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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DUPILUMAB MONOTHERAPY IN PEDIATRIC PATIENTS WITH PEANUT ALLERGY

Compound:	REGN668 (Dupilumab)
Clinical Phase:	2
Protocol Number:	R668-ALG-1702
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AMENDMENT HISTORY

Amendment 2

The purpose of this amendment is to revise the sample size of this study in order to expose the minimum number of patients to serial food challenges, thereby reducing the number of patients enrolled from 35 to 24. Other minor changes were made for clarification. A detailed list of changes and their rationales can be found in the table below.

Change	Rationale	Section Changed
The statistical hypothesis and sample size calculation were re-evaluated. It is now assumed that the rate of a tolerated cumulative dose of at least 444 mg of peanut protein on double-blind placebo-controlled food challenge (DBPCFC) at week 24 is 29% in dupilumab and 8% in placebo, based on assessment of clinical data from the Aimmune Therapeutics AR101 phase 3 study. The number of patients enrolled was thus reduced from 35 to 24.	In order to expose the minimum number of patients to serial food challenges in this proof of mechanism study, the power analysis was re-evaluated. This allowed for enrollment of fewer patients to meet study endpoints.	Clinical Study Protocol Synopsis: Population; Statistical Plan Section 3.2.1 Rationale for Study Design Figure 1 Schematic of Study Design Section 7.1 Number of Patients Planned Section 8.5 Method of Treatment Assignment Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size
Clarified language pertaining to dupilumab prefilled syringes, packaging, and disposition of treatments.	For clarification.	Section 8.1 Investigational and Reference Treatments Section 8.6.1 Packaging, Labeling, and Storage Section 8.6.2 Supply and Disposition of Treatments
Text was added to specify that, while this is an open-label study, the study team will remain blinded to the order of the exposure for each DBPCFC at weeks 24 and 36.	For clarification.	Section 6.1 Study Description and Duration Appendix 1 Peanut DBPCFC Schedule of Dosing Performed at screening and weeks 24 and 36
The text stating that no adjustments for multiplicity are planned was specified to be “for the secondary endpoints.”	For clarification.	Section 11.4.3.3 Multiplicity Considerations
The word “tolerated” was changed to “passed” for the DBPCFC.	For clarification.	Clinical Study Protocol Synopsis: Study Design Section 6.1 Study Description and Duration Section 9.2.2.1 Double-Blind Placebo-Controlled Food Challenge

Change	Rationale	Section Changed
Specified "at least" 444 mg in the description of passing the DBPCFC.	For clarification.	Clinical Study Protocol Synopsis: Study Design; Procedures and Assessments; Statistical Plan Section 3.2.1 Rationale for Study Design Section 6.1 Study Description and Duration Section 9.1.1 Footnotes for the Schedule of Events Table, #10 Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Section 11.3.1 Efficacy Analysis Sets

Amendment 1

The purpose of this amendment is to change the 2-arm placebo-controlled study design to single-arm open-label and to remove the week 12 double-blind placebo-controlled food challenge (DBPCFC) as a means of increasing enrollment. Subsequent changes were made to the statistical analysis plan (SAP) based on this new study design. Changes were also made to align with the most recent dupilumab data. The following table outlines the changes made to the protocol and the affected sections:

Change and Rationale for Change	Section Changed
This phase 2, multicenter, proof of concept (POC) study was amended from a 2-arm randomized double-blind study to a single-arm open-label study to increase enrollment. The rationale is that an open-label design in which all patients have access to dupilumab will decrease barriers to enrollment regarding concerns related to the risk of anaphylaxis in studying peanut protein tolerability in pediatric patients with a history of peanut allergy. This is further justified by a low historical placebo effect in peanut allergy (less than 8%).	Clinical Study Protocol Synopsis: Objectives; Study Design; Population; Treatments; Endpoints; Statistical Plan Section 2.1 Primary Objective Section 2.2 Secondary Objective Section 3.2.1 Rationale for Study Design Section 3.2.2 Rationale for Dose Selection Section 4.1.1 Primary Endpoint Section 4.1.2 Secondary Endpoints Section 6.1 Study Description and Duration Figure 1 Schematic of Study Design Section 6.3 Study Committees Section 7.1 Number of Patients Planned Section 8.1 Investigational Reference Treatments Section 8.3.2.1 Reasons for Permanent Discontinuation of Dupilumab and Food Challenge Section 8.5 Method of Treatment Assignment Section 8.5.1 Blinding Table 1 Schedule of Events Section 10.2 Obligations of Sponsor Section 10.5.2 Evaluation of Causality Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Section 11.3 Analysis Sets Section 11.4 Statistical Methods

Change and Rationale for Change	Section Changed
The week 12 DBPCFC was removed, leaving only the DBPCFC at screening, week 24, and potentially at End of Study week 36. This prevents an IgE priming effect, and further reduces the burden on patients.	Clinical Study Protocol Synopsis: Statistical Plan Section 3.2.1 Rationale for Study Design Section 4.1.1 Primary Endpoint Section 4.1.2 Secondary Endpoints Section 6.1 Study Description and Duration Figure 1 Schematic of Study Design Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events, Footnote #1 Section 10.4.1 Adverse Events Section 11.2 Justification of Sample Size Section 11.3 Analysis Sets Appendix 1 Peanut DBPCFC Schedule of Dosing Performed at Screening and Weeks 24 and 36
The number of patients enrolled was changed to 35 in this single-arm study, instead of 48 (24 per group) in the prior 2-arm study. This change was made because of changes in the study design.	Clinical Study Protocol Synopsis: Population; Statistical Plan Section 7.1 Number of Patients Planned Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Section 11.3 Analysis Sets Section 11.4 Statistical Methods
The dose regimen for this study was changed from 100 mg every 2 weeks (Q2W) for patients weighing <30 kg, to 200 mg Q2W for patients weighing ≥20 kg and <60 kg. This change was based on recent data from pediatric patients (6 to 12 years of age) with atopic dermatitis (AD). It was determined that 100 mg Q2W may be a suboptimal dose regimen for patients weighing ≥20 and <30 kg.	Clinical Study Protocol Synopsis: Study Design Section 3.2.2 Rationale for Dose Selection Section 7.2.2 Exclusion Criteria #23 Section 8.1 Investigational Reference Treatments
Changes were made to expand the pool of patients who may be eligible for the study by decreasing the level of serum peanut specific IgE required for inclusion from ≥24 kUA/L to ≥10 kUA/L and/or Skin Prick Test (SPT) to peanut of ≥10 mm to ≥8 mm. The previous criteria were too restrictive compared to similar peanut allergy studies and the change will still enroll only severely allergic patients who react to screening double-blind peanut challenge at ≤144 mg (cumulative).	Section 3.2.3 Rationale for Study Population Section 7.2.1 Inclusion Criteria, #4 Section 9.2.2.2 Peanut Skin Prick Test
After day 1, patients or their caregivers may administer drug at home with adequate training. Additionally, phone visits will be used (for visit # 3, 5, 7, 9, 11 and 13) between clinic visits. These changes were made to increase enrollment by decreasing the burden of visits.	Section 6.1 Study Description and Duration Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events, Footnote # 1

Change and Rationale for Change	Section Changed
Post-treatment follow-up at week 36 is not optional if patients pass DBPCFC at week 24. This change is due to the smaller sample size.	Section 6.1 Study Description and Duration
DNA and research sample are no longer mandated for sites who have regulatory or IRB concerns. This change was made to comply with regulations in Canada.	Table 1 Schedule of Events Section 9.2.7 Exploratory Research Section 9.2.7.1 Genomics Analysis
The protocol was updated for accuracy to reflect that approximately 10 study sites will be used in the United States (US) and Canada (CAN), rather than the US and European Union (EU).	Clinical Study Protocol Synopsis: Site Location(s) Section 7.1 Number of Patients Planned
Minor changes have been made to align with the most recent Investigator's Brochure for dupilumab, Edition 13.	Section 1 Introduction Section 3 Hypothesis and Rationale Section 3.3 Safety Considerations Section 3.3.1 Risk Benefits for Dupilumab
Other minor changes have been made throughout for accuracy, clarity, and to correct errors in spelling or grammar.	Section 5.5 Anti-Drug Antibody Variables Section 5.6 Pharmacodynamic and Biomarker Variables Section 6.2 Planned Interim Analysis Section 7.2.1 Inclusion Criteria Section 7.2 Study Population Section 8.7.1 Prohibited Medications and Procedures Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events, Footnotes # 2, 3, 6, 9 Section 9.2.2.1 Double-Blind Placebo-Controlled Food Challenge Section 9.2.2.3 Food Allergy Quality of Life Questionnaire Section 9.2.3.3 Spirometry Section 9.2.6 Pharmacodynamic and Exploratory Biomarkers Procedures Section 9.2.6.3 Fractional Exhaled Nitric Oxide Section 10.3.2 Serious Adverse Event Section 10.4.3 Other Events that Require Accelerated Reporting to Sponsor Section 11.3.4 Immunogenicity Analysis Sets Section 11.4.6 Analysis of Immunogenicity Data Section 15.5 Clinical Study Data Transparency Section 23 References

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Study to Evaluate the Efficacy and Safety of Dupilumab Monotherapy in Pediatric Patients with Peanut Allergy
Site Location(s) **Principal Investigator**	Approximately 10 sites in the United States (US) and Canada (CAN).
Objective(s)	The primary objective of the study is to assess the tolerability of peanut protein in pediatric patients (6 to 17 years old) treated with dupilumab, in which tolerability is defined as the proportion of patients who safely pass a double-blind placebo-controlled food challenge (DBPCFC) at week 24. The secondary objectives are: • 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 • To evaluate the treatment effect of dupilumab on the average wheal size after a titrated skin prick test (SPT), as measured by area under 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
Study Design	This is a phase 2, multicenter, single-arm open-label proof-of-concept (POC) study in pediatric patients aged 6 to 17 years inclusive who are allergic to peanut, to evaluate the effects of dupilumab on allergenic tolerance to peanut protein during a DBPCFC. The study consists of an 8-week screening period, a 24-week treatment period with dupilumab, followed by a 12-week safety follow-up period. **Screening Period:** During screening visit 1 (day -57 to day -43), patients will undergo a medical history, physical examination, spirometry, standard peanut skin prick test (SPT), and laboratory testing (including peanut-specific IgE [sIgE]) and be evaluated for study eligibility criteria. During screening visit 1a (day -42 to day -15), under direct study investigator monitoring, patients will undergo a DBPCFC to confirm peanut allergy. This will consist of 5 doses (1, 3, 10, 30, and 100 mg) 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 (artificially peanut flavored oat protein) given also in 5 doses (1, 3, 10, 30, and 100 mg).

Both peanut and oat protein will be concealed in a food that masks the taste. 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. All food challenges will be performed under physician supervision. Only patients, who experience dose-limiting symptoms at or before the 100 mg challenge dose of peanut protein, will be enrolled in the study.

Treatment Period: Dupilumab will be dosed subcutaneously (SC) as follows based on weight at enrollment 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 will be given in the study clinic on day 1 and then, with adequate training, study drug may be administered at home Q2W. Study drug can be administered in the clinic at patient's request and Principle Investigator's discretion.

Patients will have monthly clinic visits and phone calls in-between visits to collect adverse events (AEs), concomitant medications and compliance to study drug administration.

Double-Blind Placebo-Controlled Food Challenge: 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. Vital signs will be assessed 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 mg, and 1000 mg resulting in a total challenge of up to 2044 mg peanut protein (cumulative). Both peanut and oat protein will be concealed in a food that masks the taste. 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 grading system.

Follow-up Period: 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 sustained unresponsiveness.

Study Duration	The duration of the study for a patient is approximately 36 weeks, excluding the screening period.
End of Study Definition	The end of study for this study is defined as the last visit of the last patient.
Population	
Sample Size:	Approximately 24 patients.
Target Population:	Male and female pediatric patients ages 6 to 17 years with a history of peanut allergy confirmed by peanut SPT, sIgE and by the amount of peanut protein (mg) safely ingested during a peanut DBPCFC.
Treatment(s)	
Study Drug	Dupilumab
Dose/Route/Schedule:	200 mg or 300 mg SC Q2W (weight based) following a loading dose of 400 mg or 600 mg, respectively, on day 1.
Endpoint(s)	
Primary:	• Proportion of patients treated with dupilumab that pass a DBPCFC with at least 444 mg (cumulative) peanut protein at week 24
Secondary:	• 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 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
Procedures and Assessments	The efficacy of dupilumab will be assessed by DBPCFC at week 24. Patients who passed a DBPCFC of at least 444 mg (cumulative) at week 24 will undergo a final DBPCFC (up to 2044 mg cumulative) at week 36.

	Overall safety will be assessed by monitoring/evaluation of treatment-emergent adverse events (TEAEs), physical examinations, pulse rate, and clinical safety laboratory tests at pre-specified time points.
Statistical Plan	**Sample Size 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 study, 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 29% in dupilumab and 8% in placebo. A sample size of 20 patients will have 80% power to detect the 29% tolerated rate in dupilumab group 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. **Efficacy Analysis Set:** The full analysis set (FAS) includes all enrolled patients. The week 36 FAS includes patients who pass a DBPCFC of at least 444 mg (cumulative) of peanut protein at week 24. **Safety Analysis Set:** The safety analysis set (SAF) includes all patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF. **Analysis Methods** **Primary Efficacy Analysis:** The FAS will be used for the primary efficacy endpoint. The primary endpoint will be analyzed using one-sample Chi-square test. Estimate of proportion, p-value, and the 2-sided 95% confidence interval will be provided. If a patient does not have available DBPCFC data at week 24, the patient will be considered as a non-responder regardless of reasons for missing data. Sensitivity analyses of the primary endpoint will include an analysis of the subset of patients with available week 24 DBPCFC. Other sensitivity analyses may be proposed in the statistical analysis plan (SAP). Subgroup analysis (eg, by dose group) will be performed. **Secondary Efficacy Analysis:** All secondary endpoints will be analyzed descriptively at given visits. FAS will be used for efficacy analysis at week 24, and week 36 FAS will be used for efficacy analysis at week 36. For binary endpoints, the analysis and imputation methods will be similar to the primary analysis. A one-sample t-test will be performed to assess the change from baseline to week 24 in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC. Estimate of change from baseline to week 24, p-value, and the 2-sided 95% confidence interval will be provided. If the data is extremely skewed, nonparametric method may be applied. Details will be provided in the SAP. The missing data will be imputed by the last non-missing DBPCFC assessment including baseline.

	For other continuous endpoints, the analysis and imputation methods will be applied similarly. Sensitivity analysis will include an analysis based on the observed cases. Other sensitivity analysis may be proposed in the SAP. **Safety Analysis:** Safety analysis will be based on the SAF. This includes reported TEAEs and other safety data (ie, clinical laboratory evaluations and vital signs results). A descriptive summary of safety results will be presented.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	Atopic Dermatitis
ADA	Anti-Drug Antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under curve
BUN	Blood urea nitrogen
CoFAR	Consortium of Food Allergy Research
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CRSwNP	Chronic rhinosinusitis with nasal polyposis
DBPCFC	Double-blind, placebo-controlled food challenge
DMC	Data monitoring committee
DLS	Dose limiting symptom
EASI	Eczema Area and Severity Index
EC	Ethics Committee
EDC	Electronic data capture
EoE	Eosinophilic Esophagitis
FAQLQ	Food allergy quality of life questionnaire
FAS	Full analysis set
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
IDMC	Independent Data Monitoring Committee
IL-4Rα	Interleukin 4 Receptor Alpha
IL-13	Interleukin 13
IM	Intramuscular
IL	Interleukin
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
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
QW	Weekly
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
SCORAD	Scoring AD
sIgE	Peanut-specific IgE
SOC	System organ class
SPT	Skin prick test
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
Tx	Treatment
ULN	Upper limit of normal
WBC	White blood cell

1. INTRODUCTION

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 OIT is to induce desensitization and increase the threshold for peanut ingestion, and reduce the risks of allergic reactions after accidental ingestion. However, many patients 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. Cross-linking of peanut-specific IgE (sIgE) bound to high affinity IgE receptors on mast cells and basophils triggers immediate degranulation. Subsequent release of a diverse array of inflammatory mediators results in severe allergic symptoms such as hives, wheezing, vomiting and, in severe cases, anaphylactic shock. Release of these mediators also initiates IL-4 and IL-13 release, which results in eosinophil gastrointestinal (GI) tissue infiltration and creates a cycle of chronic Type 2 allergic inflammation (Wong, 2016).

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). As of October 2019, dupilumab has been approved for the adult atopic dermatitis (AD) indication in over 40 countries worldwide. Additionally, dupilumab has been approved for severe asthma with type 2 inflammation in both adult and adolescent patients, and recently in adult patients with chronic rhinosinusitis with nasal polyposis (CRSwNP), and adolescents with AD. Dupilumab is also under development for a range of type 2 inflammatory diseases such as food allergies and eosinophilic esophagitis (EOE) amongst others.

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 important in the allergic response to peanuts such as a reduction in allergen-specific IgE and/or increase in allergen-specific IgG4.

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. Primary Objective

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

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
- 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

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

In pediatric patients with peanut allergy, treatment with dupilumab will result in inhibition of the Type 2 immune response and increase the threshold amount of peanut protein that triggers a clinically measurable allergic reaction.

3.2. Rationale

3.2.1. Rationale for Study Design

Dupilumab will be tested in a single-arm open-label POC study of 24 weeks subcutaneous (SC) dupilumab (every 2 weeks [Q2W]) treatment period and 12-week safety follow-up period in approximately 24 pediatric patients with confirmed peanut allergy.

Assessing the proportion of patients who tolerate at least 444 mg (cumulative) peanut protein during a DBPCFC before and after 24 weeks of dupilumab therapy will provide clinically relevant information about the potential increase in the peanut allergic threshold for protection from accidental exposure to approximately 2 peanut kernels.

The time course of dupilumab efficacy in peanut allergy is not yet established. It is thought the onset of action could coincide with reduction of sIgE and suppression of Type 2 effector cells. Dupilumab suppresses Type 2 inflammation, as measured by circulating markers such as Chemokine (C-C motif) Ligand 17 (also known as thymus and activation regulated chemokine [TARC]), within 4 to 12 weeks of treatment in all indications tested to date. Type 2 T-helper and effectors also play a major role in the onset of peanut allergy. In past AD studies, CD3+ T-cell infiltration in the skin was shown to significantly decrease from weeks 4 to 16. This suggests dupilumab may suppress the activity of pathogenic Th2 cells effectively in 16 weeks. Thus, a 24 week study is expected to be sufficient to evaluate the onset of effects of dupilumab on peanut protein tolerability. Evaluation of effect at week 36 when the dupilumab concentration should be below the lower limit of quantitation will assess the persistence of immune modulation following 12 weeks off treatment.

3.2.2. Rationale for Dose Selection

The approved dosing regimen in the US and EU for the treatment of AD in adults is 300 mg Q2W. Doses of 300 mg Q2W and 300 mg weekly (QW) were shown to have an acceptable safety profile in adult AD patients in 2 phase 3 studies. In addition, 300 mg Q2W had an acceptable safety profile in a phase 2b study in adults with persistent asthma (Wenzel, 2016) and in a phase 3 study in patients ≥12 years of age with uncontrolled moderate-to-severe asthma (Busse, 2018). The dose justification for pediatric patients aged 6 to <12 years old is based on the efficacy and safety observed in the global phase 3 monotherapy studies in adult AD patients (R668-AD-1334 and R668-AD-1416) and adolescent patients (R688-AD-1526), together with the observed efficacy, safety and PK modeling of data gathered from a study of AD patients aged 6 to 18 years (R668-AD-1412). In pediatric patients receiving 4 mg/kg QW for 4 doses, exposures similar to those in adults receiving 300 mg Q2W dupilumab were achieved in the first study (R668-AD-1412), where significant improvement in measures of AD were noted, with an acceptable safety profile. Similarly, in the pivotal, phase 3 study in adolescent patients (R668-AD-1526), dupilumab monotherapy resulted in significant improvements in measures of AD and had an acceptable safety profile. Considering these data, 300 mg Q2W dupilumab is a suitable dose for adolescent and adult patients >60 kg with confirmed peanut allergy. The weight-based doses chosen for treatments in this study represent the doses of dupilumab, which are modeled to result in exposure to dupilumab that is associated with efficacy in AD in adults and adolescents. The dupilumab SC dose will be 300 mg Q2W in children ≥60 kg following a loading dose of 600 mg on day 1. Children who weigh 20 kg or more but less than 60 kg, will receive 200 mg Q2W following a loading dose of 400 mg on day 1. These dose regimens are also being tested in the pediatric AD studies.

Bi-weekly dupilumab dosing should allow for adequate drug exposure without adversely impacting safety. Study drug may be administered in the clinic or at home by the study team, patient's caregiver, or patient. For patients under 12 years old, caregiver injections will be required.

The administration of the loading dose of dupilumab is the approach that was used for other symptomatic conditions where early onset is appropriate, and the same approach is followed here.

3.2.3. Rationale for Study Population

Dupilumab has been well tolerated with a favorable safety profile in pediatric patients in studies to date (see below). The lower cutoff of 6 years of age was selected to include only patients with sufficient blood volumes to perform the mechanistic and safety studies blood measurements every month or per schedule of events (±1 clinic visit). A weight cut off of 20 kg to be compliant with Institutional Review Board (IRB) guidelines (ie, for children: 5 mL/kg at any single draw, no more than 9.5 mL/kg over an 8-week period; adults: the smaller of 10.5 mL/kg or 550 ml total at any single draw). The upper age limit of 17 years was selected because the majority of patients with peanut allergy are in the pediatric population. Patients will be enrolled with proven peanut allergy with serum IgE to peanut of ≥10 kUA/L and/or an SPT to peanut ≥8 mm compared to a negative control. In addition, a clinical reaction during a DBPCFC ≤100 mg peanut protein (144 mg cumulative) and no clinical reaction during placebo (oat) will ensure the enrollment of only highly reactive patients.

3.3. Safety Considerations

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). Although recent progress has been made in the treatment of food allergy through allergen-specific OIT, side effects, primarily GI related, often limit its full efficacy in many patients and there is an unmet need for a new therapy in food allergy. It is known that allergic response to food is an IgE mediated event; however, recent data suggest that non-IgE related, IL-4/13 mediated Type 2 inflammation may also play a significant role in food allergy pathogenesis (Yu, 2016). Consequently, dupilumab treatment would be expected to provide benefit by blocking the activity of IL-4 and IL-13 and decreasing Type 2 immune responses and production of peanut-specific IgE. As of 28 March 2019, dupilumab has been well tolerated in all completed studies, including studies in AD, asthma, nasal polyps, EoE, grass allergy and peanut allergy.

3.3.1. Risk Benefits for Dupilumab

At the time of writing this protocol, dupilumab 300 mg Q2W had been approved in the US, the EU, and several other countries including Japan for the treatment of adults with moderate-to-severe AD. Marketing applications are under review in additional countries. Dupilumab received approval from US Food and Drug Administration (FDA) on 11 March 2019 and from European Union European Commission on 1 August 2019 for use in adolescent patients (≥12 years) with moderate to severe atopic dermatitis. Review of this indication is ongoing in a number of other countries worldwide. Fourteen clinical studies (phases 1 through 3) of repeated-doses of dupilumab in AD patients have been completed. Dupilumab has demonstrated robust and consistent efficacy in completed clinical trials, across a variety of clinical outcomes, reflecting clinically meaningful and statistically significant improvement in AD signs, symptoms and quality of life with sustained efficacy demonstrated to 52 weeks. Dupilumab was well tolerated in these studies with a favorable safety profile.

Dupilumab's efficacy in adult patients with moderate-to-severe uncontrolled asthma has also been demonstrated at doses of 200 mg or 300 mg Q2W for 24 weeks (DRI12544) and 52 weeks (EFC13579). Dupilumab received approval from US FDA on 19 October 2018 for use in adults and adolescents (≥12 years) with moderate-to-severe asthma with an eosinophilic phenotype or

corticosteroid dependent asthma. In the European Union, dupilumab received a marketing authorization approval from the European Commission on 6 May 2019 for use in adults and adolescents (≥12 years) with severe asthma with type 2 inflammation. In Japan, dupilumab received approval from Pharmaceuticals and Medical Devices Agency on 26 March 2019 for use in adults and adolescents (≥12 years) with severe or refractory bronchial asthma. Asthma is a common comorbidity of allergy and asthma exacerbations are an important safety concern for food challenges. In these studies, treatment with dupilumab at all doses tested was generally well tolerated with a favorable safety profile.

The first clinical study of dupilumab in pediatric patients aged 6 years to <18 years old with AD (R668-AD-1412) has been completed. Data generated from this study showed that dupilumab administered as single and repeated weekly doses (up to 4 weeks) was generally well tolerated and had an acceptable safety profile similar to that for adults in both pediatric age groups included in this study (6 to 11 years and 12 to <18 years). There were no new safety signals detected with dupilumab in this pediatric population. Most of the AEs reported were mild in intensity, transient in nature and not related to the study drug. Both dose regimens of dupilumab evaluated (2 mg/kg and 4 mg/kg) showed significant clinical benefit in both pediatric age groups. In the pivotal, phase 3 study in adolescent patients (R668-AD-1526) the overall rate of AEs was comparable between the dupilumab groups and placebo (72% for dupilumab Q2W, 64% for dupilumab Q4W and 69% for placebo). There were no serious adverse events (SAEs) or events leading to treatment discontinuation in either dupilumab treatment group. Adverse events that were observed at a higher rate with dupilumab included Injection Site Reactions (8.5% for dupilumab Q2W, 6% for dupilumab Q4W, compared with 3.5% for placebo) and Conjunctivitis (10% for dupilumab Q2W, 11% for dupilumab Q4W, compared with 5% for placebo). Skin Infections were numerically lower in the dupilumab groups (11% for dupilumab Q2W, 13% for dupilumab Q4W, compared with 20% for placebo). As of 28 March 2019, the estimated total number of subjects exposed to dupilumab in clinical studies was 7781 (218 in healthy volunteer studies, 3931 in AD studies, 3073 in asthma studies, 470 in CRSwNP studies, 26 EoE studies, and 63 in grass allergy and peanut allergy studies). In all completed studies, dupilumab has been well tolerated and has demonstrated significant and prolonged efficacy in all Type 2 immune indications investigated to date.

Additional information can be found in the Investigator's Brochure.

3.3.2. Risk for Peanut Protein

Oral food challenges may induce a severe life-threatening allergic reaction; however, the risk can be greatly mitigated by conducting the challenges in a highly monitored setting and by initiating the challenge with a very small amount of the food, gradually increasing the dose, and stopping the challenge at the first sign of a reaction. If patients develop an allergic reaction during the challenges, they may need oral, intramuscular (IM), or intravenous (IV) medications. Additionally, IV catheters may be placed, at physician discretion for any visit, based on factors such as previous reactions, recent clinical history, and clinical status observed at the visit. Trained personnel, including a study physician, as well as medications and equipment, will be immediately available to treat any reaction. Based on similarly designed previous clinical studies, the anticipated rate of life-threatening anaphylactic reactions is <0.1%. There may be a risk that during the study patients may decrease their vigilance against accidental food allergen ingestion because they believe they are protected from it. Therefore, patients/caregivers will be warned that they should continue to

practice their usual vigilance against accidental ingestion of food allergens or food allergen-containing foods and reminded to carry their epinephrine autoinjector at all times.

4. STUDY ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoint

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

4.1.2. Secondary Endpoints

- 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 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

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

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

5.2. Efficacy Variables

Efficacy variables will include the DBPCFC and the peanut SPT.

5.3. Safety Variables

Safety variables will include vital signs, spirometry (Forced Expiratory Volume in 1 Second [FEV1] and/or peak expiratory flow rate [PEFR]), hematology and chemistry, urinalysis, and AEs.

5.4. Pharmacokinetic Variables

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

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, neutralizing antibody (NAb) status, and time-point/visit.

5.6. Pharmacodynamic and Biomarker Variables

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

Peanut-specific IgE, IgG, IgG4. The induction of peanut-specific IgG4 and IgG during OIT has been reported in multiple studies, and is thought to have a protective effect against IgE-mediated allergic symptoms. The gradual increase in serum allergen-specific IgG4, and decrease in allergen-specific IgEs are associated with clinical desensitization to peanut (Glaumann, 2015). In a 5-year peanut OIT study of 39 peanut-allergic children, increases in total peanut-specific IgG levels were reported during the 12-month up-dosing period (Vickery, 2014). In an open-label study of 29 peanut-allergic children, peanut-specific IgG4 increased steadily during the first year of treatment, reaching 3.5-fold increase over baseline after 3 months of OIT and roughly 10-fold increase at the end of first year (Jones, 2009). In the same study, peanut-specific IgE increased by ~3 fold after 3 months of OIT and gradually returned to baseline at one year. In a study investigating the biomarker profile of dupilumab in patients with AD (R668-AD-1307 as well as other dupilumab studies), dupilumab suppressed both total and allergen-specific IgEs. In general, dupilumab suppresses total serum IgE by ~ 50% with 12 to 16 weeks of treatment.

Titrated Skin Prick Test. The titrated SPT will assess the atopic response to peanut extract. A statistically significant reduction in wheal size has been associated with clinical desensitization for peanut allergy in a randomized controlled study of peanut OIT for 12 months (Varshney, 2011).

Fractional Exhaled Nitric Oxide. Fractional exhaled nitric oxide (FeNO) is a non-invasive marker that has been shown to correlate with allergic airway inflammation and IgE sensitization. The measurement of FeNO has shown predictive value on the outcome of peanut oral food challenge (Preece, 2014) In a 12-month-study enrolling 56 patients with peanut allergy, FeNO measurement demonstrated superior reproducibility (ICC=0.73) in comparison to peanut skin prick test (ICC=0.51), Ara h2 skin prick test (ICC=0.44) (Percival, 2016). In past studies, dupilumab significantly lowered FeNO concentrations in asthma patients. Asthma is a common comorbid condition in peanut allergic patients (>50%). It is plausible that peanut exposure during DBPCFC in these patients may trigger an increase in FeNO and asthmatic symptoms. Thus, dupilumab treatment may suppress FeNO induction after an oral food challenge. Although no

manufacturer has validated the FeNO device for children under 7 years old due to inadequate exhalation force, there are no contraindications with the use of FeNO for 6-year-old children. Additionally, specific guidance and reference ranges are available for collection in children as young as 6 years of age (Brody, 2013) (Menou, 2017). As FeNO is an exploratory biomarker, it will be collected for children 6 years old unless the investigator declines to collect. FeNO will be collected prior to spirometry.

Other Exploratory Research

Blood may be obtained for additional exploratory tests research to understand better allergy and peanut allergy. Blood samples collected for exploratory research will be kept for up to 15 years for studying the allergen response ex vivo.

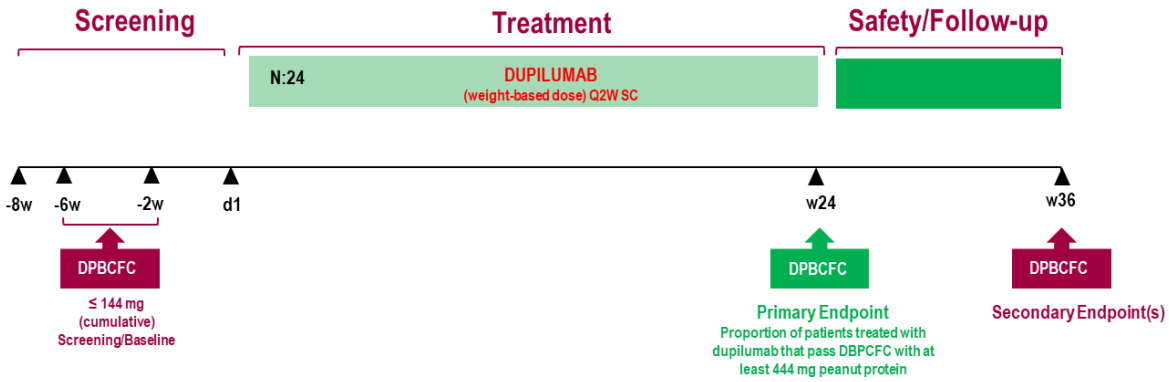
The results of exploratory analyses will not be presented in the CSR.

6. Study Design

6.1. Study Description and Duration

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

Figure 1: Schematic of Study Design



Screening

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 (day -42 to day -15), 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 (Appendix 1). 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. Both peanut and oat protein will be concealed in a food that masks the taste. 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.

Before each challenge, the patient will have a physical assessment by a trained physician's assistant, registered nurse, nurse practitioner, and/or physician of the study team who is blinded to the testing material. The supervising investigator will also be blinded to testing material.

Reactions will be scored using the Consortium of Food Allergy Research (CoFAR) grading system (see Appendix 2). The DBPCFC will be stopped when the blinded assessor finds symptoms and/or signs that indicate a definite objective allergic reaction (CoFAR grading system [see Appendix 2]) 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 physician. All food challenges will be performed under physician supervision. 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.

Treatment Period

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 (this interval was selected to ensure that accurate biomarker values at baseline are captured) and the dose will not be changes 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. Patient and/or caregiver will be trained on how to store, handle, prepare, and administer study drug at home Q2W. 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.

Double-Blind Placebo-Controlled Food Challenge

At week 24, under intensive monitoring, all patients will undergo a DBPCFC up to 2044 mg peanut protein (cumulative) or placebo (see Appendix 1) 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 (see Appendix 2). Up-dosing during the DBPCFC will be stopped when the blinded assessor finds symptoms and/or signs that indicate a definite objective allergic reaction (CoFAR grading system [see Appendix 2]) has occurred based on clinically significant changes in reported symptoms, physical findings, or vital signs that the patient is experiencing to the challenge material. Vital signs will be assessed 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 mg, and 1000 mg resulting in a total challenge of up to 2044 mg peanut protein (cumulative). Both peanut and oat protein will be concealed in a food that masks the taste. 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 grading system (see Appendix 2). If the patient experiences reactions, he/she will be treated with the necessary rescue medications. He/she will be observed for a minimum of 2 hours after the final administered dose and discharged only when deemed clinically stable by a study physician. Symptom severity will be adjudicated by an independent, blinded assessor who is not involved in patient study visit conduct (Bock, 1988; Sampson, 2006).

Study design safety considerations for DBPCFC are described in Section 3.3.2.

Post-Treatment Follow-up Period (12 weeks)

All patients will have a 12-week follow-up period after the end of treatment and will undergo safety, laboratory, and clinical assessments.

The duration of the 12-week follow-up period is based on the time expected for drug levels (to be below the lower limit of quantification) after the last dose of dupilumab. At the end of the 12-week follow-up period, 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), 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 sustained unresponsiveness.

6.1.1. End of Study Definition

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

6.1.2. Study Design Safety Considerations

The design considers important safety issues:

- All DBPCFC visits will be supervised in-clinic setting where trained study physicians are available
- Standing orders from a medical doctor are provided for all clinical study personnel to initiate treatment of reactions immediately (ie, prior to medical doctor notification), including IM administration of epinephrine, based on their own clinical judgment
- A crash cart with pediatric equipment will be available in close proximity (within 50 feet) of all patient clinic rooms
- A code team is available
- Dosing allergic symptoms and AEs will be captured throughout the study
- Patients will be prescribed an epinephrine auto-injector (if not prescribed by a treating clinician previous to study entry) and all patients/Caregivers will be trained in its use. Patients will be advised to carry the autoinjector with them at all times.
- Patients /caregivers will be cautioned against patients consuming any peanuts or peanut-containing foods other than the peanut allergen challenge while on study
- The dupilumab clinical development program in food allergy independent data monitoring committee (IDMC) will provide oversight of patient safety. The IDMC will provide Regeneron and Sanofi with appropriate recommendations on the conduct of the food allergy clinical studies to ensure the protection and safety of the patients enrolled in these studies.

6.1.3. Study Stopping Rules

6.1.3.1. Individual Patient Stopping Rules (both study drug and food challenge)

1. Missing ≥2 consecutive doses of study drug
2. Anaphylaxis resulting in severe hypotension (Appendix 3), neurological compromise or mechanical ventilation secondary to any food challenge (Simons, 2014).
3. Patient develops biopsy-documented eosinophilic esophagitis (EoE) or other eosinophilic gastrointestinal disease.
4. Any patient deemed to have severe allergic reactions and who receives aggressive therapy (eg, mechanical ventilation, 3 or more repeated doses of epinephrine for a life-threatening reaction) at any time will be discontinued from further therapy.
5. Other circumstances including, but not limited to, the following:
    - Poor control or persistent severe activation of secondary atopic disease (eg, AD, asthma)
    - Started on beta-blockers with no alternative medications available per the prescribing physician
    - Pregnancy

6.1.3.2. Anaphylaxis

The definition of anaphylaxis that has been adopted for this study is from the 2014 position paper by the European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy and Anaphylaxis Guidelines Group (Muraro, 2007), that in turn was based on the publications of Simons (Simons, 2011) and Johansson (Johansson, 2004), and is consistent with the recently published "International consensus on (ICON) anaphylaxis" (Simons, 2014). Accordingly, 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.

When the diagnosis of anaphylaxis is made, the basis for having suspected the diagnosis must be documented, using the criteria established by the Second Symposium on the Definition and Management of Anaphylaxis (Sampson, 2006). Reports of anaphylaxis will be collected in the electronic data capture (EDC). Reports of non-fatal and non-life-threatening anaphylaxis that do not require hospitalization (admitted for over 24 hours) will not require expedited safety reporting, as these are clinically anticipated events in the target population. All reports of anaphylaxis will be periodically reviewed to ensure proper patient care and prompt identification of any clinically concerning safety issues.

6.2. Planned Interim Analysis

No formal interim analysis is planned for this study.

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 as specified in the protocol (week 24 visit or earlier for those patients who are withdrawn prematurely from the study). If performed, this primary analysis will be considered the final analysis for the primary endpoint and secondary efficacy endpoints up to week 24. A description of the statistical methods to be employed is in Section 11.4.

6.3. Study Committees

6.3.1. Independent Data Monitoring Committee

The dupilumab clinical development program in food allergy IDMC, composed of members who are independent from the sponsor and the study investigators, will provide oversight of patient safety by conducting formal reviews of accumulated safety data. The IDMC will provide Regeneron and Sanofi with appropriate recommendations on the conduct of the food allergy clinical studies to ensure the protection and safety of the patients enrolled in these studies.

All activities and responsibilities of the IDMC are described in the IDMC charter.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Approximately 24 patients with a history of confirmed peanut allergy will be enrolled at approximately 10 sites in the US and Canada (CAN).

7.2. Study Population

Male and female pediatric patients ages 6 to 17 years inclusive with a history of peanut allergy confirmed by peanut SPT, sIgE, and by the amount of peanut protein (mg) safely ingested during a peanut DBPCFC.

7.2.1. Inclusion Criteria

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

1. Age 6 to 17 years (inclusive).
2. Patient has a clinical history of allergy to peanuts or peanut-containing foods (symptom[s] of reaction due to exposure).
3. Experience dose-limiting symptoms at or before the 100 mg challenge dose (≤144 mg cumulative) of peanut protein (measured as 200 mg of peanut flour) on screening DBPCFC conducted in accordance with PRACTALL (Practical Issues in Allergology, Joint United States/European Union Initiative) guidelines. And not experiencing dose limiting symptoms to placebo
4. Serum IgE to peanut of ≥10 kUA/L and/or a SPT to peanut ≥8 mm compared to a negative control.

5. Patients/legal guardians must be trained on the proper use of the epinephrine autoinjector device to be allowed to enroll in the study.

6. Patients with other known food allergies must agree to eliminate these other food items from their diet so as not to confound the safety and efficacy data from the study.

7. Written informed consent from parent/guardian.

8. Written assent from minor patients as appropriate (eg, above the age of 6 years or the applicable age per local regulatory requirements).

9. Willing and able to comply with all clinic visits and study-related procedures.

7.2.2. Exclusion Criteria

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

1. Any previous exposure to marketed dupilumab or dupilumab in a clinical trial
2. Member of the clinical site study team or his/her immediate family
3. History of other chronic disease (other than asthma, AD, or allergic rhinitis) requiring therapy (eg, heart disease, diabetes, hypertension) that, in the opinion of the Principal Investigator, would represent a risk to the patient's health or safety in this study or the patient's ability to comply with the study protocol
4. History of frequent or recent severe, life-threatening episode of anaphylaxis or anaphylactic shock as defined by more than 3 episodes of anaphylaxis within the past year and/or an episode of anaphylaxis within 60 days of screening DBPCFC
5. History of eosinophilic gastrointestinal disease
6. History of eosinophilic granulomatosis with polyangiitis
7. Current participation or participation within 6 months prior to screening in any other interventional study.
8. Severe, unstable asthma at time of enrollment or any patient with FEV1 <80% of predicted or ACQ >1.5.
9. Use of systemic corticosteroids within 2 months prior to screening
10. Use of omalizumab, benralizumab, or mepolizumab within 6 months prior to screening.
11. Use of other forms of allergen immunotherapy (eg, oral, SC, patch or sublingual) or immunomodulatory therapy (not including corticosteroids) within 3 months prior to screening.
12. Use of antihistamines within 5 days prior to screening and within 5 days prior to SPTs and day 1 of DBPCFCs.
13. Use of any agents known or likely to interact with epinephrine (eg, beta blockers, ACE-inhibitors, tri-cyclic antidepressants, or other drugs), within 3 weeks prior to screening.
14. Allergy to oat (placebo in DBPCFC).
15. Hypersensitivity to epinephrine and any of the excipients in the epinephrine product.

16. History of a mast cell disorder, including mastocytosis, urticarial pigmentosa, and hereditary or idiopathic angioedema.
17. Treatment with a live (attenuated) vaccine within 3 months before the baseline visit and during the study
18. Active chronic or acute infection requiring systemic treatment with antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks prior to the baseline visit. NOTE: patients may be rescreened after the infection resolves.
19. History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.
20. Established diagnosis of a primary immunodeficiency disorder (eg, Severe Combined Immunodeficiency, Wiskott Aldrich Syndrome, DiGeorge Syndrome, X-linked Agammaglobulinemia, Common Variable Immunodeficiency), or secondary immunodeficiency.
21. Known history of human immunodeficiency virus (HIV) infection or HIV seropositivity at the screening visit.
22. With an established diagnosis of hepatitis B viral infection at the time of screening or is positive for hepatitis surface antigen (HBsAg) or hepatitis core antibody (HBcAb) at the time of screening
23. Body weight <20 kg
24. Pregnant or breastfeeding women, women planning to become pregnant or breastfeed during the study.
25. Girls at or beyond menarche who are not sexually abstinent and are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 12 weeks after the last dose. Highly effective contraceptive measures include stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence.

†Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

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

7.3. Premature Withdrawal from the Study

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

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

Patients who are withdrawn prematurely from the study will be asked to complete study assessments, as described in Section 9.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.3.2.

7.4. Replacement of Patients

Patients prematurely discontinued from study will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

Dupilumab 175 mg/mL (200mg dose): Each single-use, prefilled syringe delivers 200 mg of study drug (1.14 mL of a 175 mg/mL solution, expellable in 1mL syringe).

Dupilumab 150 mg/mL (300mg dose): Each single-use, prefilled syringe delivers 300 mg of study drug (2.0 mL of a 150 mg/mL solution, expellable in 2.25mL syringe).

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

Instructions on dose preparation are provided in the pharmacy manual.

8.1.1. Peanut for Double-Blind Placebo-Controlled Food Challenge

For the DBPCFC, peanut flour or placebo food challenge mixture will be administered in a food vehicle. Investigational sites will be provided with standardized recipes for preparation of the DBPCFC in a separate manual of procedures.

8.2. Rescue Treatments

If required, patients who experience allergic reactions will be treated with IM or SC administration of epinephrine at the discretion of the clinical study personnel based on their own clinical judgement. The clinical site will also collect rescue medications taken at home in the event of accidental exposure to peanut. For more details, see Section 6.1.2.

8.3. Dose Modification and Study Treatment Discontinuation Rules

8.3.1. Dose Modification

Dose modification for an individual patient is not allowed.

8.3.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug and who do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.2.

8.3.2.1. Reasons for Permanent Discontinuation of Dupilumab and Food Challenge

Study drug dosing will be permanently stopped in the event of:

- Anaphylactic reaction or other severe systemic reaction to dupilumab
- Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immuno-compromised status
- Severe laboratory abnormalities that are deemed to be related to dupilumab:
  - Neutrophil count $\leq 0.5 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$
  - ALT and/or AST values greater than 3 × ULN with total bilirubin >2 × ULN (unless elevated bilirubin is related to confirmed Gilbert's Syndrome)
  - Confirmed AST and/or ALT >5 × ULN (for more than 2 weeks)
- Diagnosis of a malignancy during the study
- Evidence of pregnancy
- Treatment with any prohibited concomitant medication or procedure
- Missing ≥2 consecutive doses of study drug (dupilumab)

8.3.2.2. Reasons for Temporary Discontinuation of Dupilumab

Study drug dosing will be temporarily discontinued in the event of:

- Clinically important laboratory abnormalities such as:
  - ALT or AST 3 × ULN but ≤5 × ULN
  - CPK >2.5 x ULN
  - Serum creatinine >1.5 x ULN

- Severe laboratory abnormalities (as noted in Section 8.3.2.1) where a causal relationship to dupilumab can be reasonably excluded (ie, an alternative cause is evident). In these cases, study treatment will be discontinued while the clinical circumstances are being assessed but it may be resumed when the laboratory parameters normalize sufficiently. A decision to resume treatment will be made jointly by the investigator and medical monitor.
- Other intercurrent illnesses or major surgery
- An infection that requires parenteral treatment with antibiotic, antifungal, antiviral, antiparasitic, or antiprotozoal agents, or requires oral treatment with such agents for longer than 2 weeks.

After the condition leading to suspension of dosing normalizes sufficiently, study treatment may resume at the discretion of the principal investigator in consultation with the medical monitor. A decision to discontinue study drug and/or to reinstitute study treatment should be discussed with the medical monitor. Note that dosing may NOT be resumed if patient met conditions for permanently discontinuing study drug described in Section 7.3 . The investigator may suspend study treatment at any time, even without consultation with the medical monitor, if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation. Resumption of study treatment after temporary discontinuation should always be discussed with the medical monitor.

8.4. Management of Acute Reactions

8.4.1. Acute Injection Reactions

8.4.1.1. Systemic Injection Reactions

Acute systemic reactions following injection of study drug (SC) should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

8.4.1.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to the Food and Drug Administration (FDA) September 2007 Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (provided in the study Regulatory Binder, also see Section 10.5.1).

8.5. Method of Treatment Assignment

Approximately 24 patients will be enrolled using an interactive web response system (IWRS).

8.5.1. Blinding

This is an open-label study.

For the DBPCFC, an unblinded pharmacist or designee will mix the peanut protein or oat protein in a chocolate food matrix that masks taste for administration in the DBPCFC. For each patient, a "blinded" evaluating physician (Blinded Assessor) is to be designated to assess the tolerability of the challenge doses presented in the DBPCFC. The blinded evaluating physician is not to be involved directly in the oversight of study product dosing or the assessment or management of AEs (for details refer to the Masking Plan). To the extent practicable, the same blinded evaluating physician who determines dose limiting symptoms (DLS) in the screening DBPCFC should determine DLS in the week 24 and 36 DBPCFCs.

8.6. Treatment Logistics and Accountability

8.6.1. Packaging, Labeling, and Storage

Study drug for injection will be provided as open-label kits. Each carton box will contain 1 labeled prefilled syringe. The carton box and prefilled syringe label will indicate the protocol number, product identity and strength, medication/reference number, batch number, directions for use, route of administration, expiry date, sponsor information, and storage conditions, and will correspond to all regulatory requirements.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

8.6.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed on site after approval from sponsor or designee, or returned to a destruction depot after accountability and reconciliation.

8.6.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

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

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

8.6.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

8.7. Concomitant Medications and Procedures

Any treatment administered from the time of the first dose of study drug to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

The use of prohibited medications should only be considered when necessary for the patient's care and well-being and when there are no other options. Their use results in permanent treatment discontinuation but not discontinuation from study.

8.7.1. Prohibited Medications and Procedures

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

- Treatment with a live (attenuated) vaccine; below is a list of examples of such vaccines. Refer to study manual for a current, comprehensive list of prohibited vaccines

Chickenpox (Varicella)	Oral typhoid
FluMist-Influenza	Rubella
Intranasal influenza	Smallpox (Vaccinia)
Measles (Rubeola)	Yellow fever
Measles-mumps-rubella combination	Bacillus Calmette-Guerin
Measles-mumps-rubella-varicella combination	Rotavirus
Mumps	Varicella Zoster (shingles)
Oral polio (Sabin)	

- Treatment with an investigational drug (other than dupilumab)
- Treatment with immunomodulating 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
- Treatment with any agents known or likely to interact with epinephrine (eg, 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

8.7.2. Permitted Medications

Other than the prohibited medications listed in Section 8.7.1, treatment with concomitant medications is permitted during the study.

Medications used to treat chronic disease other than those listed in Section 8.7.1 are also permitted. Patients/parents/caregivers should be advised not to reduce or stop taking medications for concomitant conditions throughout the entire study period. If there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the medical monitor.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1.

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		
Safety:																			
Weight[5]	X		X		X		X		X		X		X		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		
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
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]:																			

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		
Buccal swab samples for DNA			X																

WOCBP = women of childbearing potential

9.1.1. 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).

9.1.2. Early Termination Visit

Patients who are withdrawn from the study before the primary endpoint visit (week 24) will be asked to return to the clinic for study assessments described in Table 1. Patients who are withdrawn from the study after the primary endpoint visit will be asked to return to the clinic for early termination assessments only.

9.1.3. Unscheduled Visits

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

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population: peanut SPT, HIV Ab, HBsAg, HBcAb, Hep C Ab, height. Demographics and medical history will be collected.

9.2.2. Efficacy Procedures

9.2.2.1. Double-Blind Placebo-Controlled Food Challenge

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 (see Appendix 2). Up-dosing during the DBPCFC will be stopped when the blinded assessor finds symptoms and/or signs that indicate a definite objective allergic reaction (CoFAR grading system (see Appendix 2) 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 challenge will consist of 8 doses (peanut or placebo), given every 15 to 30 minutes: 1, 3, 10, 30, 100, 300, 600, 1000 mg, up to 2044 mg peanut protein (cumulative). Both peanut and oat protein will be concealed in a food that masks the taste. 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. After the last dose of the DBPCFC, the patient will be monitored for at least 2 hours and then discharged from the clinic. Patients will be considered to have passed the DBPCFC if they do not experience any objective Grade 1 reaction by the CoFAR grading system (see Appendix 2). If the patient experiences reactions, they will be treated with the necessary rescue medications. Symptom severity will be adjudicated by an independent, blinded assessor who is not involved in performing the baseline food challenge.

9.2.2.2. Peanut Skin Prick Test

The standard SPT is performed on the volar surface of the patient's forearm using standard whole peanut extract, 1:10 w/v (ALK-Abello) and will only be performed at screening. A positive result is ≥3 mm determined by averaging maximal perpendicular wheal diameters 15 minutes after applying the lancet. The positive control is histamine base, 6 mg/mL (ALK-Abello) and with a wheal ≥3 mm indicating a valid test. The negative control is glycerol saline.

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 test will be performed at time points shown in Table 1. The SPTs will be performed starting at the following dilutions: neat, 1:20, 1:200, 1:2000, 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.

9.2.2.3. 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 emotional 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 the 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 accordance with Table 1. Patients will continue using the FAQLQ version first administered at baseline regardless of moving to the next age bracket.

9.2.3. Safety Procedures

9.2.3.1. Vital Signs

Vital signs, including temperature, sitting blood pressure, pulse, and respiration will be collected at time points according to Table 1. 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.

9.2.3.2. Physical Examination

A thorough and complete physical examination will be performed at time points according to Table 1. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

9.2.3.3. Spirometry

A spirometer that meets the American Thoracic Society (ATS) / 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. The same spirometer and standard spirometric techniques, including calibration, should be used to perform spirometry at different visits and, whenever possible, the same person should perform the measurements. FeNO should be done prior to spirometry.

9.2.3.4. Laboratory Testing

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

Samples for laboratory testing will be collected at visits according to Table 1. 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 child-bearing 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.

Abnormal Laboratory Values and Laboratory Adverse Events

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

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

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

Criteria for reporting laboratory values as an AE are provided in Section 10.4.5.

9.2.4. Drug Concentration and Measurements

Samples for drug concentration will be collected at time points listed in Table 1.

Any unused samples may be used for exploratory biomarker research.

9.2.5. Immunogenicity Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Table 1.

Detailed instructions for blood sample collection are included in the laboratory manual provided to study sites. Any unused samples may be used for exploratory research.

9.2.6. Pharmacodynamic and Exploratory Biomarker Procedures

Biomarker samples will be collected at time points according to Table 1. Biomarker measurements will be performed to determine effects on relevant physiological and pathogenic processes.

The biomarkers studied will be ones believed to be relevant to the pathophysiology of peanut allergy, immunology, mechanism of action of dupilumab and possible toxicities. Biomarkers studied may include but need not be limited to: Total IgE, TARC, sIgE, sIgG4, sIgG, TruCulture study of ex vivo peanut stimulation of whole blood (supernatant cytokine and chemokine profiling, mRNA analyses [including transcriptome sequencing] of the resulting cell pellet), and basophil allergen sensitivity to allergen stimulation and peanut-specific T-cell and Th2A subset profiling. Additional serum and plasma samples will be banked for research. Any unused samples collected for PK, ADA, and biomarkers may also be used for exploratory research.

Exploratory biomarker results not required for protocol-defined endpoint analyses will not be included in the clinical study report.

9.2.6.1. Serum Thymus and Activation-Regulated Chemokine and Total IgE

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

9.2.6.2. Serum Peanut-Specific Antibody Assays (Peanut-specific IgE, IgG, IgG4)

In prior dupilumab studies, dupilumab suppressed both total and allergen-specific IgEs. In general, dupilumab suppresses total IgE by ~ 50% within 12 to 16 weeks of treatment initiation.

9.2.6.3. Fractional Exhaled Nitric Oxide

Fractional exhaled nitric oxide (FeNO) is a non-invasive marker that has been shown to correlate with allergic airway inflammation and IgE sensitization. The measurement of FeNO was reported to be predictive of peanut oral food challenge outcome (Preece, 2014). Although no manufacturer has validated the FeNO device for children under 7 years old due to inadequate exhalation force, there are no contraindications with the use of FeNO for 6-year-old children. Also, specific guidance and reference ranges are available for collection in children as young as 6 years of age (Brody, 2013) (Menou, 2017). As FeNO is an exploratory biomarker, it will be collected for children 6 years old unless the investigator declines to collect. Fractional exhaled nitric oxide will be performed prior to spirometry.

9.2.7. Exploratory Research

Research samples (whole blood/PBMCs) will be banked, unless there are local regulatory or IRB restrictions at the study site, for exploratory research related to immunology of peanut allergy, other allergic diseases, IL-4/IL-13-mediated Type 2 inflammation, and dupilumab (including mechanism of action, efficacy, toxicity). Research may also include, T-cell and B-cell receptor repertoire analyses, which requires RNA sequencing). The list may be altered or expanded as it is recognized that more relevant or novel biomarkers may be discovered during the course of this study. Banked research samples (serum/plasma/PBMCs), as well as any unused samples for study-related research (including PK and ADA samples), will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for the scope of research described above. After 15 years, any residual samples will be destroyed. Results of these exploratory analyses will not be reported in the CSR.

9.2.7.1. Genomics Analysis

DNA samples will be collected for the genomics analyses unless there are local regulatory or IRB restrictions at the study site. Samples will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response, other clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of peanut allergy, as well as related diseases may also be studied. Samples may also be used as controls in genetic research unrelated to the scientific purposes stated above. Patient's genetic data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug and related diseases. Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, and transcriptome sequencing (eg, TruCulture cell pellet) may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analysis will not be reported in the CSR.

10. SAFETY DEFINITIONS, REPORTING, AND MONITORING

10.1. Obligations of Investigator

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

10.2. Obligations of Sponsor

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

Any AE not listed as an expected event in the Reference Safety Information section of the Investigator's Brochure will be considered as unexpected. Any worsening of or new onset of symptoms related to (add underlying condition intended to be studied) which occur during the screening/washout period prior to study drug administration will be considered expected.

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

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

10.3. Definitions

10.3.1. Adverse Event

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

10.3.2. Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.

- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or that is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

10.3.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (Section 10.4.3).

10.4. Recording and Reporting Adverse Events

10.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of study. However, allergic reactions to the DBPCFC during the screening phase, at endpoint challenges (at week 24 and 36) will be recorded as allergic signs and symptoms since they are anticipated to allergen. Refer to the study reference manual for the procedures to be followed.

Information on follow-up for AEs is provided in Section 10.4.6. Laboratory, vital signs abnormalities are to be recorded as AEs as outlined in Section 10.4.5.

10.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours. Refer to the study reference manual for the procedure to be followed.

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

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

- SAE with an onset within 30 days of the end of study or within 12 weeks of last study drug administration if the patient early terminated from the study - the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of study/early termination visit - only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

10.4.3. Other Events that Require Accelerated Reporting to Sponsor

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

Symptomatic Overdose of Study Drug: Dupilumab is administered every 14±3 days Q2W. The doses of this investigational product must be separated by ≥11 days to avoid overdose. Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

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

Adverse Events of Special Interest: All AESI, serious and nonserious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 10.4.2. Adverse events of special interest 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)

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

10.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

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

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

10.4.5. Abnormal Laboratory, Vital Signs Results

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

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

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

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

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 10.5.1.

10.4.6. Follow-up

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

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

10.5. Evaluation of Severity and Causality

10.5.1. Evaluation of Severity

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

Mild: Does not interfere in a significant manner with the patient normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

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

Injection Site Reactions

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

Mild: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity

Moderate: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity

Severe: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires ER visit or hospitalization; necrosis or exfoliative dermatitis

10.5.2. Evaluation of Causality

Relationship of Adverse Events to Dupilumab:

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

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

The possible answers are:

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

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

The investigator should justify the causality assessment of each SAE.

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

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

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- do not reappear or worsen when dosing with study drug is resumed
- are not a suspected response to the study drug based upon preclinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition

- follow a reasonable temporal sequence following the time of administration of the dose of study drug
- resolve or improve after discontinuation of study drug
- reappear or worsen when dosing with study drug
- are known or suspected to be a response to the study drug based upon preclinical data or prior clinical data

10.6. Safety Monitoring

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

10.7. Investigator Alert Notification

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

11. STATISTICAL PLAN

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

Analysis variables are listed in Section 5.

11.1. 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 at least 444 mg peanut protein during a DBPCFC at week 24 for dupilumab. The following hypothesis for the superiority testing will be tested at the 2-sided 5% significance level:

Null hypothesis H0: $\mu_D = 8\%$, ie, the proportion of patients who achieve a cumulative dose of at least 444 mg peanut protein during a DBPCFC at week 24 is 8%.

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

11.2. Justification of Sample Size

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

A sample size of 20 patients will have 80% power to detect the 29% tolerated rate in dupilumab group 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.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all enrolled patients. The week 36 FAS includes patients who pass a DBPCFC of at least 444 mg (cumulative) of peanut protein at week 24.

11.3.2. Safety Analysis Set

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

11.3.3. Pharmacokinetic Analysis Sets

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

11.3.4. Immunogenicity Analysis Sets

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 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).

11.4. Statistical Methods

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

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

All dupilumab patients, regardless of whether it is 200 mg dupilumab or 300 mg dupilumab, will be combined for analysis.

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the informed consent form (ICF)
- The total number of enrolled patients
- The total number of patients in each analysis set (eg, FAS, provided in Section 11.3 for analysis sets)
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively.

11.4.3. Efficacy Analyses

Efficacy analyses will be conducted using the FAS population and week 36 FAS population. The FAS will be used for efficacy analysis at week 24, and week 36 FAS will be used for efficacy analysis at week 36.

11.4.3.1. Primary Efficacy Analysis

The FAS will be used for the primary efficacy endpoint. The primary endpoint will be analyzed using one-sample Chi-square test. Estimate of proportion, p-value, and the 2-sided 95% confidence interval will be provided.

If a patient does not have available DBPCFC data at week 24, the patient will be considered as a non-responder regardless of reasons for missing data.

Sensitivity analyses of the primary endpoint will include an analysis of the subset of patients with available week 24 DBPCFC. Other sensitivity analyses may be proposed in the SAP.

Subgroup analysis (eg, by baseline weight group) will be performed.

11.4.3.2. Secondary Efficacy Analysis

All secondary endpoints (Section 4.1.2) will be analyzed descriptively at given visits. FAS will be used for efficacy analysis at week 24, and week 36 FAS will be used for efficacy analysis at week 36.

All secondary endpoints will be analyzed descriptively at given visits. FAS will be used for efficacy analysis at week 24, and week 36 FAS will be used for efficacy analysis at week 36. For binary endpoints, the analysis and imputation methods will be similar to the primary analysis.

A one-sample t-test will be performed to assess the change from baseline to week 24 in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC. Estimate of change from baseline to week 24, p-value, and the 2-sided 95% confidence interval will be provided. If the data is extremely skewed, nonparametric method may be applied. Details will be provided in the SAP. The missing data will be imputed by the last non-missing DBPCFC assessment including baseline.

For other continuous endpoints, the analysis and imputation methods will be applied similarly.

Sensitivity analysis will include an analysis based on the observed cases. Other sensitivity analysis may be proposed in the SAP.

11.4.3.3. Multiplicity Considerations

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

11.4.3.4. Timing of Analyses

A primary analysis may be performed when the last patient completes 24 weeks of the treatment period as specified in the protocol (week 24 visit or earlier for those patients who are withdrawn prematurely from the study). No changes in the conduct of the study will be made based on this primary analysis. The analyses of primary and secondary endpoints up to week 24 as specified in Section 11.4.3.1 and Section 11.4.3.2 will be the final analysis of the primary endpoint and the secondary endpoints up to week 24.

11.4.4. Safety Analysis

11.4.4.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-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

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

Analysis

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

Summaries of all TEAEs will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.5.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be listed and summarized.

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

11.4.4.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time as well as the vital signs according to Bock's scale during the challenge (Appendix 2) with descriptive statistics.

Laboratory Tests

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

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

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

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

11.4.4.3. Treatment Exposure

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

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

The number (%) of patients exposed to the study drug will be presented by specific time periods. The time periods of interest will be specified in the SAP.

In addition, duration of exposure during the study will be summarized using number of patients, means, standard deviation, minimums, Q1, medians, Q3, and maximums.

A summary of the number of doses will be provided.

11.4.4.4. Treatment Compliance

The compliance with study treatment will be calculated as follows:

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

The treatment compliance of study drug will be presented by specific ranges. The ranges of interest will be specified in the SAP.

11.4.5. Analysis of Drug Concentration Data

Descriptive statistics will be used to summarize the concentration data at each sampling time.

No formal statistical analysis will be performed.

11.4.6. Analysis of Immunogenicity Data

Analysis of ADA will be conducted on samples collected at baseline, week 12, week 24, and week 36. Samples that are positive in the ADA assay will be further characterized for ADA titers and for the presence of an NAb response.

Anti-drug antibody response categories and titer categories that will be assessed are as follows:

- Pre-existing immunoreactivity
- Treatment-emergent response

  The treatment-emergent responses will be further characterized as persistent, indeterminate, and transient.

- Treatment-boosted ADA response
- Titer value category (tier range)
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)
- NAb response in ADA positive patients.

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers and NAb positivity presented by patient, time point, and dose group cohort/group will be provided. Incidence of treatment-emergent ADA and NAb will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts dose group and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs and NAbs on individual PK profiles may be evaluated. Assessment of impact of ADA and NAbs on safety and efficacy may be provided.

11.4.7. Analysis of Pharmacodynamics Data

The exploratory biomarker data will be summarized by descriptive statistics.

11.5. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

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

General rules for handling missing data:

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

Visit windows:

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

Unscheduled assessments:

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

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 17.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

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

12.1. Data Management and Electronic Systems

12.1.1. Data Management

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

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

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

12.1.2. Electronic Systems

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

- IWRS system – study drug supply
- EDC system – data capture
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

13. STUDY MONITORING

13.1. Monitoring of Study Sites

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

The investigator must allow study-related monitoring.

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

13.2. Source Document Requirements

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

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

13.3. Case Report Form Requirements

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

14. AUDITS AND INSPECTIONS

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

Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection

Providing access to all necessary facilities, study data, and documents for the inspection or audit

Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately

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

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

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

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Good Clinical Practice Statement

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

15.2. Assent and Informed Consent

The principles of informed consent are described in ICH guidelines for Good Clinical Practice.

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

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient and his/her parent(s) or legal guardian(s) prior to the patient's participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the fullest possible extent in language that the patient and the parent(s) or legal guardian(s) can understand. The ICF should be signed and dated by the patient's parent(s) or legal guardian(s) and the same investigator or designee who explained the ICF.

Local law must be observed in deciding whether 1 or both parents/guardians consent is required. If only 1 parent or guardian signs the consent form, the investigator must document the reason the other parent or guardian did not sign. The patient may also be required to sign and date the ICF, as determined by the IRB/EC and in accordance with the local regulations and requirements.

- Patients who can write but cannot read will have the assent form read to them before writing their name on the form.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient's parent(s) or legal guardian(s).

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients and their parent(s) or legal guardian(s) must be informed of the new information and provide their written consent if they wish the patient to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient's parent(s) or legal guardian(s).

15.3. Patients Confidentiality and Data Protection

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

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

15.4. Institutional Review Board/Ethics Committee

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

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

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

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

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

15.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

16. PROTOCOL AMENDMENTS

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

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

17.1. Premature Termination of the Study

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

17.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

18. STUDY DOCUMENTATION

18.1. Certification of Accuracy of Data

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

18.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant

regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

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

19. DATA QUALITY ASSURANCE

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

Data Management

The sponsor is responsible for the data management of this study including quality checking of the data (Section 12.1.1).

Study Monitoring

The investigator must allow study-related monitoring, IRB/EC review, audits, and inspections from relevant health regulatory authorities, and provide direct access to source data documents (Section 13.1, Section 13.2, Section 14).

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements (Section 13.1).

All patient data collected during the study will be recorded on paper or electronic CRF unless the data are transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for affirming that data entries in the CRF are accurate and correct by electronically signing a declaration that accompanies each set of patient final CRF (Section 13.3 and Section 18.1).

Study Documentation

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF (Section 13.2).

The investigator will retain all records and documents, including signed ICFs, pertaining to the conduct of this study for at least 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor (Section 18.2).

20. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

21. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

22. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

23. REFERENCES

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24. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: "A Study to Evaluate the Efficacy and Safety of Dupilumab Monotherapy in Pediatric Patients with Peanut Allergy" and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

APPENDIX 1. PEANUT DBPCFC SCHEDULE OF DOSING PERFORMED AT SCREENING AND WEEKS 24 AND 36

	Challenge Doses			
	Amount of Peanut Protein at Each Challenge Dose (mg)	**Amount of Peanut Flour with 50% Protein Content (mg)**	**Cumulative Amount of Peanut Protein (mg) at Screening**	**Cumulative Amount of Peanut Protein (mg) on Study (Weeks 24 and 36)**
Screening	1	2	1	1
Screening	3	6	4	4
Screening	10	20	14	14
Screening	30	60	44	44
Screening	100	200	144	144
Endpoint	300	600	-	444
Endpoint	600	1200	-	1044
Endpoint	1000	2000		2044

Note: The DBPCFC is to be conducted as 2 challenges, each on a separate day using a placebo (artificially peanut-flavored oat protein) for one challenge and peanut (as defatted peanut protein) for the other. The oral food challenge is to be performed under double-blind conditions so that neither the patient, nor the patient's caregiver, nor any of the clinic staff (save for the unblinded preparer of the challenge foods) knows which challenge contains the peanut or the placebo. The clinic staff may not be unblinded as to the order of the 2 parts (peanut and placebo) of the DBPCFC until after completion of the observation period of the second part of the challenge for the screening challenge only. For weeks 24 and 36, the study team will remain blinded to the order of the exposure for each challenge date.

APPENDIX 2. ALLERGY REACTION SEVERITY GRADING

The Consortium of Food Allergy Research (CoFAR) grading system for allergic reactions

Grade 1 - Mild	Grade 2 - Moderate	Grade 3 – Severe	Grade 4 - Life Threatening	Grade 5 – Death
Transient or mild discomforts (< 48 hours), no or minimal medical intervention/therapy required. These symptoms may include pruritus, swelling or rash, abdominal discomfort or other transient symptoms.	Symptoms that produce mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy is required. Hospitalization is possible. These symptoms may include persistent hives, wheezing without dyspnea, abdominal discomfort/ increased vomiting or other symptoms	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible Symptoms may include Bronchospasm with dyspnea, severe abdominal pain, throat tightness with hoarseness, transient hypotension among others. Parenteral medication(s) are usually indicated.	Extreme limitation in activity, significant assistance required; significant medical/therapy. Intervention is required; hospitalization is probable. Symptoms may include persistent hypotension and/or hypoxia with resultant decreased level of consciousness associated with collapse and/or incontinence or other life-threatening symptoms.	Death

PRACTALL consensus report on DBPCFC, and with the CoFAR grading system for allergic reactions, are provided as a general guide.

Mild Symptoms:

- Skin – limited (few) or localized hives, swelling (eg, mild lip edema), skin flushing (eg, few areas of faint erythema) or pruritus (mild, eg, causing occasional scratching)
- Respiratory – rhinorrhea (eg, occasional sniffling or sneezing), nasal congestion, occasional cough, throat discomfort
- Gastrointestinal (GI) – mild abdominal discomfort (including mild nausea), minor vomiting (typically a single episode) and/or a single episode of diarrhea

Moderate Symptoms:

- Skin – systemic hives (eg, numerous or widespread hives), swelling (eg, significant lip or face edema), pruritus causing protracted scratching, more than a few areas of erythema or pronounced erythema
- Respiratory – throat tightness without hoarseness, persistent cough, wheezing without dyspnea
- GI – persistent moderate abdominal pain/cramping/nausea, more than a single episode of vomiting and/or diarrhea

Severe Symptoms:

- Skin – severe generalized urticaria/angioedema/erythema
- Respiratory – laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea, stridor
- GI – severe abdominal pain/cramping/repetitive vomiting and/or diarrhea
- Neurological – change in mental status
- Circulatory – clinically significant hypotension

APPENDIX 3. CRITERIA FOR SUSPECTED DIAGNOSIS AND SEVERITY GRADING OF ANAPHYLAXIS

Anaphylaxis is likely when any 1 of the 3 following sets of criteria is fulfilled:

1. Acute onset of an illness (minutes to hours) with involvement of:
   - Skin/mucosal tissue (eg, generalized hives, itch or flush, swollen lips/tongue/uvula) AND
   - Airway compromise (eg, dyspnea, stridor, wheeze/ bronchospasm, hypoxia, reduced PEF) AND/OR
   - Reduced BP or associated symptoms (eg, hypotonia, syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to the allergen (minutes to hours):
   - Skin/mucosal tissue (eg, generalized hives, itch/flush, swollen lips/tongue/uvula)
   - Airway compromise (eg, dyspnea, stridor wheeze/bronchospasm, hypoxia, reduced PEF)
   - Reduced BP or associated symptoms (eg, hypotonia, syncope, incontinence)
   - Persistent GI symptoms (eg, nausea, vomiting, crampy abdominal pain)
3. Reduced BP after exposure to the allergen (minutes to hours):
   - Infants and Children: low systolic BP (age-specific) or >30% drop in systolic BP*
   - Adults: systolic BP <90 mm Hg or >30% drop from their baseline

* Low systolic BP for children is defined as <70 mm Hg from 1 month to 1 year; less than (70 mm Hg + [2 x age]) from 1 to 10 years; and <90 mm Hg from age 11 to 17 years.

Note: Isolated skin or mucosal lesions following the ingestion of a food constitute a "food-induced allergic reaction".

Criteria for Severity Grading (Muraro 2007)

Staging System of Severity of Anaphylaxis	
Stage	**Defined By**
1. *Mild (skin & subcutaneous tissues, GI, &/or mild respiratory)*	Flushing, urticaria, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and/or emesis
2. *Moderate* (mild symptoms + features suggesting moderate respiratory, cardiovascular or GI symptoms)	Marked dysphagia, hoarseness and/or stridor; shortness of breath, wheezing & retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness
3. *Severe* (hypoxia, hypotension, or neurological compromise)	Cyanosis or SpO_2 ≤92% at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

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

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

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

Protocol Number: R668-ALG-1702

Protocol Version: R668-ALG-1702 Amendment 2

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

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Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00101740 v1.0

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