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
OIT	Oral immunotherapy
PBMC	Peripheral blood mononuclear cells
PCSV	Potentially clinically significant value
PEFR/PEF	Peak expiratory flow rate
PK	Pharmacokinetic
POC	Proof-of-concept
PT	Preferred term
Q2W	Every 2 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
sIgE	Peanut-specific IgE
SOC	System organ class
SPT	Skin prick test
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell

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-1702 study.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. These revisions will be based on review of the study and data, and a final plan will be issued prior to data lock.

1.1. Background/Rationale

Food allergy is a potentially life-threatening condition that affects up to 8% of young children and 3% to 5% of the entire United States (US) population (Gupta, 2011) (Sicherer, 2010) (Nwaru, 2014). Unlike many other childhood allergies, peanut allergy typically persists into adulthood and is associated with a higher incidence of severe anaphylaxis as compared with other food allergies (Dyer, 2015). The prevalence of peanut allergy by self-reports in US and European Union (EU) children varies from 1.2% to 2.0% (Dunlop, 2018). The current remedies for food allergy are food avoidance and treatment with medications such as injectable epinephrine for accidental exposures associated with severe allergic symptoms. Although recent progress has been made in the treatment of food allergy through allergen-specific oral immunotherapy (OIT), there is an unmet need for a new therapy in food allergy. (Jones, 2009) (Anagnostou, 2011) (Anagnostou, 2014). The aim of oral immunotherapy (OIT) is to induce desensitization and increase the threshold for peanut ingestion and reduce the risks of allergic reactions after accidental ingestion. However, many subjects in OIT trials continue to have side effects that can hinder their compliance and the overall efficacy of OIT. There is also a subsequent rapid loss of tolerance upon cessation of OIT (Vickery, 2014) (Wood, 2017).

The immune system in the gut actively induces an immune tolerant state to the proteins that are normally consumed. Food allergy occurs when the body has a break in this tolerance, which results in an abnormal immune reaction to food. It is known that allergic response to food including peanut protein is an immunoglobulin E (IgE) mediated event; however, recent data suggest that interleukin (IL-4) and IL-13 may also play a significant role in food allergy pathogenesis.

Dupilumab, a fully human VelocImmune-derived monoclonal antibody directed against interleukin-4 receptor alpha (IL-4Rα), blocks the activity of IL-4 and IL-13 and is approved as a treatment for atopic dermatitis (AD).

This phase 2 proof-of-concept (POC) study will explore whether dupilumab has immunomodulatory effects on type 2 immune responses, which may result in improved safety and tolerance to peanut exposure as determined by the ability to tolerate a higher cumulative peanut protein dose level during a double-blind, placebo-controlled food challenge (DBPCFC) after 24 weeks of monotherapy treatment. In addition, the study will evaluate whether dupilumab influences known biomarkers that are important in the allergic response to peanuts such as a reduction in allergen-specific IgE and/or increase in allergen-specific IgG4.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objective of this study is to assess the tolerability of peanut protein in pediatric patients (6 ot 17 years old) treated with dupilumab monotherapy, in which tolerability is defined as the proportion of patients who safely pass a double-blinded placebo-controlled food challenge (DBPCFC) at week 24.

1.2.2. Secondary Objectives

The secondary objectives of the study include:

- To determine whether dupilumab treatment improves peanut tolerability, defined as a change in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC (up to 2044 mg cumulative)
- To evaluate the safety and tolerability of dupilumab treatment in peanut allergic patients
- To evaluate the effects of dupilumab treatment on the levels of peanut-specific IgE, IgG, IgG4 and peanut-specific IgG4/sIgE ratio, and peanut-specific IgG/sIgE ratio
- To evaluate the treatment effect of dupilumab on the average wheal size after a titrated skin prick test (SPT), as measured by area under the curve (AUC) of the average wheal size induced by peanut extract at different concentrations
- To assess the incidence of treatment-emergent anti-drug antibodies (ADA) to dupilumab in patients over time

1.2.3. Modifications from the Statistical Section in the Final Protocol

Modifications from protocol amendment 2:

- Removed the FAS and week 36 FAS for efficacy analysis. This study design is an open-label, single-arm study, and all patients receive study drug treatment. The SAF includes all patients who received any dupilumab that can be applied to either safety or efficacy endpoint; Also, the efficacy analyses at week 36 are based on SAF for patients who pass a DBPCFC of at least 444 mg (cumulative) of peanut challenge at week 24.
- The primary analysis for primary and secondary endpoints will be analyzed using descriptive statistics instead of inferential statistics. Therfore, the p-value stated in the protocol will be removed from analysis.

1.2.4. Revision History for SAP Amendments

NA

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a phase 2, multicenter, single-arm open-label POC study in pediatric patients aged 6 to 17 years inclusive who are allergic to peanut, to evaluate the effects of dupilumab on tolerability of peanut protein during a DBPCFC.

2.2. Statistical Hypothesis

The statistical hypothesis is on the primary endpoint, the proportion of patients who achieve a cumulative dose of at least 444 mg peanut protein during a DBPCFC at week 24.

Let μ_D be the true proportion of patients who achieve a cumulative dose of 444 mg peanut protein during a DBPCFC at week 24 for dupilumab. The following hypothesis will be tested at the 2-sided 5% significance level:

Null hypothesis H_0: $\mu_D = 8\%$, ie, the proportion of patients who achieve a cumulative dose of 444 mg peanut protein during a DBPCFC at week 24 is 8% (Vickery, 2018).

Alternative hypothesis H_a: $\mu_D \neq 8\%$, ie, the proportion of patients who achieve a cumulative dose of 444 mg peanut protein during a DBPCFC at week 24 is different from 8%.

2.3. Sample Size and Power Considerations

The sample size is determined to adequately power the primary endpoint of the proportion of patients who pass at least a DBPCFC of 444 mg (cumulative) of peanut protein at week 24. Based on assessment of clinical data from Aimmune Therapeutics AR101 phase 3 peanut OIT study (ARC003), it is assumed that the rate of a tolerated cumulative dose of at least 444 mg of peanut protein on DBPCFC at week 24 is 8% in placebo (Vickery, 2018) and 29% in dupilumab.

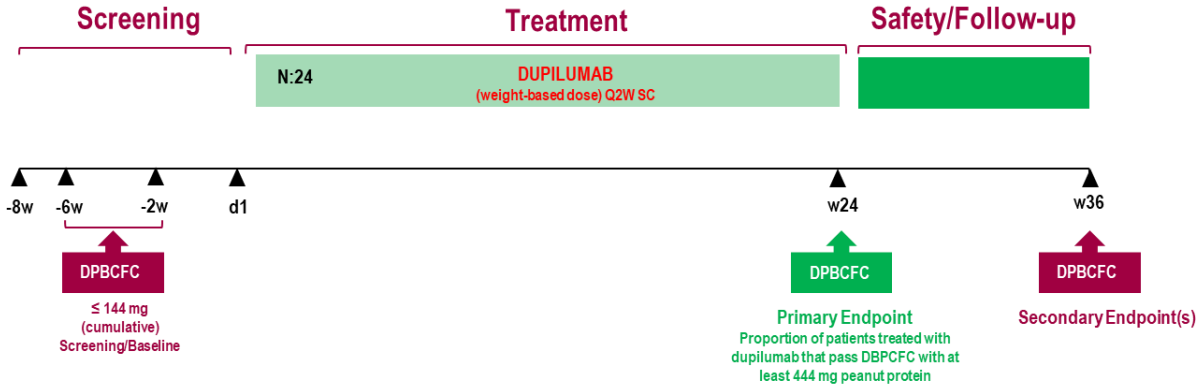
A sample size of 20 patients will have 80% power to detect the 21% difference in tolerated rate at the 2-sided 5% significance level. Allowing for a dropout rate of around 15%, approximately 24 patients will be required. The sample size calculations were done by one-sample Chi-square test (normal approximation) using nQuery + nTerim 4.

2.4. Study Plan

The study consists of 8-week screening period, 24-week open-label treatment period with dupilumab, followed by 12-week safety follow-up period (Figure 1).

The Schedule of Events table is presented in Section 10.2.

Figure 1. Schematic of Study Design



After obtaining informed consent/assent, patients will be assessed for eligibility during a 2-part screening period. During screening visit 1 (day -57 to day -43), patients will undergo a medical history, physical examination, spirometry, peanut SPT, and laboratory testing (including sIgE) and will be evaluated for the study eligibility criteria. During screening visit 1a, under direct study investigator monitoring, patients will undergo a DBPCFC to confirm current peanut allergy. This will consist of 5 doses of peanut protein with a dose given every 15 to 30 minutes in increasing amounts up to a cumulative total of 144 mg of peanut protein. Vital signs will be assessed every 15 to 30 minutes. If the study team suspects a reaction may be developing, they may exercise their clinical judgment to separate doses by up to an additional 30 minutes (1 hour maximum between doses). The matching placebo challenge will consist of placebo material (oat protein) given also in 5 doses. The food challenges will be performed on different days (1 day placebo [oat] protein, 1 day peanut protein, with order determined at random) at least 24 hours, but not more than 7 days, apart. The doses will be 1, 3, 10, 30, and 100 mg of peanut protein (or placebo). Both food challenge days (placebo and peanut) must be done to evaluate eligibility.

Reactions during DBPCFCs will be scored using the Consortium of Food Allergy Research (CoFAR) grading system. The DBPCFC will be stopped when the blinded assessor finds symptoms and/or signs that indicate a definite objective allergic reaction has occurred based on clinically significant changes in reported symptoms, physical findings, or vital signs that the patient is experiencing to the challenge material. The patient will be observed for a minimum of 2 hours after the final administered dose and discharged only when deemed clinically stable by a study physican. If the patient does not experience dose-limiting symptoms at or before the 100 mg challenge dose (≤144 mg cumulative) of peanut protein or if he/she experiences symptoms at any dose of placebo, he/she will not be enrolled in the study. Investigator/site personnel will be unblinded only to the results of the screening food challenge upon completion of the second part of the challenge to assess eligibility. A 2-week washout period is needed after the screening DBPCFC where peanut was given. All other on-study food challenges in the study will remain blinded to the clinic study team.

Patients with a history of confirmed peanut allergy signs and symptoms at screening who continue to meet eligibility criteria at baseline will be enrolled. Dupilumab will be dosed SC on day 1 at least 14 days after the screening DBPCFC and the dose will not be changed regardless of weight gain or loss:

- Patients weighing ≥20 kg and <60 kg will receive dupilumab 200 mg Q2W following a loading dose of 400 mg on day 1
- Patients weighing ≥60 kg will receive dupilumab 300 mg Q2W following a loading dose of 600 mg on day 1

Study drug may be administered in the clinic on day 1 by the study team, patient's caregiver, or patient. The last dose of study drug will be at week 22. For patients under 12 years of age, adult caregiver will need to administer the study drug injections. Patients will have monthly clinic visits and phone calls in-between visits to collect AEs, concomitant medications and compliance to study drug administration.

At week 24, under intensive monitoring, all patients will undergo a DBPCFC up to 2044 mg peanut protein (cumulative) or placebo to assess tolerability.

All patients who complete or prematurely discontinue the treatment will be assessed for safety, laboratory, and clinical assessments 12 weeks after the end of treatment. At the end of the 12-week follow-up period, patients who passed a DBPCFC of at least 444 mg (cumulative) at week 24 will undergo a final DBPCFC (up to 2044 mg cumulative), under intensive monitoring, at week 36 to assess the level of peanut sensitivity after 12 weeks off dupilumab to determine whether there is evidence of persistent effects and unresponsiveness.

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 Safety Analysis Set (SAF)

SAF includes all patients who received any dupilumab. Efficacy, treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

Efficacy at week 36 (Subset of SAF at week 36) will be analyzed using SAF patients who pass a DBPCFC of at least 444 mg (cumulative) of peanut protein at week 24.

For safety summaries, three analysis periods are defined as follows for SAF:

- Treatment period is defined as
  - Day 1 to the date of second DBPCFC at week 24 EOT visit for those patients who completed week 24 visit with week 24 visit date present
  - Day 1 to the early terminiation (ET) visit date for those patients who early terminated before week 24 visit
- Follow-up period is defined as
  - The day after the week 24 EOT visit date to the date of the end of study visit for those patients who completed week 24 visit with week 24 visit date present
  - The day after the ET visit date during treatment period to the date of the end of study visit for those patients who early terminated in the treatment period
- Overall study period is defined as Day 1 to the date of the end of study visit.

3.2. The Pharmacokinetic Analysis Set (PKAS)

The PK population includes all treated patients who received any study drug and who had at least 1 non-missing drug concetration result following the first dose of study drug.

3.3. The Immunogenicity Analysis Set

The ADA analysis set consists of all patients who received any study drug and who had at least 1 non-missing ADA result following the first dose of study drug.

The NAb analysis set (NAS) includes all patients who received any study drug and who are negative in the ADA assay or with at least 1 non-missing result in the NAb assay (patients who are ADA negative are set to negative in the NAb analysis set).

3.4. Subgroups

Subgroups are defined by key baseline factors recorded on the eCRF (unless otherwise specified) and listed as follows.

Subgroups to be considered for both efficacy and safety analyses:

- Age group (>=6 to <12 years, >=12 to <=17 years)
- Sex (Male, Female)
- Screening peanut-specific IgE level (≤100 kUA/L, >100 kUA/L)
- Baseline body weight (≥20 kg and <60 kg, ≥60 kg)

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 group (≥6 to <12 years; ≥12 to ≤17 years)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Other)
- Ethnicity (Hispanic/Latino, Not Hispanic or Latino)
- Baseline weight (kg)
- Baseline weight category (≥20 kg and <60 kg, ≥ 60 kg)
- Baseline height (m)
- Baseline Body Mass Index (BMI) (kg/m^2)
- Baseline Characteristics variables
- Duration of peanut allergy diagnosis (year)
- Age at peanut allergy onset (year; <5, ≥5 and <10, ≥ 10 and ≤17)
- Number of co-morbid atopic diseases (atopic dermatitis, asthma, nasal polyps, allergic rhinitis or eosinophilic esophagitis)
- Baseline Fractional Exhaled Nitric Oxide (FeNO) value
- Baseline Food Allergy Quality of Life Questionnaire (FAQLQ) score for different types of FAQLQ form
- Screening serum peanut-specific IgE
- Screening serum peanut-specific IgG4
- Screening serum total IgE
- Screening peanut-specific IgE/IgG4 ratio
- Screening peanut-specific IgE level (≤100 kUA/L, >100 kUA/L)
- Baseline predicted FEV1 (L)
- Baseline percent predicted FEV1 (%)
- Baseline predicted FVC (L)
- Baseline percent predicted FVC (%)

- Maximum tolerated dose of peanut protein at screening DBPCFC
- Use of epinephrine at screening DBPCFC (Yes, No)
- Normalized mean peanut wheal diameter at screening SPT

Note: Normalized mean peanut wheal diameter is defined by mean peanut wheal minus mean saline wheal.

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA®) by coding CRO.

Conditions related to patient's allergic and atopic medical history include peanut allergy, atopic dermatitis, asthma, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyps, eosinophilic esophagitis, hives, contact dermatitis, egg allergy, milk allergy, tree nut allergy, fish allergy, shellfish allergy, wheat allergy, soy allergy, sesame or mustard seeds allergy, and other allergies (food, medications, animals, plants, mold, dust mite, etc.).

Conditions related to patient's family allergic and atopic medical history include atopic dermatitis, asthma, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyps, eosinophilic esophagitis, food allergy, hives, contact dermatitis, other allergies (medications, animals, plants, mold, dust, mite, etc.).

4.3. Prior / Concomitant Medication and Procedures

Medications/Procedures will be recorded from the day of informed consent/assent until the end-of-study (EOS) 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). 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.

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

Concomitant medications/procedures (CMs/CPs): medications taken or procedures performed following the first dose of study drug through the EOS visit. This includes medications/procedures that were started before the study and are ongoing during the study. Furthermore, CMs/CPs will be categorized according to the analysis periods (as defined in Section 3.1):

- CMs/CPs during the treatment period
- CMs/CPs during the follow-up period

Note: Medications/procedures taken during the treatment period and continued afterwards into follow-up period will be counted only once as CMs/CPs during the treatment period.

4.4. Rescue Medication/or Prohibited Medication During Study

Prohibited concomitant medications/procedures

Treatment with the following concomitant medications is prohibited during the study:

- Treatment with a live (attenuated) vaccine (see protocol Section 8.7.1 for the list of vaccine)
- Treatment with any agents known or likely to interact with epinephrine (e.g., beta blockers, ACE-inhibitors, tri-cyclic antidepressants, or other drugs)
- Treatment with antihistamines within 5 days prior to screening and within 5 days prior to SPTs and day 1 of DBPCFCs

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures

Rescue Treatment (including both medications and procedures)

The following concomitant treatments will require permanent study drug discontinuation:

- Treatment with an investigational drug (other than dupilumab)
- Treatment with immunodulating biologic agents, including anti-IgE
- Treatment with allergen immunotherapy
- Treatment with systemic (oral, IV, IM, SC) corticosteroids for a duration of more than 5 continuous days, more than 15 days in total, or within 2 days prior to DBPCFCs

The following concomitant treatments of allergic reactions will NOT require permanent study drug discontinuation:

- IM or SC administration of epinephrine
- Oral antihistamines
- Short acting inhaled bronchodilators
- Inhaled corticosteriods
- Systemic (oral, IV, IM, SC) corticosteroids for a duration of less than 5 continuous days, less than 15 days in total, and at least 2 days prior to DBPCFCs

Treatment of acute-allergic reactions will be categorized as follow,

- Screening DBPCFC of peanut protein
- Week 24 DBPCFC of peanut protein
- Week 36 DBPCFC of peanut protein

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 Variable

4.5.1. Primary Efficacy Variable (s)

The primary endpoint in this study is:

- Proportion of patients treated with dupilumab that pass a DBPCFC with at least 444 mg (cumulative) peanut protein at week 24

Double-blind placebo-controlled food challenge (DBPCFC)

At week 24, under intensive monitoring, all patients will undergo a DBPCFC up to 2044 mg peanut protein (cumulative) or placebo to assess tolerability. The patient's sensitivity to peanut allergen is defined as the dose at which the patient experiences allergic reactions. All symptoms and signs will be evaluated and rated based on a standardized oral food challenge scoring system. Up-dosing during the DBPCFC will be stopped when the Principal Investigator (or designee) finds symptoms and/or signs that indicate a definite objective allergic reaction (CoFAR grading system) has occurred based on clinically significant changes in reported symptoms, physical findings, or vital signs that the patient is experiencing to the challenge material. Vtial signs will be measured every 15 to 30 minutes. The DBPCFC will consist of 8 doses (peanut protein or placebo), with a dose given every 15 to 30 minutes: 1, 3, 10, 30, 100, 300, 600, and 1000 mg resulting in a total challenge of up to 2044 mg peanut protein (cumulative). The food challenges will be performed on different days (1 day placebo [oat] protein, 1 day peanut protein, with order determined at random) at least 24 hours but not more than 7 days apart and not within 24 hours of a dose of study drug. Patients will be considered to have passed the DBPCFC if they do not experience any objective Grade 1 reaction by the CoFAR garding system.

Consortium of Food Allergy Research (CoFAR) Grading System

The CoFAR is a grading system based on clinically significant changes in reported symptoms, physical findings, or vital signs that the patient is experiencing to the challenge food material. The allergic reaction is measured on a 1-5 scale, with grade 1 being mild, grade 2 being moderate, grade 3 being severe, grade 4 being life threatening, and grade 5 as death.

4.5.2. Secondary Efficacy Variable(s)

The secondary efficacy endpoints include:

- Change in the cumulative tolerated dose (log transformed) mg of peanut protein during a DBPCFC from baseline to measured DBPCFC visits at weeks 24 and 36
- Proportion of patients treated with dupilumab that pass a DBPCFC with at least 444 mg (cumulative) peanut protein at week 36
- Proportion of patients treated with dupilumab that pass a DBPCFC with at least 1044 mg (cumulative) peanut protein at weeks 24 and 36
- Proportion of patients treated with dupilumab that pass a DBPCFC with at least 2044 mg (cumulative) peanut protein at weeks 24 and 36
- Percent change from baseline in sIgE to post-baseline visits (weeks 4, 8, 12, 24, and 36)

- Change from baseline in titrated SPT at week 4, 12, 24, 36 as measured by the average wheal size AUC after peanut allergen stimulation at different concentrations
- Proportion of patients with Grade II or above allergic reactions during the DBPCFC at week 24
- Proportion of patients using epinephrine as a rescue medication during the DBPCFC at week 24

Titrated Skin Prick Test (SPT)

The titrated SPT is the skin testing for atopic response at different concentrations of peanut extract with saline as negative control and histamine as positive controls. The SPTs will be performed starting at the following dilutions: neat, 1:20, 1:200, 1:2,000, 1:20,000. Wheal size induced by peanut extract at each concentration will be calculated as the average of the largest diameter and the perpendicular midpoint diameter.

The formula used to calculate the average wheal diameter at each concentration described in Section 6.3.

4.5.3. Exploratory Efficacy Variable(s)

- Change from baseline in total FAQLQ score at week 12, week 24, and week 36 for different types of FAQLQ form
- Change from baseline to week 12, week 24, and week 36 in peanut-specific IgE
- Change and percent change from baseline to week 12, week 24 and week 36 in peanut-specific IgG
- Change and percent change from baseline to week 12, week 24 and week 36 in peanut-specific IgG4
- Change and percent change from baseline to week 12, week 24 and week 36 in peanut-specific IgG4/sIgE ratio and sIgG/sIgE ratio
- Change and percent change from baseline to week 12, week 24, and week 36 in basophil sensitivity to peanut allergen, as measured by EC50, which is the concentration of peanut protein required to achieve 50% of maximal basophil activation
- Change and percent change from baseline to week 12, week 24, and week 36 in the frequency of peanut-specific T cell subsets (e.g. Th2A cell)

Food Allergy Quality of Life Questionnaire

The Food Allergy Quality of Life Questionnaire (FAQLQ) is a validated food allergy-specific health-related quality of life (HRQL) questionnaire, which measures the impact of social and dietary limitations and assesses the emontional impact of these restrictions on the lives of patients.

Patients self-report the impact of food allergy on HRQL using different forms of FAQLQ depending on their age; the child form (FAQLQ-CF) is used by patients aged 8 to 12 years and the teenager form (FAQLQ-TF) is used for patients aged 13 to 17 years. The parent form (FAQLQ-PF) is a measure of children's HRQL that is reported by parent proxy from child's perspective and can be used for patients of ages 0 to 12 years. The FAQLQ will be administered to patients and,

when appropriate, parents at time points in Section 10.2. Patients will continue using the FAQLQ version first administered at baseline regardless of moving to the next age bracket.

The number of questions and domains varies by questionnaire administered. Each question is scored based on a seven-point scale which ranges from 1 (minimal impairment in HRQL) to 7 (maximal impairment in HRQL). The total score is the arithmetic average of all non-missing answers.

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

An **Adverse Event** (AE) 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.

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

A **Serious Adverse Event** is any untoward medical occurrence that at any dose results in death; is life-theratening; 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.

Adverse events and serious adverse events will be collected from the time of informed consent/assent signed until the end of the study. However, allergic reactions to the DBPCFC during the screening phase, at endpoint challenges (at week 24 and 36) will be recorded since allergic signs and symptoms are expected to occur after exposure to allergen.

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 the latest available version).

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

- 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 and treatment-emergent periods are defined as following:

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent period is defined as the day from first dose of study drug to the end of the study. The treatment-emergent period includes the 24-week treatment period and follow-up period.

The pre-treatment AE and treatment-emergent AE (TEAE) are defined as following:

- Pre-treatment signs and symptoms (Pre-treatment AEs) are AEs that developed or worsened in severity during the pre-treatment period.
- Treatment-emergent adverse events (TEAEs) are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the treatment period and follow-up period.

4.6.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) for this study include the following:

- Anaphylactic reactions
- Systemic or extensive hypersensitivity reactions
- Malignancy
- Helminthic infections
- Suicide-related events
- Conjunctivitis (any type or etiology), keratitis or blepharitis (for all these AEs only events that are severe or serious or lasting ≥4 weeks will be reported as AESIs)

Section 10.4 provides a list of AESIs search criteria.

Anaphylaxis: is defined as a severe, potentially life-threatening systemic hypersensitivity reaction, characterized by being rapid in onset with life-threatening airway, breathing, or circulatory problems that is usually, though not always, associated with skin and mucosal changes.

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:

Blood Chemistry

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

* Low-density lipoprotein [LDL] and high-density lipoprotein [HDL]

Hematology

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

Urinalysis

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

Other Laboratory Tests

For female patients of childbearing potential, a serum pregnancy test will be performed at screening and end of study visits. For other visits where a pregnancy test is scheduled, a urine pregnancy test will be performed.

4.6.4. Vital Signs

The following vital signs parameters will be collected at predose at every in-clinic visit and the unscheduled visit or ET visit:

- Respiratory rate (bpm)
- Heart rate (bpm)
- Sitting systolic and diastolic blood pressure (mmHg)
- Body temperature (°C) with the measure method (oral/tympanic/axillary/rectal/temporal)

During the DBPCFC, vital signs will be monitored every 15 to 30 minutes. After initial DBPCFC dose, only pulse and blood pressure need to be taken as part of safety monitoring.

4.6.5. Body Weight and Height

Body height is measured at the screening visit 1. Body weight is measured at the screening visit 1, and every in-clinic visit (except for screening visit 1a).

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 screening visits (screening visit 1 and visit 1a), week 12, week 24, week 36 or ET visit. Physical examination is performed at each DBPCFC day.

4.6.7. Spirometry

A spirometer that meets the American Thoracic Society (TS) / European Respiratory Society (ERS) recommendations will be used to measure FEV1 and/or PEFR. During DBPCFC, spirometry should be performed before and after the challenge. FeNO should be done prior to spirometry.

4.7. Pharmacokinetic (PK) Variables

Concentration of functional dupilumab in serum at each time point, obtained prior to dosing, will be considered to be trough values ($C_{trough.time\ point}$).

4.8. Anti-Drug Antibody Variable

Anti-drug antibody (ADA) variables include ADA status, titer, NAb status, and timepoint/visit. Samples for ADA assessment will be collected at time points according to Section 10.2. Samples positive in the ADA assay will be further characterized for ADA titers and for the presence of NAb to dupilumab.

Immunogenicity will be characterized by ADA responses and titers observed in patients. The ADA response and titer categories are defined as follows:

- ADA Negative, defined as a negative response in the dupilumab ADA assay at all time points, regardless of any missing samples.
- 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 of 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. The treatment-emergent responses will be further characterized as Persistent, Indeterminate or Transient.
  - Persistent Response: Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points, separated by greater than 12-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.
  - Indeterminate Response: Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples.
  - Transient Response: Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.
- 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)

4.9. Pharmacodynamic and Biomarker Variables

Pharmacodynamic and biomarker variables are:

- Serum TARC and total IgE
- Peanut-specific IgE, IgG, IgG4
- Titrated Skin Prick Test
- Fractional Exhaled Nitric Oxide (FeNO)
- Basophil sensitivity to peanut allergen (EC50)
- Frequency of peanut specific Th2A cells

Biomarker samples will be collected at time points according to according to Section 10.2.

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.

5.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for SAF. Listing of demographics and baseline characteristics will be presented.

5.2. Medical History

Medical history will be summarized by primary SOC and PT based on SAF. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence. Medical history will be listed based on the SAF.

Subject allergic/atopic medical history and subject family allergic/atopic medical history will be summarized and listed.

5.3. Prior and Concomitant Medications/Procedures

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

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

In addition, the summary of prior/concomitant medications/procedures will be performed for patients who were impacted by COVID-19 pandemic and not impacted by COVID-19 pandemic, respectively. The summary will be performed for pre-, during, and post-COVID-19 periods for patients impacted by COVID-19 pandemic, if applicable.

Number and proportion of patients taking at least one epinephrine for treatment of acute-allergic reactions will be summarized during the following periods,

- Screening DBPCFCs of peanut protein
- Week 24 DBPCFCs of peanut protein
- Week 36 DBPCFCs of peanut protein

Kaplan-Meier curves for time to first rescue treatment use will be created.

Listing of pre-treatment and concomitant medications will include generic name, ATC levels 2 and 4, indication, the study day of onset (for medications started before treatment, the study day of onset = date of medication start – date of the first dose; for medication started on or after treatment, the study day of onset = date of medication start – date of the first dose + 1), the study day of medication end date, ongoing status, dose, frequency, and route.

5.4. Patient Disposition

The following summaries will be provided:

- The total number of screened patients and the screen failure reasons including screen failure at visit 1 and visit 1a
- The total number of enrolled patients
- The total number of patients in each analysis set
- The total number of patients who discontinued the study and the reasons for discontinuation (including COVID-19 related reasons)
- The total number of patients who discontinued the study treatment permanently and the reasons for discontinuation (including COVID-19 related reasons)

The following listings will be provided:

- Listing of patients disposition including: date of enrollment, date of first study drug injection, date of the last visit, completed study or discontinued by reason
- Listing of patients enrolled but not treated, and treated but not enrolled
- Listing of patients prematurely discontinued from the study or study treatment, along with reasons for discontinuation
- A listing of protocol deviations will be provided

Kaplan-Meier curve for time to withdraw from the study and from the study treatment will be created, respectively.

5.5. Extent of Study Treatment Exposure and Compliance

5.5.1. Measurement of Compliance

The compliance with study treatment will be calculated as follows:

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

where temporary dose discontinuation is ignored.

Loading doses for the same patient will be counted as 1.

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: <80%, and ≥80%.

Listing of study drug compliance will be presented with study drug, study drug injection date/time, study day, injection location, kit number, whether or not the total dose is administered for each dose, and compliance rate.

5.5.2. Exposure to Investigational Product

The duration of treatment exposure during the study in day will be presented and is calculated as:

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

Note: the calculations are regardless of temporary dosing interruption.

Summary of exposure to study drug will include the number of study drug administered and duration of exposure. The duration of exposure during the study will be summarized using number of patients, mean, SD, median, Q1, Q3, minimum and maximum.

In addition, the duration of exposure to study drug will be summarized categorically by counts and percentages for each of the following categories as well:

≥14 days , ≥28 days, ≥42 days, ≥56 days, ≥70 days, ≥84 days, ≥ 98 days, ≥112 days, ≥ 126 days, ≥140 days, ≥154 days, and ≥168 days

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

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

The duration of observation period will be summarized descriptively using number of patients, mean, SD, median, Q1, Q3, minimum and maximum. In addition, the number (%) of patients with observation periods will be presented by specific time periods. The time periods of interest are specified as:

<15 days, ≥15 days , ≥29 days, ≥43 days, ≥57 days, ≥71 days, ≥85 days, ≥ 99 days, ≥113 days, ≥ 127 days, ≥141 days, ≥155 days, and ≥169 days

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

5.6. Analyses of Efficacy Variables

The primary efficacy analyses for all the efficacy endpoints will be conducted at week 24 using the SAF population. The continuous efficacy variables will be summarized using number of patients, mean, SD, minimum, median, Q1, Q3 and maximum. The categorical efficacy variable will be summarized using patient count and proportion. The analyses of efficacy variables are described in the subsections below and summarized in Section 10.1.

5.6.1. Analysis of Primary Efficacy Variable

The primary endpoint will be analyzed using descriptive statistics. Estimate of proportion and the 2-sided 95% Clopper-Pearson confidence interval will be provided. The number and percentage of patients at each dose level for highest tolerated peanut protein dose at week 24 DBPCFC will also be summarized.

Missing data for week 24 DBPCFC will be handled according to the reason for missingness as follows:

- If a patient misses the week 24 DBPCFC due to COVID-19, the missing data will be imputed by multiple imputation (MI) method for 10 times utilizing available week 24 DBPCFC data. The MI will utilize logistic regression method with baseline tolerated cumulative amount of peanut protein DBPCFC.
- If a patient does not have available DBPCFC data at week 24 due to reasons not related to COVID-19, the patient will be considered as a non-responder at week 24.

Each of complete datasets after the above steps will be summarized with estimated proportions and standard errors. The SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results using Rubin's formula (Rubin, 1987).

Supportive analysis of the primary endpoint will include an analysis of patients who have available week 24 DBPCFC of peanut protein.

5.6.2. Analysis of Secondary Efficacy Variables

All secondary endpoints will be analyzed descriptively at given visits. SAF will be used for efficacy analysis at week 24, and subset of SAF at week 36 will be used for efficacy analysis at week 36.

Continuous Endpoint at week 24

The change from baseline to week 24 in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC will be summarized descriptively. Estimate of change from baseline to week 24 and the 2-sided 95% confidence interval will be provided. If patients do not tolerate any dose level of peanut protein challenge, they will be assigned a cumulative tolerated dose of 1 mg prior to converting to the log scale.

Missing data for week 24 DBPCFC will be handled according to the reason for missingness as follows:

- If a patient misses the week 24 DBPCFC due to COVID-19, the missing data will be imputed by MI method for 10 times utilizing available week 24 DBPCFC data. The MI will utilize logistic regression method with baseline tolerated cumulative amount of peanut protein DBPCFC.
- If a patient does not have an available week 24 DBPCFC due to reasons not related to COVID-19, the baseline value at screening DBPCFC will be used to impute the missing week 24 DBPCFC data.

Each of the complete datasets after the above steps will be summarized with estimated means and standard errors of change from baseline to week 24 in the cumulative tolerated dose (log transformed) of peanut protein. The SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results.

Supportive analysis will include an analysis of patients who have available week 24 DBPCFC of peanut protein.

Binary Endpoint at week 24

For the below binary endpoints of passing a DBPCFC at week 24, the analysis and imputation methods will be similar to the primary analysis.

- Proportion of patients treated with dupilumab that pass a DBPCFC with at least 1044 mg (cumulative) peanut protein at week 24
- Proportion of patients treated with dupilumab that pass a DBPCFC with at least 2044 mg (cumulative) peanut protein at week 24

Proportion of patients with Grade II or above allergic reactions during the DBPCFC at week 24 will summarized descriptively as well as proportion of patients using ephinephrine as a rescue medication during the DBPCFC at week 24.

Continuous Endpoint at week 36

Change in the cumulative tolerated dose (log transformed) mg of peanut protein during a DBPCFC from baseline to measured DBPCFC at week 36 will be summarized descriptively based on a subset of SAF at week 36.

Binary Endpoints at Week 36

Proportion of patients treated with dupilumab that pass a DBPCFC with at least 444 mg (cumulative) peanut protein at week 36 will be summarized descriptively based on a subset of SAF at week 36. Similar binary endpoints at week 36 will be summarized in a similar fashion.

5.6.3. Analysis of Exploratory Efficacy Analysis

The analysis of other efficacy variables will be the same as the primary analysis described in Section 5.6.1 and Section 5.6.2.

5.6.4. Adjustment for Multiple Comparison

No adjustments for multiplicity for the secondary endpoints are planned for this study.

5.6.5. Subgroup Analysis

Subgroup analysis for the primary endpoint and the following secondary endpoints will be performed on the SAF. Subgroups are defined in the Section 3.4.

- Change in the cumulative tolerated dose (log transformed) mg of peanut protein during a DBPCFC from baseline to measured DBPCFC visits at week 24
- Proportion of patients treated with dupilumab that pass a DBPCFC with at least 1044 mg (cumulative) peanut protein at week 24
- Proportion of patients treated with dupilumab that pass a DBPCFC with at least 2044 mg (cumulative) peanut protein at week 24

The analysis method for the subgroup analysis will be the same as the primary analysis described in Section 5.6.1 and Section 5.6.2.

5.7. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the SAF, as defined in Section 3.1.

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

Thresholds for treatment-emergent Potential Clinically Significant Values (PCSV) 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 baseline when determining treatment-emergent PCSV refers to the baseline value of the study.

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

5.7.1. Adverse Events

The number and proportion of patients reporting TEAEs will be summarized for treatment period and follow-up period separately, as described in Section 3.1.

AE incidence tables will be presented for the SAF as well as subgroups. Summary of TEAEs will present the number (n) and percentage (%) of patients experiencing an TEAE by SOC and PT, sorted by the decreasing frequency of SOC and PT. Multiple occurrences of AEs of the same PT (or SOC) in the same patient will be counted only once for that PT (or SOC). For AE tables presenting severity, the worst severity will be chosen for patients with multiple instances of the

same event. The denominator for computation of percentage is the number of patients for the corresponding analysis period as specified in Section 3.1.

An overall summary of TEAEs will be provided with number and proportion of patients with any:

- TEAE
- Serious TEAE
- TEAE/Serious TEAE leading to death
- TEAE/Serious TEAE leading to permanent treatment discontinuation
- Study drug related TEAE/serious TEAE
- Maximum intensity for TEAE

Detailed summaries of TEAEs will include:

- TEAEs
  - TEAEs by primary SOC/PT
  - TEAEs by primary SOC/HLT/PT
  - TEAEs by PT
  - TEAEs by primary SOC/PT with incidence of PT $\geq$ 5%
  - TEAEs by severity and by primary SOC/PT
  - TEAEs related to study drug as assessed by the investigator by primary SOC/PT
  - Severe TEAEs by primary SOC/PT
  - Severe TEAEs related to study drug as assessed by the investigator by primary SOC/PT
  - TEAEs leading to permanent discontinuation of study treatment by primary SOC/PT
- Serious TEAE
  - Serious TEAEs by primary SOC/PT
  - Serious TEAEs related to study drug as assessed by the investigator by primary SOC/PT
  - Time to first occurrence of serious TEAEs
- Death by primary SOC/PT

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

The number and proportion of patients with injection site reaction by PT will be summarized.

The number and proportion of TEAE per 100 patient-year will be tabulated by primary SOC/HLT/PT. The number of patients with at least one event per 100 patient-year will be calculated and summarized for the following:

- TEAE by primary SOC/HLT/PT
- Severe TEAE by primary SOC/HLT/PT
- Serious TEAE by primary SOC/HLT/PT

Listing of TEAEs, serious TEAEs, and TEAEs resulting in death and study drug discontinuation will be generated. The following variables will be included in the listing:

- Patient ID
- Age/sex/race
- System Organ Class (SOC)
- High Level Term (HLT)
- Preferred Term (PT)
- Verbatim Term
- AE start date and end date/ongoing (including both calendar days and study days)
- AE duration
- Relationship of AE to study drug: Related or Not Related
- Action taken with study drug: Dose not changed, Drug interrupted, Drug withdrawn, Not applicable, or Unknown
- Severity: mild, moderate, or severe
- Outcome: Fatal, Not recovered/not resolved, Recovered/resolved, Recovered/resolved with sequelae, Recovering/resolving, or Unknown
- Impact by COVID-19 pandemic: Yes or No

In addition, summary of adverse events will be categorized by the status of impact by COVID-19 pandemic. For patients who were impacted by COVID-19 pandemic, the summary of adverse events will include overall summary of adverse event, TEAEs by SOC/PT, serious TEAEs by SOC/PT (if applicable), TEAEs of special interest (if applicable), TEAEs leading to discontinuation of study treatment by SOC/PT (if applicable). The summary of adverse events for patients who were not impacted by COVID-19 pandemic will be summarized similarly. The summary of adverse events will be performed for pre-, during-, and post-COVID-19 periods for patients impacted by COVID-19 pandemic, if applicable.

5.7.2. 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, it will be summarized by AESI category only.

The time to first AESIs (AESI by category) will be assessed by Kaplan-Meier estimates. Kaplan-Meier curves will be provided. The time is defined as the date of first event – date of first dose + 1. Patients without an event will be censored at the end of study visit.

The number of anaphylactic reactions, the number and percentage of patients experiencing an anaphylactic reaction, the number and percentage of patients experiencing an anaphylactic reaction by maximum severity using the Muraro Grading Scale (Muraro 2007), the number of patients experiencing an anaphylactic reaction was an SAE, the number of patients experiencing an anaphylactic reaction that required use of epinephrine will be summarized during DBPCFCs.

5.7.3. 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 treatment-emergent PCSVs. This summary will be provided based on all patients in the SAF as well as in the subgroup of SAF patients who did not meet the PCSV criterion at baseline
- 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 ranges, abnormal flag, treatment-emergent PCSV by patient, visit and the status of impact by COVID-19 pandemic will be provided.

In addition, summaries of laboratory variables will be performed for patients who were impacted by COVID-19 pandemic and not impacted by COVID-19 pandemic, respectively. The summaries will be performed for pre-, during-, and post-COVID-19 periods for patients impacted by COVID-19, if applicable.

The graph of mean change and/or percent change from baseline value for lab parameters by visit will be provided.

5.7.4. Analysis of Vital Signs

Summaries of vital sign variables excluding measurements at each challenge level of DBPCFCs will include:

- Descriptive statistics of vital sign variables and change from baseline by visit
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Summaries of vital sign variables (only systolic and diastolic blood pressure) at DBPCFCs of peanut protein at screening visit 1a, week 24 and week 36 will include:

- Descriptive statistics of vital sign variables (only systolic and diastolic blood pressue) and change from pre-dose by challenge dose level
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

The number (n) and percentage (%) of patients with treatment-emergent PCSV will be summarized. This summary will be provided based on all patients in the SAF as well as in the subgroup of SAF patients who did not meet the PCSV criterion at baseline.

Listings will be provided with flags indicating the treatment-emergent PCSVs and the status of impact by COVID-19 pandemic, depending on the data.

In addition, summaries of vital signs will be performed for patients who were impacted by COVID-19 pandemic and not impacted by COVID-19 pandemic, respectively. The summaries will be performed for pre-, during-, and post-COVID-19 period for patients impacted by COVID-19 pandemic, if applicable.

The graph of mean change and/or percent change from baseline value for vital sign parameters excluding measurements at DBPCFCs by visit will be provided.

5.7.5. Physical Exams

Shift tables based on baseline normal/abnormal status will be provided for assessments of each physical exam category and presented by visit. Only the physical examination on the second DBPCFC day at week 24 will be summarized in the shift table.

5.7.6. Spirometry and Peak Expiratory Flow (PEF)

Summaries of spirometry and PEF variables excluding measurement after DBPCFCs will include:

- Descriptive statistics of spirometry and PEF variables and change from baseline by visit will be presented
- Spaghetti plots of spirometry and PEF data will be displayed by visit

Summaries of spirometry and PEF variables for pre- and post-DBPCFCs of peanut protein will include:

- Descriptive statistics of spirometry and PEF variables and change from pre-dose will be presented
- Bar plots of spirometry and PEF data will be displayed

Summaries of spirometry and PEF variables for post-DBPCFCs of peanut protein by visit will include:

- Descriptive statistics of spirometry and PEF variables and change from post-DBPCFC of peanut protein at screening visit 1a by visit will be presented
- Bar plots of spirometry and PEF data will be displayed

Listing of spirometry and PEF data will be provided with flag indicating the status of impact by COVID-19 pandemic.

In addition, summaries of spirometry and PEF will be performed for patients who were impacted by COVID-19 pandemic and not impacted by COVID-19 pandemic, respectively. The summaries will be performed for pre-, during, and post-COVID-19 periods for patients impacted by COVID-19 pandemic, if applicable.

5.8. 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

No formal statistical 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.

5.9. Analysis of Immunogenicity Data

5.9.1. Analysis of ADA Data

The immunogenicity variables described in Section 4.8 will be summarized using descriptive statistics. Immunogenicity will be characterized by ADA responses and titers observed in patients in the ADA analysis set.

The following will be summarized by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative subjects (pre-existing immunoreactivity or negative in the dupilumab ADA assay at all time points)
- Number (n) and percent (%) of treatment-emergent ADA-positive patients
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive patients
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive patients
  - Number (n) and percent (%) of transient treatment-emergent ADA positive patients
- Number (n) and percent (%) of treatment-boosted ADA-positive patients

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

5.9.2. 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.

5.10. Association of Immunogenicity with Exposure, Safety and Efficacy

5.10.1. Immunogenicity and Exposure

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

5.10.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables 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])

Potential association between immunogenicity variables and primary efficacy endpoints may be explored (e.g. scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above 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
- Patients with persistent treatment-emergent ADA response
- 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

5.11. Analysis of Biomarker Data

All biomarker analyses will be performed on the SAF using all observed data. Descriptive statistics for the observed values, change from baseline and percent change from baseline values by visit will be provided for the biomarker variables as described in Section 4.9.

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

Correlation of baseline biomarkers [including serum peanut sIgE, sIgG, sIgG4, total IgE, and basophil sensitivity to peanut allergen stimulation measured by EC50, frequency of peanut specific T-cell subsets (e.g. Th2A cells)], absolute change or percent change at week 24 and 36 from baseline in these biomarkers with the following continuous clinical endpoint will be explored using Spearman's rho test. Both Spearman correlation coefficients and p-value will be reported. The correlation between post-baseline biomarkers and clinical outcome will only be evaluated at the same visit.

- Change in the cumulative tolerated dose (log transformed) mg of peanut protein during a DBPCFC from baseline to measured DBPCFC visits at weeks 24 and 36

Correlation of baseline biomarkers [including serum peanut sIgE, sIgG, sIgG4, total IgE, and basophil sensitivity to peanut allergen stimulation measured by EC50, frequency of peanut specific T-cell subsets (e.g. Th2A cells)] with the following binary clinical endpoints will also be explored using logistic model. The model will include the responder/non-responder of below clinical endpoint as the dependent variable and baseline biomarker as the predictor variable. Model coefficients and p-value will be provided to indicate significance of the correlation/association.

- Proportion of patients treated with dupilumab that pass a DBPCFC with at least 444 mg (cumulative) peanut protein at week 24

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 for all measurements will be the latest available valid measurement taken prior to the administration of investigational product. The following rules specify the determination of baseline by both date/time information:

- The date and time of first injection will be used to determine the baseline for the AE, lab, PK and ADA data.
- Only the date of first injection will be used to determine the baseline for other data except the AE, lab, PK and ADA data.

6.2. General Data Handling Conventions

For the laboratory safety variables and biomarker data, if the data are below the lower limit of quantification (LLOQ)/limit of linearity, half the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ)/ limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

6.3. Data Handling Convention for Efficacy Variables

Algorithm for calculation of Area Under the Curve (AUC):

The AUC for titrated SPT will be calculated using the trapezoidal rule. The AUC will be calculated using the formula:

$$AUC = \left[\sum_{i=1}^{4}(c_i - c_{i-1}) * (D_i + D_{i-1})/2\right]/(c_4 - c_0)$$

where

- D_i is the normalized mean wheal at concentration c_i
- c_i is the concentration for which D_i is measured, $c_0 = \frac{1}{20{,}000}, c_1 = \frac{1}{2{,}000}, c_2 = \frac{1}{200}, c_3 = \frac{1}{20}, c_4 = 1$.

6.4. Data Handling Convention for Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Rules for handling missing data for primary and secondary efficacy variables are described in Section 4.5.1 and Section 4.5.2.

Adverse event

If the intensity of a TEAE is missing, it will be classified as "severe" in the frequency tables by intensity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related 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 be 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 AE start month is the same as first dose month, then AE start day will be imputed using the day of first dose. If this leads to a date after the AE end date, AE end date will be used instead. If AE start year is the same as first dose year and AE start month different from first dose month, AE start day will be imputed using the first day of the month. If this leads to a date before informed consent date, 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 before the first dose year, the informed consent day and month will be used. If AE start year is the same as first dose year, the first dose day and month will be used. If this leads to a date after AE end date, AE end date will be used instead. If AE start year is after the first dose year, January 1st will be used. Imputation flag is 'M'.

If AE start year is missing: The date of first dose will be used. If this leads to a date after the AE end date, AE end date will be used 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 start date imputation, 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: AE end date will be imputed using the last day of the month. If this leads to a date after end of study follow up date, the end of follow up date will be used instead.

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

If AE end year is missing: AE end date will be imputed using end of follow up date.

Prior or concomitant medication

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 listing.

Prior medication start date

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

If start month is missing, and start year is not missing: the day and month will be imputed using January 1st. Imputation flag is 'M'.

If start year is missing: the start date will be imputed using 2 years before informed consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However, to simplify the programming flow, the imputation is proposed to align with protocol which specifices 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: the end date will be imputed using the last day of the month. If this leads to a date on or after first dose intake date, the first dose intake date – 1 will be used. Imputation flag is 'D'.

If end month is missing, and end year is not missing: the end date will be imputed using December 31st as the day and month. If this leads to a date on or after first dose intake date, the first dose intake date – 1 will be used instead. Imputation flag is 'M'.

If end year is missing: the end date will be imputed 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: the end date will be imputed using the last day of the month. If this leads to a date after end of study follow up date, the end of follow up date will be used. Imputation flag is 'D'.

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

If end year is missing: the end date will be imputed 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=ATC 2 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.

6.5. Visit Windows

Data analyzed by-visit-analysis (including efficacy, laboratory data, vital sign and spirometry/PEF) 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 and early termination (ET) visit 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 and ET visits, based on the study day:

Visit	Target Day (TD)	Analysis Time Window Based on Study Day*
Screening 1	-57 to -43	-57 to -43
Screening 1a	-42 to -15	-42 to -15
Baseline	1	1
Visit 3 (Week 2)	15	[2, 22]
Visit 4 (Week 4)	29	[23, 36]
Visit 5 (Week 6)	43	[37, 50]
Visit 6 (Week 8)	57	[51, 64]
Visit 7 (Week 10)	71	[65, 78]
Visit 8 (Week 12)	85	[79, 92]
Visit 9 (Week 14)	99	[93, 106]
Visit 10 (Week 16)	113	[107, 120]
Visit 11 (Week 18)	127	[121, 134]
Visit 12 (Week 20)	141	[135, 148]
Visit 13 (Week 22)	155	[149, 162]
Visit 14 (Week 24)	169	[163, 176]
Visit 15 (Week 30)	211	[177, 232]
Visit 16 (Week 36)	253	≥233

*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 give visit:

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

For multiple measurements of the same test in the same window, the following rules will be used to select 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 target 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.

7. INTERIM ANALYSIS

No interim analysis is planned.

Data may be analyzed and reviewed internally by the sponsors.

A primary analysis may be performed once all patients in the study have completed the 24-week treatment period (week 24 visit or earlier for those patients who are withdrawn prematurely from the study). If performed, this primary analysis will be considered as the final analysis for the primary endpoint and secondary efficacy endpoints up to week 24.

8. SOFTWARE

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

9. REFERENCES

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10. APPENDIX

10.1. Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Populations	Primary Statistical Method	Supportive/Sensitivity Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint					
Proportion of patients treated with dupilumab that pass a DBPCFC with at least 444 mg (cumulative) peanut protein at week 24	SAF	Descriptive statistics/missing data as non-responder	Descriptive statistics with available week 24 data	Yes	Bar chart
Secondary Endpoints					
Change in the cumulative tolerated dose (log transformed) mg of peanut protein during a DBPCFC from baseline to measured DBPCFC visits at week 24	SAF	Descriptive statistics/LOCF method	Descriptive statistics with available week 24 data	Yes	Bar chart
Change in the cumulative tolerated dose (log transformed) mg of peanut protein during a DBPCFC from baseline to measured DBPCFC visits at week 36	Subset of SAF at week 36	Descriptive statistics	No	No	Bar chart
Proportion of patients treated with dupilumab that pass a DBPCFC with at least 444 mg (cumulative) peanut protein at week 36	Subset of SAF at week 36	Descriptive statistics	No	No	Bar chart
Proportion of patients treated with dupilumab that pass a DBPCFC with at least 1044 mg (cumulative) peanut protein at week 24	SAF	Descriptive statistics/missing data as non-responder	No	Yes	Bar chart

Endpoint	Analysis Populations	Primary Statistical Method	Supportive/Sensitivity Analysis	Subgroup Analysis	Other Analyses
Proportion of patients treated with dupilumab that pass a DBPCFC with at least 1044 mg (cumulative) peanut protein at week 36	Subset of SAF at week 36	Descriptive statistics	No	No	Bar chart
Proportion of patients treated with dupilumab that pass a DBPCFC with 2044 mg (cumulative) peanut protein at week 24	SAF	Descriptive statistics/missing data as non-responder	No	Yes	Bar chart
Proportion of patients treated with dupilumab that pass a DBPCFC with 2044 mg (cumulative) peanut protein at week 36	Subset of SAF at week 36	Descriptive statistics	No	No	Bar chart

Safety Analysis:

Endpoint	Analysis Populations	Primary Statistical Method	Supportive/Sensitivity Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint					
Adverse events	SAF	Descriptive Statistics and time-to-event analysis	No	Yes, for selected AE summary	No
Laboratory measures	SAF	Desriptive Statistics	No	No	No
Vital sign	SAF	Descriptive Statistics	No	No	No
Spirometry	SAF	Descriptive Statistics	No	No	No

10.2. Schedule of Time and Events

Table 1 Schedule of Events

Study Procedure	**Screening**		**Treatment Period**													**Follow-up**		**UV**	**ET**
Visit	**V1**	**V1a**	**V2 Baseline**	**V3 phone**	**V4 clinic**	**V5 phone**	**V6 clinic**	**V7 phone**	**V8 clinic**	**V9 phone**	**V10 clinic**	**V11 phone**	**V12 clinic**	**V13 phone**	**EOT V14 clinic**	**V15**	**EOS V16**	if applicable	
Day	-57 to -43	-42 to -15	1	15	29	43	57	71	85	99	113	127	141	155	169	211	253		
Week				2	4	6	8	10	12	14	16	18	20	22	24	30	36		
Visit Window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Screening/Baseline:																			
Inclusion/Exclusion	X		X																
Informed Consent/Assent	X																		
Medical History	X																		
Demographics	X																		
Enrollment			X																
Epi injection training			X																
Training on Study Drug Administration			X																
Treatment:																			
Administer Study Drug[1]			X	X	X	X	X	X	X	X	X	X	X	X					
Study Drug Dispensation/Account			X		X		X		X		X		X		X				
Phone call to collect AEs, Conmeds and IP compliance				X		X		X		X		X		X					
Concomitant Meds and Tx	X	X	X		X		X		X		X		X		X	X	X	X	X
Efficacy[5]:																			
DBPCFC[2, 3,4]		X													X		X[10]		
Peanut SPT[3]	X																		
Titrated Peanut SPT[3,7]			X		X				X						X		X		X
FAQLQ			X						X						X		X		

Study Procedure	**Screening**		**Treatment Period**													**Follow-up**		**UV**	**ET**
Visit	**V1**	**V1a**	**V2 Baseline**	**V3 phone**	**V4 clinic**	**V5 phone**	**V6 clinic**	**V7 phone**	**V8 clinic**	**V9 phone**	**V10 clinic**	**V11 phone**	**V12 clinic**	**V13 phone**	**EOT V14 clinic**	**V15**	**EOS V16**	if applicable	
Day	-57 to -43	-42 to -15	1	15	29	43	57	71	85	99	113	127	141	155	169	211	253		
Week				2	4	6	8	10	12	14	16	18	20	22	24	30	36		
Visit Window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Safety:																			
Weight[5]	X		X		X		X		X		X		X		X	X	X	X	X
Height[5]	X																		
Vital Signs[5]	X	X	X		X		X		X		X		X		X	X	X	X	X
Physical Examination[5]	X	X							X						X		X		X
Spirometry[6]	X	X							X						X		X		X
Adverse Events[5]	X	X	X		X		X		X		X		X		X	X	X	X	X
Laboratory Testing:																			
HIV Ab, HBsAg, HBcAb, Hep C Ab[5]	X																		
Hematology/Chemistry[5]	X		X						X						X		X	X	X
FeNO Test[6]		X							X						X		X		X
Pregnancy Test (WOCBP)[5]	S	U	U		U		U		U		U		U		U	U	S		U
Urinalysis[5]	X	X	X						X						X		X	X	X
Total IgE[5]			X						X						X		X		X
Peanut sIgE, sIgG, and sIgG4[5]	X		X		X		X		X		X				X	X	X		X
Research Samples (serum/plasma)[5]		X	X						X						X		X		X
Blood samples for additional exploratory[5] research[7]			X						X						X		X		X

Study Procedure	Screening		Treatment Period													Follow-up		UV	ET
Visit	V1	V1a	V2 Baseline	V3 phone	V4 clinic	V5 phone	V6 clinic	V7 phone	V8 clinic	V9 phone	V10 clinic	V11 phone	V12 clinic	V13 phone	EOT V14 clinic	V15	EOS V16	if applicable	
Day	-57 to -43	-42 to -15	1	15	29	43	57	71	85	99	113	127	141	155	169	211	253		
Week				2	4	6	8	10	12	14	16	18	20	22	24	30	36		
Visit Window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
PK/Drug Concentration and ADA Samples[8]:																			
PK/Drug conc. sample			X				X		X						X		X		X
ADA sample			X						X						X		X		X
Genomic DNA sample[9]:																			
Buccal swab samples for DNA			X																

WOCBP = women of childbearing potential

Footnotes for the Schedule of Events Table

1. Study drug will be administered in the clinic on day 1 by the study team, patient's caregiver, or patient. With adequate training, study drug may be administered at home Q2W for the remaining injections. Patient/caregiver will complete an injection log to document compliance with injection of study drug and to document any AEs and concomitant medications.
2. During DBPCFC, vital signs will be collected every 15 to 30 minutes. After initial DBPCFC dose, only pulse and blood pressure need to be taken as part of safety monitoring.
3. Patients should not take antihistamines within 5 days prior to SPTs and day 1 of the DBPCFCs.
4. The food challenges (DBPCFC) will be performed on different days (1 day placebo [oat] protein, 1 day peanut protein, with order determined at random) at least 24 hours, but no more than 7 days, apart and not within 24 hours of a dose of study drug. After the last dose of the DBPCFC, the patient will be monitored for at least 2 hours and then discharged from the clinic.
5. Assessments will be performed before the administration of study drug.

6. FeNO measurement and spirometry will be performed on the same day, except for visit 1, in which only spirometry is performed. If the DBPCFC is scheduled on the day of the visit, then both FeNO measurement and spirometry will be performed twice before the patient goes home: once before DBPCFC, once after DBPCFC. FeNO should be done prior to spirometry.
7. On the day of the DBPCFCs, blood draws for exploratory research, including TruCulture, basophil sensitivity, and peripheral blood mononuclear cells (PBMC) samples will be performed before the DBPCFC is performed. On the day of the DBPCFC, titrated SPTs will be performed before the DBPCFC.
8. Samples for PK and ADA analysis should be collected prior to drug administration.
9. Two buccal swabs for genomic analysis can be collected on day 1 or any day after day 1.
10. Only patients who passed a DBPCFC of at least 444 mg (cumulative) at week 24 will undergo a final DBPCFC (up to 2044 mg cumulative).

10.3. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	Treatment Emergent PCSV	Comments
Clinical Chemistry		
Alanine Aminotransferase (ALT)	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently.
Aspartate Aminotransferase (AST)	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently.
Alkaline Phosphatase (ALP)	>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.
Bilirubin (BILI)	>1.3 ULN and baseline ≤ 1.3 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Based on normal range: <1 mg/dL, CF = mg x 1.7 = µmol Concept paper on DILI – FDA draft Guidance Oct 2007. Based on normal ranges: <6 mg/dL (Term 0-1 day), <8 mg/dL (Term 1-2 days), <12 mg/dL (Term 3-5 days), <1 mg/dL (Term >5 days)
Conjugated Bilirubin	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin >1.3 ULN) and (Direct Bilirubin ≤35% Total Bilirubin or Total Bilirubin ≤1.3 ULN) at baseline	Conjugated bilirubin will be measured when the total Bilirubin is above the ULN Based on normal range: 0 to 0.4 mg/dL
(ALT or AST) and Bilirubin (BILI)	((ALT > 3 ULN or AST >3 ULN)) and BILI >2 ULN) and baseline ((ALT ≤3 ULN and AST ≤3 ULN) or BILI ≤2 ULN)	Concept paper on DILI – FDA draft Guidance Oct 2007.
Creatine Kinase (CK)	>5 ULN and ≤10 ULN and baseline ≤5 ULN >10 ULN and baseline ≤10 ULN	

Parameter	Treatment Emergent PCSV	Comments
Creatinine (CREAT)	>=30% increase from individual patient baseline >=60% increase from individual patient baseline	
Urate (URATE) Hyperuricemia Hypouricemia	>=30% increase from individual patient baseline >=60% increase from individual patient baseline	
Urea Nitrogen (UREAN)	>=30% increase from individual patient baseline >=60% increase from individual patient baseline	
Chloride (CL) Hypochloremia Hyperchloremia	<80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	Two independent criteria
Sodium (SODIUM) Hyponatremia Hypernatremia	<129 mmol/L and baseline ≥129 mmol/L >150 mmol/L and baseline ≤ 150 mmol/L	Two independent criteria
Potassium (K) Hypokalemia Hyperkalemia	<3.5 mmol/L and baseline ≥ 3.5 mmol/L >5.0 mmol/L and baseline ≤ 5.0 mmol/L	Two independent criteria
Cholesterol (Cholesterol)	>6.20 mmol/L and ≤ 6.20 mmol/L at baseline	
Triglycerides (TRIG)	> 5.64 mmol/L and ≤ 5.64 mmol/L at baseline	Threshold for therapeutic intervention with pharmacotherapy in children. (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; 2011). CF = g x 1.14 = mmol
Glucose (GLUC) Hypoglycaemia Hyperglycaemia	≤ 2.7 mmol/L ≥10 mmol/L	
Albumin (ALB)	<25 g/L and ≥25 g/L at baseline	
Calcium (CA)	<2 mmol/L and baseline ≥2 mmol/L >2.9 mmol/L and baseline ≤2.9 mmol/L	

Parameter	Treatment Emergent PCSV	Comments
LDL Cholesterol (LDL)	>4.91 mmol/L and ≤4.91 mmol/L at baseline	Threshold for therapeutic intervention with pharmacotherapy in children (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; 2011).
Hematology		
Leukocytes (WBC)	<4.0 Giga/L and ≥4.0 Giga/L at baseline >13.5 Giga/L and ≤13.5 Giga/L at baseline	
Lymphocytes (LYM)	<0.6 Giga/L and ≥0.6 Giga/L at baseline >6.0 Giga/L and ≤6.0 Giga/L at baseline	
Neutrophils (NEUT)	<1.2 Giga/L and ≥1.2 Giga/L at baseline >ULN and baseline ≤ ULN	
Monocytes (MONO)	>1.2 Giga/L and ≤ 1.2 Giga/L at baseline	
Basophils (BASO)	>0.2 Giga/L	
Eosinophils (EOS)	(>0.5 Giga/L and >ULN) and (≤ 0.5 Giga/L or ≤ ULN at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin (HGB)	<100 g/L and ≥100 g/L at baseline or any decrease ≥ 20 g/L >200 g/L and ≤200 g/L at baseline	Two criteria are independent
Hematocrit (HCT)	<0.37 v/v and ≥ 0.37 v/v at baseline for Male; <0.33 v/v and ≥0.33 v/v at baseline for Female >0.52 v/v and ≤0.52 v/v at baseline for Male; >0.47 v/v and ≤0.47 v/v at baseline for Female	Two criteria are independent
Platelets (PLAT)	<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 (PH)	<5 or >8	
Ketones (KETONES) Ketonuria	Presence and absence at baseline	Semi-quantitative methods

Parameter	Treatment Emergent PCSV	Comments
Glucose (GLUC) Glycosuria	Presence and absence at baseline	Semi-quantitative methods
Erythrocytes (RBC) Microscopic Hematuria	> 5 RBCs/ HPF and ≤5 RBCs/ HPF at baseline	Semi-quantitative methods
Protein (PROT) Proteinuria	≥ 1+ and <1+ at baseline	Semi-quantitative methods, ≥ 1+ means concentration ≥30 mg/dL
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	≤90 mmHg and decrease from baseline ≥20 mmHg ≥119 mmHg and increase from baseline ≥20 mmHg.	
DBP	≤54 mmHg and decrease from baseline ≥10 mmHg ≥78 mmHg and increase from baseline ≥10 mmHg	
Temperature	Rectal, Tympanic: >100.4 °F/38.0 °C Oral: >99.5 °F/37.5 °C Axillary or skin infrared (temporal): >99 °F/37.2 °C	
Respiratory rate	< 12 per minute and ≥12 per minute at baseline >20 per minute and ≤20 per minute at baseline	
Weight	≥5% weight loss from baseline	Based on identification of trends in the child's growth with a series of visits WHO Multicentre Reference Study Group, 2006; Center for Disease Control. Growth chart 2007.

10.4. Adverse Event of Special Interest (AESI)

AESI	Search Criteria
Anaphylactic reactions	SMQ narrow "Anaphylactic Reactions"
Systemic hypersensitivity reactions	Narrow SMQ for hypersensitivity Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock
Malignancy	Malignant tumours (SMQ) [Broad or Narrow]
Helminthic infections	• HLT = Cestode infections • HLT = Helminthic infections NEC • HLT = Nematode infections • HLT = Trematode infections
Suicidal behavior	Include the following PTs • Completed suicide • Suicidal ideation • Suicide attempt • Depression suicidal • Suicidal behaviour • Assisted Suicide
Any type of conjunctivitis or blepharitis (severe or serious)	Broad CMQ conjunctivitis PTs (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 (Bacterial blepharitis, blepharitis allergic) **AND** Serious AE= "Yes" OR Severity= "severe"
Keratitis	CMQ Keratitis PTs: 1. Allergic keratitis 2. Atopic keratoconjunctivitis 3. Diffuse lamellar keratitis 4. Exposure keratitis 5. Keratitis 6. Keratitis interstitial 7. Keratitis sclerosing 8. Keratopathy 9. Keratorhexis 10. Keratouveitis 11. Neurotrophic keratopathy 12. Punctate keratitis 13. Superior limbic keratoconjunctivitis 14. Ulcerative keratitis 15. Vernal keratoconjunctivitis 16. Acanthamoeba keratitis 17. Infectious crystalline keratopathy 18. Infective Keratitis 19. Keratitis bacterial 20. Keratitis fungal 21. Keratitis viral 22. Keratoconjunctivitis measles

AESI	Search Criteria
	23. Varicella keratitis 24. Viral keratouveitis 25.Corneal neovascularization 26. Limbal swelling 27. Corneal abrasion 28. Corneal abscess 29. Corneal bleeding 30. Corneal defect 31. Corneal disorder 32. Corneal epithelium defect 33. Corneal erosion 34. Corneal infection 35. Corneal irritation 36. Corneal lesion 37. Corneal leukoma 38. Corneal opacity 39. Corneal perforation 40. Corneal scar 41. Infective corneal ulcer 42. Injury corneal 43. Limbal stem cell deficiency

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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