REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: 1.0

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study in Pediatric Subjects with Peanut Allergy to Evaluate the Efficacy and Safety of Dupilumab as Adjunct to AR101 (Peanut Oral Immunotherapy)

Compound: Dupilumab (REGN668)

Protocol Number: R668-ALG-16114 Amendment 4

Clinical Phase: Phase 2

Sponsor: Regeneron Pharmaceuticals, Inc.

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Version/Date: Original Statistical Analysis Plan / MM DD, YR

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACQ	Asthma Control Questionnaire
ADA	Anti-Drug Antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT (SGOT)	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST (SGPT)	Aspartate aminotransferase
BUN	Blood urea nitrogen
CoFAR	Consortium, of Food Allergy Research
CRF	Case report form
DBPCFC	Double-blind, placebo-controlled food challenge
EASI	Eczema Area and Severity Index
EOS	End of study
EOT	End of treatment
ET	Early termination
FAQLQ	Food Allergy Quality of Life Questionnaire
FAS	Full analysis set
mFAS	Modified Full Analysis Set
HIV	Human Immunodeficiency Virus
HLT	High Level Term
ICF	Informed consent form
ICH	International conference on harmonization
IDED	initial dose escalation day
IL	Interleukin
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
NAb	Neutralizing Antibody
OIT	Oral immunotherapy
PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PK	Pharmacokinetic

PKAS	Pharmacokinetic analysis set
PT	Preferred term
Q2W	Once 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 software
sIgE	Specific immunoglobulin E
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SOC	System organ class
SPT	Skin prick test
TEAE	Treatment emergent adverse event
Th2	Type-2 T helper cells
WBC	White blood cell
WHODD	World health organization drug dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for R668-ALG-16114 study. For subjects impacted by the COVID-19 pandemic, the up-dosing period for AR101 protein is permitted to be extended an additional 12 weeks such that visit 16 may be extended from week 28 to up to week 40. The dosing of study drug is extended as well.

This SAP will describe the descriptive and inferential statistical analysis for 28 to 40 weeks AR101 pre-dosing and up-dosing periods. The SAP will also describe the descriptive summary of 24 weeks AR101 maintenance period and 12-week safety follow-up period. The statistical inference may be performed for AR101 maintenance period, if needed.

1.1. Background/Rationale

Food allergy is a potentially life-threatening condition that affects up to 8% of young children and 3% to 5% of the entire United States (US) population (Gupta, 2011) (Sicherer, 2010). 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 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 due to the incomplete response to OIT. The aim of oral immunotherapy (OIT) is to induce desensitization and increase the threshold for peanut ingestion and reduce the risks of allergic reactions after accidental ingestion. However, many subjects in OIT trials continue to have side effects that can hinder their compliance and the overall efficacy of OIT. It is known that allergic response to food is an IgE-mediated event; however, recent data suggest that IL-4 and IL-13 may also play a significant role in food allergy pathogenesis. For instance, IL4 andIL13 signaling is involved in the increased production of allergen specific IgE and activation of effector cells such as basophils and mast cells. This clinical study proposes to examine the effect of dupilumab, a monoclonal antibody, which blocks the action of these cytokines, to enhance the safety, tolerability, and efficacy of AR101 (investigational oral biologic drug) in subjects with significant allergy to peanuts.

Peanut allergy is an immunoglobulin E (IgE)- mediated hypersensitivity reaction following the ingestion of normally innocuous peanut protein. 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 Type 2 T-helper cell (Th2) cytokine release, which results in eosinophil infiltration and creates a vicious cycle of chronic allergic inflammation. Like other forms of allergy immunotherapy, OIT to peanut involves a slow up-dosing of exposure to allergen, in this case peanut, over time to desensitize or increase the threshold of reactivity to peanut. Once reaching a target level of peanut protein, subjects are continued on a maintenance dose of peanut protein to maintain desensitization. Although many subjects on a maintenance dose of peanut

protein have demonstrated desensitization to peanut (i.e., the ability to tolerate a level of exposure to peanut without an allergic reaction), up to 80% of subjects exhibit related adverse events (AEs) during OIT, with 42% experiencing systemic reactions and 49% experiencing gastrointestinal (GI) symptoms; the majority of these are mild and decline with prolonged treatment (Virkud, 2016). Up to 20% of subjects, however, are unable to complete the up-dosing regimen due to side effects, which are primarily GI related. An additional issue with current OIT is its limited ability to induce clinical tolerance when subjects are taken off daily peanut intake (Vickery, 2014). In many of the studies with peanut OIT, despite years of immunotherapy, subjects never achieve tolerance and are re-sensitized within weeks of halting daily peanut intake, with a small percentage (~10%) maintaining a sustained unresponsiveness even after 3 months off OIT.

Dupilumab, a fully human monoclonal antibody directed against IL-4 receptor alpha (IL-4Rα), blocks the activity of IL-4 and IL-13. These 2 cytokines are critical to the induction and perpetuation of the Type 2 response and have been implicated in multiple atopic diseases. This clinical study proposes to examine the effect of dupilumab, a monoclonal antibody, which blocks the action of these cytokines, to enhance the safety, tolerability, and efficacy of AR101 in subjects with significant allergy to peanuts.

This study will explore whether dupilumab has the ability to enhance immunomodulatory effects of OIT by decreasing Type 2 responses, decreasing production of peanut-specific IgE, which will result in improved safety and tolerability of OIT up-dosing as well as improved efficacy as determined by the ability to tolerate a higher cumulative dose of peanut protein during a double blind, placebo-controlled food challenge (DBPCFC) after 28 weeks of dupilumab therapy compared to placebo. The inhibition of IL-4/IL-13 signaling may reduce immune cell activation (e.g. eosinophils, Th2 cells). In addition, by blocking IL-4R and B-cell class switching to IgE, the decreased production of serum sIgE may reduce the IgE receptor on basophil and mast cell surface over time, thereby preventing the IgE mediated effector cell activation. In addition, the study will evaluate whether dupilumab influences known biomarkers important in the allergic response such as a reduction in allergen-specific immunoglobulin class switching to IgE, decrease in basophil activation, and decreased Th2 cell activities and the associated cytokine/chemokine levels. A maintenance phase where subjects previously treated with dupilumab in the treatment period are randomized to continue to receive dupilumab (indefinite [continuously]) with OIT or are re-randomized to placebo (limited [previously]) with OIT has been included.

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

1.2. Study Objectives

1.2.1. Primary Objective

To assess whether dupilumab as adjunct to AR101 compared to placebo as adjunct to AR101 improves desensitization at the completion of the up-dosing period, defined as an increase in the proportion of subjects who pass a post up-dosing DBPCFC at visit 16

1.2.2. Secondary Objectives

- To assess whether dupilumab as adjunct to AR101 compared to placebo as adjunct to AR101 improves desensitization at the completion of up-dosing, defined as an increase in the cumulative tolerated dose (log transformed) of peanut protein during a post up-dosing DBPCFC at visit 16
- To assess whether dupilumab as (indefinite [continuously]) adjunct to AR101 compared to placebo maintains desensitization, defined as an increase in the proportion of subjects who pass a post maintenance DBPCFC at visit 22
- To assess whether dupilumab as (limited [previously]) adjunct to AR101 compared to placebo maintains desensitization, defined as an increase in the proportion of subjects who pass a post maintenance DBPCFC at visit 22
- To evaluate the safety and tolerability of dupilumab as adjunct to AR101 compared to placebo
- To assess the effect of dupilumab (compared to placebo) as adjunct to AR101 on the change in peanut-specific IgE, IgG, IgG4, peanut-specific IgG4/IgE ratio, and peanut-specific IgG/IgE ratio

1.2.3. Modifications from the Statistical Section in the Final Protocol

Modifications from protocol amendment 4

- Added that the data will be summarized by treatment groups during pre-dosing period of AR101 (4 weeks) separately.
- Revised the secondary objective “To assess the effect of dupilumab (compared to placebo) as adjunct to AR101 on the change in peanut-specific IgE, IgG, IgG4, and peanut-specific IgG4/IgE ratio ” as “To assess the effect of dupilumab (compared to placebo) as adjunct to AR101 on the change in peanut-specific IgE, IgG, IgG4, peanut-specific IgG4/IgE ratio and peanut-specific IgG/IgE ratio”.
- Removed the last secondary objective “To assess if dupilumab increases the tolerability of AR101 as measured by the daily symptoms (e-diary) during the up-dosing phase” and corresponding secondary endpoints “Proportion of subjects experiencing allergic symptoms by treatment group during the up-dosing phase, mean severity score for each symptom by treatment during up-dosing phase, maximum severity score for each symptom by treatment during up-dosing phase, and difference in mean/median duration of symptoms by treatment group during up-dosing phase (all endpoints measured by the daily symptom e-diary)” due to the low compliance of the allergy symptoms entry in eDiary. Instead, the following exploratory endpoints are added:
  - Proportion of days with one or more of any peanut allergy symptoms excluding food challenge test days during the updosing period up to visit 16
  - Proportion of days with one or more severe form of any peanut allergy symptoms (i.e. severity score of 7 or more) excluding food challenge test days during the updosing period up to visit 16

  - Proportion of days with one or more symptoms for each symptom category excluding food challenge test days during the updosing period up to visit 16

- The following exploratory endpoints are added as well:
  - Change in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from visit 22 to visit 25
  - Proportion of subjects who "pass" a DBPCFC with 2044 mg (cumulative) peanut protein at visit 25
  - Change from baseline in total FAQLQ score at visit 16, visit 22 and visit 25 for different types of FAQLQ form
  - Proportion of subjects experiencing none, mild, moderate, severe or higher allergic symptoms by treatment group during DBPCFCs of peanut protein at visit 16, visit 22, and visit 25
  - Change and percent change from baseline to visit 16, visit 22 and visit 25 in peanut-specific IgG
  - Change and percent change from baseline to visit 16, visit 22, and visit 25 in peanut-specific IgG4
  - Change and percent change from baseline to visit 16, visit 22, and visit 25 in total IgE
  - Change from baseline to visit 16, visit 22, and visit 25 in log- transformed peanut-specific IgG4/ peanut-specific IgE ratio
  - Change from baseline to visit 16, visit 22, and visit 25 in log- transformed peanut-specific IgG/ peanut-specific IgE ratio
  - Change from baseline to visit 16, visit 22 and visit 25 in peanut-specific IgE
  - Change from baseline to visit 16, visit 22 and visit 25 in log- transformed peanut-specific IgE/total IgE ratio
  - Change and percent change from baseline to visit 16, visit 22 and visit 25 in Ara h1 sIgE, Ara h1 sIgG4, Ara h2 sIgE, Ara h2 sIgG4, Ara h3 sIgE, Ara h3 sIgG4
  - Change from baseline to visit 16, visit 22 and visit 25 in log- transformed Ara h1-specific IgG4/ Ara h1-specific IgE ratio
  - Change from baseline to visit 16, visit 22 and visit 25 in log- transformed Ara h2-specific IgG4/ Ara h2-specific IgE ratio
  - Change from baseline to visit 16, visit 22 and visit 25 in log- transformed Ara h3-specific IgG4/ Ara h3-specific IgE ratio
  - Change from baseline to visit 16, visit 22 and visit 25 in Ara h1-specific IgE/ peanut-specific IgE ratio
  - Change from baseline to visit 16, visit 22 and visit 25 in Ara h2-specific IgE/ peanut-specific IgE ratio

- Change from baseline to visit 16, visit 22 and visit 25 in Ara h3-specific IgE/ peanut-specific IgE ratio
- Change and percent change from baseline to visit 16, visit 22 and visit 25 in basophil sensitivity to peanut allergen, as measured by EC50, which is the concentration of peanut protein required to achieve 50% of maximal basophil activation
- Change and percent change from baseline to visit 16, visit 22 and visit 25 in the frequency of peanut-specific T cell subsets (e.g. Th2A cell)

1.2.4. Revision History for SAP Amendments

NA

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a Phase 2, multicenter, randomized, double-blind, parallel-group, 2-arm study in subjects aged 6 to 17 years inclusive who are allergic to peanut. The study consists of a screening period of up to 16 weeks, a 28 to 40-week double-blind treatment period, a 24-week maintenance phase, and a 12-week post-treatment follow-up period. In protocol amendment 3 to accommodate COVID-19 restrictions, double-blind treatment period was extended from 28 weeks to up to 40 weeks. Subjects who attend optional visits between week 28 and week 40 will have increased duration of exposure to AR101 and dupilumab.

Approximately 156 subjects will be randomized at baseline in a 2:1 ratio into one of 2 treatment arms (n=104 to dupilumab and 52 to placebo, in combination with up-dosing of AR101) according to a central randomization scheme provided by an IWRS. Randomization will be stratified by screening peanut-specific IgE level (≤100 kUA/L or >100 kUA/L) and body weight (<30 kg, ≥30 kg and <60 kg, or ≥60 kg) at randomization. A minimum of 15 subjects for each weight group will be enrolled.

At visit 16 (or at the early termination visit for those who discontinue from study prior to visit 16), subjects previously in the dupilumab plus AR101 arm will be re-randomized in a 1:1 ratio into one of 2 treatment arms (dupilumab versus placebo, in combination with AR101), according to a central randomization scheme provided by IWRS. Randomization will be stratified by whether subjects achieve 300 mg/day AR101 for at least 2 weeks by visit 16 (Yes or No).

Subjects previously in the placebo plus AR101 arm will continue their treatment of placebo plus AR101 in the maintenance phase if they achieve 300 mg/day AR101 for at least 2 weeks at visit 16.

2.2. Statistical Hypothesis

The primary efficacy endpoint is the proportion of subjects who achieve a cumulative dose of 2044 mg peanut protein during a post up-dosing DBPCFC at visit 16. The comparison between the dupilumab + AR101 arm and the placebo + AR101 arm will be made.

Let p_D and p_P be the true proportions of subjects who achieve a cumulative dose of 2044 mg of peanut protein during a post up-dosing DBPCFC at visit 16 in the treatment arms of dupilumab + AR101 and placebo + AR101, respectively. The following hypothesis for the superiority testing will be tested at the 5% 2-sided significance level for the up-dosing phase:

H0: $p_D = p_P$, i.e., the proportion of subjects who achieve a cumulative dose of 2044 mg peanut

protein during a DBPCFC at visit 16 is the same between dupilumab + AR101 arm and the placebo + AR101 arm

against the alternative

Ha: $p_D \neq p_P$, i.e., the proportion of subjects who achieve a cumulative dose of 2044 mg peanut protein during a DBPCFC at visit 16 are different between the dupilumab + AR101 arm and the placebo + AR101 arm

2.3. Sample Size and Power Considerations

It is assumed that the proportion of subjects who achieve a cumulative dose of 2044 mg of peanut protein during a post up-dosing DBPCFC at visit 16 in placebo plus AR101 arm will be 40%, based on an Aimmune presentation at the 2018 American Academy of Allergy, Asthma & Immunology–World Allergy Organization Joint Congress; with the proportion of subjects in dupilumab plus AR101 arm assumed to be 65%, which is considered to be clinical meaningful benefit by adding on dupilumab treatment. A sample size of approximately 156 subjects (104 in dupilumab plus AR101 and 52 in placebo plus AR101) will have 80% power to detect the treatment difference of 25% between placebo plus AR101 and dupilumab plus AR101 at the 2-sided 5% significance level (the minimum significant difference is approximately 17.8%). The sample size calculations were done by Fisher exact test using nQuery (7.0).

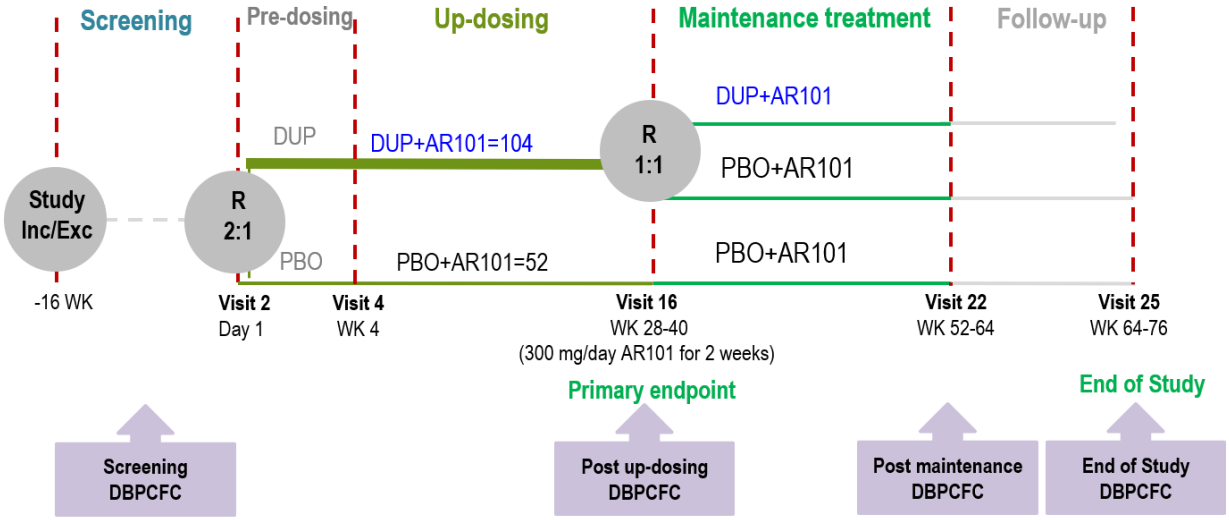
Approximately 122 subjects who undergo the post up-dosing DBPCFC at Week 28 (visit 16 with a window of -7/+30 days) as per protocol or discontinue from study prior to Week 28 (visit 16 with a window of -7/+30 days) will be included in the primary efficacy analysis. These subjects receive AR101 dose escalation per the original protocol's 24-week up-dosing schedule. The minimum significant difference with approximately 122 subjects is approximately 20.7% between placebo plus AR101 and dupilumab plus AR101 assuming placebo plus AR101 treatment effect is 40% at the 2-sided Fisher exact test with 5% significance level.

2.4. Study Plan

The study consists of a screening period of up to 16 weeks, a 28 to 40-week double-blind treatment period, which includes 4 weeks of pretreatment with dupilumab or placebo followed by 24 to 36 weeks of treatment with dupilumab or placebo in combination with a gradual up-dosing of AR101, a 24-week maintenance phase with 300 mg/day AR101 with concomitant dupilumab or matching placebo (for subjects who achieve 300 mg/day AR101 for at least 2 weeks in the up-dosing period), and a 12-week post-treatment follow-up period (Figure 1). Subjects who do not achieve 300 mg/day will still enter the 12-week follow-up. Excluding the screening period, the duration of the study is approximately 64 to 76 weeks for subjects who enter the maintenance period, and 40 to 52 weeks for subjects who do not achieve 300 mg/day AR101 for at least 2 weeks at visit 16 and do not enter the maintenance period.

Figure 1. Schematic of Study Design

Enroll 2-arms (2:1), up-dose AR101 from week 4 to week 28 to 40. Subjects in DUP (dupilumab) +AR101 group will be re-randomized to DUP+AR101 and PBO (placebo) + AR101, but only those subjects who achieve 300 mg/day AR101 for at least 2 weeks will be eligible to enter the 24-week maintenance treatment. Subjects who do not achieve 300 mg/day AR101-CODIT will enter a 12-week follow-up.



During screening visit 1 (Day -113 to day -17), subjects will undergo a medical history, physical examination, spirometry, a standard peanut skin prick test (SPT), and laboratory testing (including peanut sIgE), and will be evaluated for the study eligibility criteria. Subjects must meet all eligibility for Screening Visit 1 before proceeding with the DBPCFC in Visit 1a, which will consist of 5 doses of peanut or placebo oat protein given every 15 to 30 minutes in increasing amounts up to a cumulative total of 144 mg of peanut protein. The doses will be 1, 3, 10, 30 and 100 mg. 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 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 apart. Both food challenge days (placebo and peanut) must be done. Subjects will be considered to have tolerated the DBPCFC if they do not experience any objective Grade 1 (mild) reaction by the Consortium of Food Allergy Research (CoFAR) grading system to the peanut protein ingestion ≤144 mg (cumulative) or experience any symptoms at any dose of placebo and will be excluded from the study.

Subjects with a history of confirmed peanut allergy who continue to meet eligibility criteria at baseline will undergo Day 1/baseline assessments and will be randomized in a 2:1 ratio stratified by screening peanut-specific IgE level (≤100 kUA/L or >100 kUA/L) and body weight (<30 kg, ≥30 kg and <60 kg, or ≥60 kg) at randomization into one of 2 Treatment Arms (104 for dupilumab and 52 for placebo). A minimum of 15 subjects for each weight group will be enrolled.

Dupilumab and placebo will be dosed subcutaneously (SC) as follows based on weight at randomization and dose will not be changed regardless of weight gain or loss:

- subjects weighing <30 kg will receive dupilumab 100 mg every 2 weeks (Q2W) following a loading dose of 200 mg or matching placebo Q2W

- subjects weighing ≥30 kg and <60 kg will receive dupilumab 200 mg Q2W following a loading dose of 400 mg or matching placebo Q2W
- subjects weighing ≥60 kg will receive dupilumab 300 mg Q2W following a loading dose of 600 mg or matching placebo Q2W

After the first 4 weeks, subjects will begin AR101 with an up-dosing regimen to a maximum of 300 mg/day over the next 24 to 36 weeks of the study, for a total of 28 to 40 weeks (including pretreatment) with 28 weeks being ideal and 40 weeks being the maximum. (The flexible up-dosing period is to accommodate COVID-19 restrictions of in-clinic visits, as well as dose reductions and re-escalation, if necessary). Thus, the up-dosing period will consist of 4 weeks pretreatment, 22 to 34 weeks of flexible up-dosing, and at least 2 weeks at the maximum dose of 300 mg/day. During concomitant AR101, study drug will be administered SC at home (at least 24 hours after in-clinic AR101 dose escalation and at least 8 hours apart from the at-home daily AR101 dose). All subjects will go up to visit 15 (Week 26). Visits 15a-f (Week 28 to 38) will be optional in order to reach 300mg/day AR101 for a minimum of 2 weeks. Subjects will undergo a post up-dosing DBPCFC at visit 16 if they have reached 300 mg/day for at least 2 weeks (on a day after the last dose of AR101). Dosing with AR101 should continue on the days between the two parts of the DBPCFC.

Starting on Day 1, subjects will have weight-based dose of placebo or dupilumab Q2W SC for 28 to 40 weeks. At Week 4, all subjects will be administrated AR101 using a standardized regimen of single initial dose escalation day (IDED) from 0.5 mg to a maximum of 6 mg peanut protein (12 mg cumulative) over 5 hours in-clinic (home dosing will be 3 mg peanut protein every evening for the next 2 weeks until up-dosing) (Table 1) followed by bi-weekly in-clinic up-dosing from the highest tolerated initial day dose to a maximum of 300 mg/day at home for 22 to 34 additional weeks. If the scheduled bi-weekly up-dosing is not possible, the up-dosing period may be extended by up to 12 weeks to accommodate COVID-19 restrictions of in-clinic visits, as well as dose reductions and re-escalation, if necessary. Thus, the up-dosing period will end at Week 28 to 40 (including 4 weeks pretreatment, 22 to 34 weeks of flexible up-dosing, and at least 2 weeks at the maximum dose).

Table 1: AR101 Initial Dose Escalation Day at Week 4

	Dupilumab/Placebo + AR101
Week 4 (1 to 5 h) IDED	**Dose of Protein (mg)**
Q30 min	**0.5**
	1
	1.5
	3
	6
Cumulative	**12**

Abbreviations: IDED, initial dose escalation day; Q30, every 30 min

At visit 16, subjects who achieve 300 mg/day of AR101 for at least 2 weeks will undergo a post up-dosing DBPCFC to assess the level of peanut sensitivity. And all dupilumab group subjects will be re-randomized 1:1 to placebo or dupilumab. Only subjects from either treatment group who achieve 300 mg/day AR101 at visit 16 will be eligible to enter the maintenance phase, in which subjects will continue to receive AR101 300 mg/day for 24 weeks. Subjects who do not achieve 300 mg/day AR101 for at least 2 weeks will enter a 12-week follow-up period. In the analysis, subjects not achieving 300mg for a least 2 weeks are considered as the non-responders in DBPCFC. Placebo group subjects will continue to receive placebo in the maintenance phase. At visit 22, subjects will undergo a DBPCFC to access the level of peanut sensitivity at the end of maintenance period.

The post up-dosing and post maintenance DBPCFCs will consist of 8 doses (peanut or placebo) given every 15 to 30 minutes: 1, 3, 10, 100, 300, 600, 1000 mg resulting in a total challenge of up to 2044 mg.

All subjects will have a 12-week follow-up period after the end of treatment and will undergo safety, laboratory, and clinical assessments. At the end of the 12-week follow-up period, subjects who passed a 444 mg (cumulative) peanut protein DBPCFC at visit 22 (end of maintenance period, Week 52 to 64) will be eligible to undergo a final DBPCFC (up to 2044 mg cumulative) under intensive monitoring, at visit 25 (end of study, Week 64 to 76) to assess the level of peanut sensitivity after 12 weeks off peanut and dupilumab to determine whether there is evidence of persistent effects and sustained unresponsiveness.

3. ANALYSIS POPULATIONS

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

3.1. The Full Analysis Set (FAS)

FAS includes all randomized subjects. Efficacy analyses will be based on the treatment allocated by the IWRS at randomization (as randomized).

The modified full analysis set (mFAS) includes all FAS subjects who undergo bi-weekly in-clinic up-dosing as described/specified in the protocol and undergo the post up-dosing DBPCFC at Visit 16/Week 28 (a window of -7/+30 days).

The mFAS will be considered as primary analysis set for all efficacy endpoints. The FAS will also be done for all efficacy endpoints as supportive analyses.

FAS-maintenance is a subset of FAS and includes subjects in the FAS who achieve 300 mg/day AR101 for at least 2 weeks in the up-dosing phase and re-randomized based on the treatment allocated by the IWRS at visit 16. The FAS-maintenance is the primary analysis set for efficacy analyses at visit 22.

3.2. The Per Protocol Set (PPS)

PPS includes all subjects in the mFAS except for those who are excluded because of important protocol violations. An important protocol violation is one that may affect the interpretation of study efficacy results. A preliminary list of such important protocol violations is provided in Section 10.6 and a final list of subjects excluded from FAS will be generated prior to primary analysis database lock. Final determinations of the PPS will be made in the blinded manner before data base lock.

The primary endpoint and first secondary endpoint will be evaluated on the PPS in addition to mFAS and FAS.

3.3. The Safety Analysis Set (SAF)

SAF includes all randomized subjects who receive at least one injection of dupilumab/placebo and be analyzed as treated. Treatment assignment will be based on the actual treatment received not the treatment assigned by IWRS randomization. Treatment compliance/administration for investigational product including both dupilumab/placebo and AR101, as well as all clinical safety variables will be summarized based on SAF.

For the safety analyses during the maintenance period, a subset of SAF which is defined as SAF-maintenance includes re-randomized subjects at visit 16 who received at least one injection of dupilumab/placebo during the maintenance period. Treatment compliance/administration for investigational product and all clinical safety variables during maintenance period will be summarized based on SAF-maintenance.

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

- For a subject randomized to dupilumab Q2W (any dose level), if the subject received all placebo injections, the actual treatment will be assigned as placebo.
- Regardless of the treatment group a subject is randomized to, if the subject received at least 1 dupilumab injection, the actual treatment will be assigned as dupilumab Q2W (any dose level).

For safety summaries, the analysis periods are defined as follows:

- Pre-dosing period (4 weeks) is defined as:
  - Day 1 to the day before the date of AR101 IDED in the up-dosing period if subjects completed the IDED at Week 4
  - Day 1 to early termination (ET) visit date before Week 4 if subjects early terminated from the pre-dosing period
- Up-dosing period (24 to 36 weeks) is defined as:
  - For subjects who entered maintenance period: The date of AR101 IDED to the date of second post up-dosing DBPCFC at visit 16.
  - For subjects who did not enter maintenance period:
    - The date of AR101 IDED at Week 4 to the date of visit 16 if subjects entered follow-up period
    - The date of AR101 IDED at Week 4 to the last dose date of dupilumab/placebo + 14 days if subjects completed dosing to visit 16 but did not enter follow-up period
    - The date of AR101 IDED at Week 4 to early termination (ET) visit date before visit 16 if subjects did not complete dosing to visit 16
- Maintenance period (24 weeks) for subjects who entered maintenance period is defined as:
  - The day after the date of second post up-dosing DBPCFC at visit 16 to the date of second post maintenance DBPCFC at visit 22 if subjects completed the visit 22 with known visit date
  - The day after the date of second post up-dosing DBPCFC at visit 16 to study day 365 (52 weeks times 7 days/week + 1 day) if subjects had missing visit 22 date
  - The day after the date of second post up-dosing DBPCFC at visit 16 to ET visit date before visit 22 if subjects early terminated from maintenance period
- Follow-up period (12 weeks) for subjects who entered follow-up period is defined as:
  - For subjects who completed maintenance period: The day after the date of second post maintenance DBPCFC at visit 22 to the subject end of study visit date or the date of second end of study DBPCFC at visit 25, whichever comes later

  - For subjects who did not receive 300 mg/day of AR101 for at least two weeks by visit 16 : The day after the visit 16 date to the subject end of study visit date
  - For subjects who early terminated from study treatment in the up-dosing period or maintenance period: The day after the last visit date in the treatment period to the subject end of study visit date
- Overall study period is defined as Day 1 to the date of end of study visit.

The SAF and SAF-maintenance will be the basis for the analyses of the pre-dosing/up-dosing period and maintenance period, respectively; however, for the analyses of the follow-up period, only a subset of the corresponding safety analysis sets will be included, which is defined as the subjects who entered the follow-up period from pre-dosing/up-dosing period and had at least one visit after visit 16 (for SAF) or subjects who entered the follow-up period from maintenance period and had at least one visit after visit 22 (for SAF-maintenance).

3.4. The Pharmacokinetic Analysis Set (PKAS)

The pharmacokinetic analysis set includes all treated subjects who received any study drug and who had at least one non-missing drug concentration result following the first dose of study drug.

3.5. The Immunogenicity Analysis Sets

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

The neutralizing antibody (NAb) Analysis Set (NAS) includes all treated subjects who received any study drug and who are negative in the dupilumab ADA assay or with at least 1 non-missing result in the dupilumab NAb assay. Subjects who are negative in the ADA assay are set to negative in the NAb analysis set. Subjects will be analyzed according to the treatment actually received.

3.6. Subgroups

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

Subgroups to be considered for both efficacy and safety analyses:

- Age group (>=6 to <12 years, >=12 to <=17 years)
- Sex (Male, Female)
- Baseline weight group (<30 kg, ≥30-<60 kg, ≥60 kg)
- Screening peanut-specific IgE level (≤100 kUA/L or >100 kUA/L)
- Asthma and non-asthma history for primary and key secondary efficacy endpoint only
- AD and non-AD history for primary and key secondary efficacy endpoint only

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline characteristics variables will be summarized:

- Demographic variables
  - Age at screening (year)
  - Age group (≥6 to <12 years; ≥12 to ≤17 years)
  - Sex (Male, Female)
  - Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Other)
  - Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
  - Baseline weight (kg)
  - Baseline weight category (<30 kg, ≥30 kg and <60 kg, ≥ 60 kg)
  - Baseline height (m)
  - Baseline Body Mass Index (BMI) (kg/m^2)
- Baseline characteristics
  - Duration of peanut allergy diagnosis (year)
  - Age at peanut allergy onset (year; <5, ≥5 and <10, ≥ 10 and ≤17)
  - Number of co-morbid atopic diseases (atopic dermatitis, asthma, nasal polyps, allergic rhinitis or eosinophilic esophagitis)
  - Baseline Fractional Exhaled Nitric Oxide (FeNO) value
  - History of atopic dermatitis (Yes, No)
  - Duration of atopic dermatitis disease with grouping (year; <=1 and >1)
  - Eczema Area and Severity Index (EASI) score for subjects with atopic dermatitis
  - History of asthma (Yes, No)
  - Asthma Control Questionnaire (ACQ-5) score for subjects with asthma
  - Baseline Food Allergy Quality of Life Questionnaire (FAQLQ) score for different types of FAQLQ form
  - Screening serum peanut-specific IgE
  - Screening serum peanut-specific IgG4
  - Screening serum total IgE
  - Screening peanut-specific IgG4/sIgE ratio

- Screening peanut-specific IgE level (≤100 kUA/L, >100 kUA/L)
- Baseline predicted FEV1 (L)
- Baseline percent predicted FEV1 (%)
- Baseline predicted FVC (L)
- Baseline percent predicted FVC (%)
- Maximum tolerated dose of peanut protein at screening DBPCFC
- Use of epinephrine at screening DBPCFC (Yes, No)
- Normalized mean peanut wheal diameter at screening SPT

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

4.2. Medical History

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

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

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

4.3. Prior / Concomitant Medication and Procedures

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

Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD) at the coding CRO. Subjects will be counted once in all ATC categories linked to the medication.

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

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

Concomitant medications/procedures (CMs/CPs): medications taken or procedures performed following the first dose of dupilumab/placebo through the EOS visit. This includes medications/procedures that were started before the study and are ongoing during the study. Furthermore, CM/CP will be categorized according to analysis periods (as defined in Section 3.3):

- CMs/CPs taken during the pre-dosing period
- CMs/CPs taken during the up-dosing period
- CMs/CPs taken during the maintenance period
- CMs/CPs taken during the follow-up period

4.4. Prohibited or Rescue Medication/Procedure During Study

Prohibited concomitant medications/procedures:

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

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

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures

Rescue Treatment (including both medications and procedures)

The following concomitant treatments will require permanent study drug discontinuation:

- Treatment with an investigational drug (other than dupilumab)
- Treatment with immunomodulating biologic agents, including anti-IgE and anti-IL-5
- Treatment with allergen immunotherapy other than AR101
- Treatment with systemic (oral, IV, IM, SC) corticosteroids for a duration of more than 5 continuous days, more than 15 days in total, or within 2 days prior to DBPCFCs

The following concomitant treatments of allergic reactions will not require permanent study drug discontinuation.

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

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

- Screening DBPCFC of peanut protein
- Post up-dosing DBPCFC of peanut protein
- Post maintenance DBPCFC of peanut protein
- End of study DBPCFC of peanut protein
- Pre-dosing/up-dosing period (excluding post up-dosing DBPCFC)
- Maintenance period (excluding post maintenance DBPCFC)

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

4.5. Efficacy Variable

4.5.1. Primary Efficacy Variable (s)

The primary endpoint in this study is:

- Proportion of subjects treated with dupilumab plus AR101 vs placebo plus AR101 who "pass" a post up-dosing DBPCFC with 2044 mg (cumulative) peanut protein at visit 16

Double-blind placebo-controlled food challenge (DBPCFC)

At visit 16, under intensive monitoring, all subjects who achieve 300 mg/day AR101 during the up-dosing phase for at least 2 weeks will undergo a post up-dosing DBPCFC up to 2044 mg (cumulative) peanut protein or placebo to assess desensitization. At visit 22, all subjects who maintain 300 mg/day AR101 will undergo a post maintenance DBPCFC up to 2044 (cumulative) peanut protein or placebo to assess desensitization. The subject's sensitivity to peanut allergen is defined as the dose at which the subject experiences allergic reactions. All symptoms and signs will be evaluated and rated based on a standardized oral food challenge scoring system (CoFAR). Up-dosing during the DBPCFC will be stopped when the principal investigator (or designee) finds symptoms and/or signs that indicate a definite objective (Grade 1 [mild]) allergic reaction (CoFAR grading system) has occurred based on clinically significant changes in reported symptoms, physical findings, or vital signs that the subject is experiencing to the challenge material. Vital signs will be assessed every 15 to 30 minutes. In addition, subjects will be considered to have dose-limiting reactions if they experience any mild subjective reactions requiring pharmacologic intervention and/or any moderate/severe reaction.

The DBPCFC will consist of 8 doses (peanut protein 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 challenge 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. Subjects will be considered to have passed the DBPCFC if they do not experience any objective Grade 1 (mild) reaction by CoFAR grading system. If the subject experiences reactions,

he/she will be treated with the necessary rescue medications. In addition, subjects will be considered to have passed the DBPCFC if they do not experience any mild subjective symptoms requiring pharmacological intervention and/or moderate or severe symptoms. He/she will be observed for a minimum of 2 hours after the final administered dose and discharged only when deemed clinically stable by study physician. Symptom severity will be adjudicated by an independent, blinded assessor who is not involved in performing the baseline food challenge. When dosing elicits an acute reaction characterized by the appearance of only a mild subjective symptom or symptoms, the investigator will be required to assess whether the dose was or was not tolerated.

Consortium of Food Allergy Research (CoFAR) Grading System

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

4.5.2. Secondary Efficacy Variable(s)

The secondary efficacy endpoints are:

- Change in cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline to visit 16 in subjects treated with dupilumab plus AR101 vs placebo plus AR101

Note: Due to the positive skew for the distribution of the "cumulative amount of peanut protein", a log transformation will be applied to reduce the skewness

- Proportion of subjects treated with dupilumab plus AR101 vs placebo plus AR101 who reach the 300 mg/day dose of AR101 by visit 16
- Time from randomization to the first-time when subjects reach the 300 mg/day dose of AR101 during the treatment phase (up to visit 16)
- Proportion of subjects (continuously) treated with dupilumab plus AR101 vs placebo plus AR101 who "pass" a post maintenance DBPCFC with 2044 mg (cumulative) peanut protein at visit 22
- Change in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline to visit 22 in subjects (continuously) treated with dupilumab plus AR101 vs placebo plus AR101
- Proportion of subject (previously) treated with dupilumab plus AR101 (and re-randomized to placebo plus AR101) vs placebo plus AR101 who "pass" a post maintenance DBPCFC with 2044 mg (cumulative) peanut protein at visit 22
- Change in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline to visit 22 in subjects (previously) treated with dupilumab plus AR101 (and re-randomized to placebo plus AR101) vs placebo plus AR101
- Percent change from baseline to visit 16 in peanut-specific IgE in subjects treated with dupilumab plus AR101 vs subjects treated with placebo plus AR101

- Percent change from baseline to visit 22 in peanut-specific IgE in subjects (continuously) treated with dupilumab plus AR101 vs subjects treated with placebo plus AR101
- Percent change from baseline to the end of study visit 25 in peanut-specific IgE in subjects (continuously) treated with dupilumab plus AR101 vs subjects treated with placebo plus AR101

4.5.3. Exploratory Efficacy Variable (s)

Exploratory efficacy endpoints include:

- Proportion of subjects who "pass" an end of study DBPCFC with 2044 mg (cumulative) peanut protein at visit 25
- Change from baseline in total FAQLQ score at visit 16, visit 22, and visit 25 for different types of FAQLQ form
- Proportion of subjects experiencing none, mild, moderate, severe or higher allergic symptoms by treatment group during DBPCFCs of peanut protein at visit 16 and visit 22
- Change and percent change from baseline to visit 16, visit 22 and visit 25 in peanut-specific IgG
- Change and percent change from baseline to visit 16, visit 22 and visit 25 in peanut-specific IgG4
- Change and percent change from baseline to visit 16, visit 22 and visit 25 in total IgE
- Change from baseline to visit 16, visit 22 and visit 25 in log- transformed peanut-specific IgG4/ peanut-specific IgE ratio
- Change from baseline to visit 16, visit 22 and visit 25 in log- transformed peanut-specific IgG/ peanut-specific IgE ratio
- Change from baseline to visit 16, visit 22 and visit 25 in peanut-specific IgE
- Change from baseline to visit 16, visit 22 and visit 25 in log- transformed peanut-specific IgE/total IgE ratio
- Change and percent change from baseline to visit 16, visit 22 and visit 25 in Ara h1 sIgE, Ara h1 sIgG4, Ara h2 sIgE, Ara h2 sIgG4, Ara h3 sIgE, Ara h3 sIgG4
- Change from baseline to visit 16, visit 22 and visit 25 in log- transformed Ara h1-specific IgG4/ Ara h1-specific IgE ratio
- Change from baseline to visit 16, visit 22 and visit 25 in log- transformed Ara h2-specific IgG4/ Ara h2-specific IgE ratio
- Change from baseline to visit 16, visit 22 and visit 25 in log- transformed Ara h3-specific IgG4/ Ara h3-specific IgE ratio

- Change from baseline to visit 16, visit 22 and visit 25 in Ara h1-specific IgE/ peanut-specific IgE ratio
- Change from baseline to visit 16, visit 22 and visit 25 in Ara h2-specific IgE/ peanut-specific IgE ratio
- Change from baseline to visit 16, visit 22 and visit 25 in Ara h3-specific IgE/ peanut-specific IgE ratio
- Change and percent change from baseline to visit 16, visit 22 and visit 25 in basophil sensitivity to peanut allergen, as measured by EC50, which is the concentration of peanut protein required to achieve 50% of maximal basophil activation
- Change and percent change from baseline to visit 16, visit 22 and visit 25 in the frequency of peanut-specific T cell subsets (e.g. Th2A cell)
- Proportion of days with one or more of any peanut allergy symptoms excluding food challenge test days during the up-dosing period up to visit 16
- Proportion of days with one or more severe form of any peanut allergy symptoms (i.e. severity score of 7 or more) excluding food challenge test days during the up-dosing period up to visit 16
- Proportion of days with one or more peanut allergy symptoms for each symptom category excluding food challenge test days during the up-dosing period up to visit 16

Eczema Area and Severity Index (EASI)

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD. The EASI is a composite index with scores ranging from 0 to 72. Four Atopic Dermatitis (AD) disease characteristics [erythema (E), thickness (induration, papulation, edema) (L), scratching (excoriation) (X), and lichenification (L)] will each be assessed for severity by the investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

For each of major section of the body (head, upper extremities, trunk and lower extremities), EASI score = (E+I+X+L) ×Area Score. The EASI score is the weighted total of the section EASI using the weights. For subjects of age ≥8 years, the weights are 10% = head, 20% = upper extremities, 30% = trunk, 40% = lower extremities. For subjects of age <8 years, the weights are 20% = head, 20% = upper extremities, 30% = trunk, 30% = lower extremities.

Asthma Control Questionnaire

The Asthma Control Questionnaire (ACQ) is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of subjects with a medical history of asthma and who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries). The ACQ-5 is for subjects aged 11 years or more and the ACQ-interviewer administered (IA) is for subjects who aged 6 to 10 years. The ACQ has been fully validated for all children 6-17 years when the self-administered adult

version is used by children 11 years and older and the interviewer-administered version is used for children 6-10 years. Subjects will continue using the ACQ version first administered at screening regardless of moving to next age bracket.

The ACQ-IA consists of 7 questions in which the first 5 questions assess the most common asthma symptoms:

1. Frequency in the past week awoken by asthma during the night
2. Severity of asthma symptoms in the morning
3. Limitation of daily activities due to asthma
4. Shortness of breath due to asthma
5. Wheeze
6. Short-acting bronchodilator use
7. FEV1 (pre-bronchodilator % predicted)

The response options for all these questions consists of a 0 (no impairment/limitation) to 6 (total impairment/limitation) scale.

The ACQ-5 consists of 5 questions which are the same with the first 5 questions of ACQ-IA. The ACQ-5 score is a mean of values recorded for the individual questions. The answer to the first 5 questions of ACQ-IA will be used to calculate an ACQ-5 score for the analysis of the ACQ-5 endpoint.

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 subjects. Subjects 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 subjects aged 8 to 12 years and the teenager form (FAQLQ-TF) is used for subjects aged 13 to 17. 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 subjects of ages 0 to 12 years. The FAQLQ will be administered to subject and, when appropriate, parents at time points in accordance with Table 2 and Table 3. Subjects will continue using the FAQLQ version first administered at baseline regardless of moving to the next age bracket.

The number of questions and domains varies by questionnaire administered. Each question is scored based on a seven-point scale. The total score is the arithmetic average of all non-missing answers.

Daily allergy symptom

The daily allergy symptom diary is a questionnaire that was designed to capture the daily signs and symptoms of peanut OIT. In addition to daily allergy symptoms, the e-diary will also collect data on dupilumab injections, peanut OIT dosing, use of medications to treat symptoms of peanut OIT.

Daily allergy symptom in the peanut symptoms daily e-diary includes, dizziness (spinning feeling), rash (red, itchy, bumpy skin), eye swelling (eye puffiness), lip swelling (lip puffiness), swelling in your throat (throat feeling like it is tight or closing), nausea (feeling like you might throw up), vomiting (throwing up), diarrhea (runny, loose, watery poop), runny or stuffy nose, sneezing, stomach pain, itching in and around your mouth (lips, tongue), itching in your throat, skin itching, eye itching (itching around the eye or eyelid), trouble breathing, wheezing (noisy, squeaky breathing), coughing, pain in your tongue or mouth, pain in your throat, tongue swelling (tongue puffiness), itching in or around your nose, hive(s) (lumps on skin). Subjects may experience none of the symptoms, any symptom or all symptoms. The severity of each symptom will be rated on a scale of 1-10.

Symptom categories to be generated as follows:

1. Gastro-Intestinal (GI)
2. Swelling
3. Itching
4. Airway symptoms
5. Rash/hives
6. Dizziness

Symptom	**Symptom category**
Dizziness	Dizziness
Rash	Rash/hives
Eye Swelling	Swelling
Lip Swelling	Swelling
Swelling in throat	Swelling
Nausea	GI
Vomiting	GI
Diarrhea	GI
Runny or stuffy nose	Airway
Sneezing	Airway
Stomach pain	GI
Itching in or around your mouth	Itching
Itching in your throat	Itching
Skin itching	Itching
Eye itching	Itching
Trouble breathing	Airway
Wheezing	Airway
Coughing	Airway
Pain in your tongue or mouth	GI
Pain in your throat	GI
Tongue swelling	Swelling
Itching in or around your nose	Itching
Hives (lumps on skin)	Rash/hives

The proportion of days with one or more of any peanut allergy symptoms excluding food challenge test days during the up-dosing period for each patient is calculated using the follow 2 methods:

1. Number of days with symptoms / number of days of the treatment duration of the up-dosing period
2. Number of days with symptoms / number of Days with non-missing eDiary data in the up-dosing period

The proportion of days with one or more severe form of any peanut allergy symptoms (i.e. severity score of 7 or more) excluding food challenge test days and the proportion of days with one or more symptoms for each symptom category excluding food challenge test days will be calculated similarly.

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

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

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

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

Adverse events and serious adverse events will be collected from the time of informed consent/assent is signed until the end of the study. However, allergic reactions to the DBPCFC during the Screening phase, at endpoint challenges (at visits 16, 22, and 25), during AR101 in-clinic dosing visits, and daily home dosing will be recorded as allergic signs and symptoms since they are anticipated to allergen challenge.

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

Abnormal laboratory or vital signs will be graded according to the FDA September 2007. The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or

- Test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), or discontinuation from the study, significant additional concomitant drug treatment, or other therapy

The pre-treatment and treatment-emergent periods are defined as following:

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent period is defined as the day from first dose of study drug to the end of the study. The treatment-emergent period includes the 4-week pre-dosing treatment period, the 24 to 36-week up-dosing treatment period, the 24-week maintenance treatment period, and the follow-up period.

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

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

4.6.2. Adverse Events of Special Interest

Adverse event of special interest (AESI) for dupilumab in this study category includes:

- Anaphylactic reactions
- Systemic or severe hypersensitivity reactions
- Helminthic infections
- 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)

Adverse events of special interest for AR101 in this study include:

- Anaphylactic reactions
- Gastrointestinal AEs resulting in prolonged disruption of dosing

Section 10.4 provides a list of AESIs search criteria.

Anaphylactic reactions: Anaphylaxis is defined as 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.

Gastrointestinal adverse events and disruption of dosing: At each study visit, the site must solicit specific symptoms from subjects that may indicate the development of EoE. These include symptoms of both advanced and early disease such as food impaction, dysphagia, and choking or gagging with meals, gastroesophageal reflux, nausea, vomiting, and abdominal pain. Prolonged disruption of dosing is defined as withholding AR101 for >7 consecutive days and is an individual stopping rule that results in permanent discontinuation of dosing.

4.6.3. Laboratory Safety Variables

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

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

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
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 subjects of childbearing potential, a serum pregnancy test will be performed at screening and end of study visits. For other visits where a pregnancy test is scheduled, a urine pregnancy test will be performed.

4.6.4. Vital Signs

Vital signs, including temperature, sitting blood pressure, pulse, and respiration rate will be collected pre-dose at screening visit 1, screening visit 1a, every scheduled visit and the unscheduled visit or ET visit. During the DBPCFC, IDE and up-dosing, vital signs will be monitored every 15 to 30 minutes. For post-dose monitoring, only pulse and blood pressure need to be taken as part of safety monitoring.

4.6.5. Body Weight and Height

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

4.6.6. Physical Examination Variables

The physical examination variable values are dichotomized to normal and abnormal. A thorough and complete physical examination will be performed at the screening visits (visit 1 and visit 1a), visit 16, visit 22 and visit 25 or ET visits.

4.6.7. Spirometry

A spirometer that meets the 2005 American Thoracic Society/European Respiratory Society recommendations will be used to measure FEV1 and/or PEF. During DBPCFC, spirometry should be performed before and after the challenge.

4.7. Pharmacokinetic (PK) Variables

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

4.8. Anti-Drug Antibody Variable

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

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

- ADA Negative, defined as a negative response in the dupilumab ADA assay at all time points, regardless of any missing samples.
- Pre-existing immunoreactivity, defined as either an ADA positive response in the dupilumab ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 4-fold of baseline titer levels

- Treatment-emergent response, defined as a positive response in the dupilumab ADA assay post first dose when baseline results are negative or missing. The treatment-emergent responses will be further characterized as Persistent, Indeterminate or Transient.
  - Persistent Response: Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points, separated by greater than 12-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.
  - Indeterminate Response: Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples.
  - Transient Response: Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.
- Treatment-boosted response, defined as a positive response in the dupilumab ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive
- Maximum Titer Values (Titer value category)
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

4.9. Pharmacodynamic and Biomarkers Variables

Pharmacodynamic and biomarker variables are:

- Serum total IgE
- Serum peanut-specific antibody assays (IgE, IgG, IgG4 against peanut extract and peanut protein allergen components)
- Fractional Exhaled Nitric Oxide (FeNO)
- Basophil Sensitivity Test (optional)
- Peanut-reactive Th2A cells (optional)

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

4.10. Pediatric Eosinophilic Esophagitis Symptom Score Questionnaire

The Pediatric Eosinophilic Esophagitis (EoE) Symptom Score PEESS v2.0 measures subject-relevant outcomes. The PEESS v2.0 holds promise for being a valuable tool to follow the clinical course of EoE or an EoE-like immune-mediated GI syndrome. However, it was not designed to establish a diagnosis of EoE and has not been validated for use in subjects with GI symptoms of other etiologies. Furthermore, the discriminant validity of the questionnaire has not been reported in either longitudinal natural history or interventional studies. For these reasons, the use of the PEESS v2.0 to monitor the clinical course of GI symptoms must be considered exploratory.

Subjects that discontinue because of GI AEs will be asked to complete the PEESS v2.0 questionnaire, with the assistance of a parent or guardian, as appropriate, every month for 6 months.

5. STATISTICAL METHODS

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

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

All data will be summarized by the following treatment groups in each period:

1. Double-blind treatment period before dosing with AR101 (4 weeks)
   - Dupilumab
   - Placebo
2. Double-blind treatment period with up-dosing of AR101 (24 to 36 weeks):
   - Dupilumab + AR101
   - Placebo + AR101
3. Double-blind maintenance period of AR101 (24 weeks):
   - Continuously on placebo+ AR101
   - Previously on dupilumab + AR101 and re-randomized to placebo + AR101 (dupilumab + AR101/placebo + AR101)
   - Continuously on dupilumab + AR101

5.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group for mFAS, FAS and SAF. They will be summarized by treatment group for FAS-maintenance and SAF-maintenance for subjects who entered maintenance period. Listing of demographics and baseline characteristics will be presented.

5.2. Medical History

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

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

5.3. Prior and Concomitant Medications/Procedures

Number and proportion of subjects taking prior/concomitant medications, prohibited medications and rescue medications will be summarized for each treatment group and study total based on the SAF and SAF-maintenance by ATC level 2 and ATC level 4, sorted by decreasing frequency of ATC level 2 and ATC level 4 based on the overall incidence for the combined treatment groups for each study period.

Number and proportion of subjects taking prior/concomitant procedures will be summarized for each treatment group and study total based on the SAF and SAF-maintenance, sorted by decreasing frequency of SOC and PT based on the overall incidence for the combined treatment groups for each study period.

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

Number and proportion of subjects taking at least one epinephrine and short-term use of systemic corticosteroids for treatment of acute-allergic reactions will be summarized during the following periods,

- Screening DBPCFCs of peanut protein
- Week 4 IDED
- Post up-dosing DBPCFCs of peanut protein
- Post maintenance DBPCFCs of peanut protein
- End of study DBPCFCs of peanut protein

The number of episodes of epinephrine use and short-term use of systemic corticosteroids during up-dosing period (excluding post up-dosing DBPCFCs) and during maintenance period (excluding post maintenance DBPCFCs) will be summarized, respectively.

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

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

5.4. Subject Disposition

The following summaries by table will be provided:

- The total number of screened subjects and the screen failure reasons: met the inclusion criteria regarding the target indication and signed the informed consent form (ICF)
- The total number of randomized subjects in each study treatment period: received a randomization number from IWRS
- The total number of subjects in each analysis set
- The total number of subjects who discontinued the study and the reasons for discontinuation (including COVID-19 related reasons)
- The total number of subjects who discontinued the study in each study treatment period and the reasons for discontinuation (including COVID-19 related reasons)

- The total number of subjects who discontinued the study treatment in each study treatment period and the reasons for discontinuation (including COVID-19 related reasons)
- A summary table of protocol deviations

The following listings will be provided:

- Listing of subjects disposition including: date of randomization, date of first dupilumab/placebo injection, date of re-randomization, date of the last visit, completed study or discontinued by reason
- A listing of subjects randomized but not treated, treated but not randomized, and subjects randomized but not treated as randomized, if applicable
- A listing of subjects prematurely discontinued from the study treatment, along with reasons for discontinuation in each study period
- A listing of protocol deviations will be provided

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

5.5. Extent of Study Treatment Exposure

5.5.1. Measurement of Compliance

The compliance with study treatment will be calculated separately for dupilumab/placebo injection and AR101 oral home dosing for each study period as follows:

> Treatment compliance of dupilumab or placebo = (Number of dupilumab/placebo injections during exposure period) / (Number of planned dupilumab/placebo injections during exposure period) x 100%;

For treatment compliance calculation of dupilumab/placebo injection, the two injections including one loading dose at the randomization visit 2 will be counted as 1 injection.

> Treatment compliance of home dosing AR101 = (total actual peanut dose protein [mg] received during exposure period) / (total of planned dose peanut protein [mg] during exposure period) x 100%.

The treatment compliance will be presented by the following specific ranges for each treatment group: <80%, and ≥80%.

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

Listing of AR101 compliance for home dosing will be presented with AR101 dose date/time, study day, AR101 assigned dose, whether or not the full dose was taken, amount taken for partial dose, reasons for partial or missed AR101 dose.

5.5.2. Exposure to Investigational Product

The duration of exposure to Dupilumab/Placebo in day will be presented by treatment group for each study period and calculated as:

(Date of last dupilumab/placebo injection in the respective study period – date of first study drug injection) + 14 days

The duration of exposure to AR101 in day for each study period will be calculated as:

(Date of last AR101 taken in the respective study period – date of first AR101 taken) + 1 day

Note: the calculations are regardless of temporary dosing interruption.

Summary of exposure to study drug will include the number of study drug doses administered and duration of exposure. The duration of exposure to dupilumab/placebo and AR101 during the study will be summarized by treatment group using number of subjects, mean, SD, minimum, Q1, median, Q3, and maximum. These summaries will be provided for each study period separately.

In addition, the duration of exposure to study drug will be summarized categorically by counts and percentages for each of the following categories and cumulatively by these categories as well: ≥ 14 days, ≥ 28 days, ≥ 42 days, ≥ 56 days, ≥ 70 days, ≥ 84 days, ≥ 98 days, ≥ 112 days, ≥ 126 days, ≥ 140 days, ≥ 154 days, ≥ 168 days, ≥ 182 days, ≥ 196 days, ≥ 210 days , ≥ 224 days, ≥ 238 days, ≥ 252 days, ≥ 266 days, ≥ 280 days, ≥ 294 days, ≥ 308 days, ≥ 322 days, ≥ 336 days, ≥ 350 days, and ≥ 364 days.

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

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

The duration of observation period will be summarized descriptively using number of subjects, mean, SD, median, Q1, Q3, minimum and maximum. In addition, the number (%) of subjects with observation periods will be presented by specific time periods. The time periods of interest are specified as: < 15 days, ≥ 15 days, ≥ 29 days, ≥ 43 days, ≥ 57 days, ≥ 71 days, ≥ 85 days, ≥ 99 days, ≥ 113 days, ≥ 127 days, ≥ 141 days, ≥ 155 days, ≥ 169 days, ≥ 183 days, ≥ 197 days, ≥ 225 days, ≥ 239 days, ≥ 253 days, ≥ 267 days, ≥ 281 days, ≥ 295 days, ≥ 309 days, ≥ 323 days, ≥ 337 days, ≥ 351 days, ≥ 365 days, ≥ 379 days, ≥ 393 days, ≥ 407 days, ≥ 421 days, ≥ 435 days, and ≥ 449 days.

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

5.6. Analyses of Efficacy Variables

The primary efficacy analyses for all the efficacy endpoints will be conducted at Week 28 (visit 16 with a window of -7/+30 days) using the mFAS population. As supportive evidence, the same analysis approach will be repeated with the FAS population at visit 16. The efficacy analyses at visit 22 will be based on the FAS-maintenance population. The analyses of efficacy variables are described in the subsections below and summarized in Section 10.1.

5.6.1. Analysis of Primary Efficacy Variable

This primary endpoint will be analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization stratification factors (screening peanut-specific IgE level [≤100 kUA/L or >100 kUA/L] and baseline body weight [<30 kg, ≥30 kg and <60 kg, or ≥60 kg]) to assess the treatment difference in the proportion of responders (i.e., those who "pass" a post up-dosing DBPCFC with 2044 mg [cumulative] peanut protein at visit 16 [Week 28 with a visit window of -7/+30 days]) in the mFAS. Estimate of treatment difference, p-value, and the 2-sided 95% confidence interval using CMH test will be provided. The number and percent of subjects at each dose level for highest tolerated peanut protein dose at post up-dosing DBPCFC will also be summarized.

The primary estimand of interest for the primary endpoint is described as follows, based on intercurrent event(s) strategy and missing data handling methods:

- The treatment policy strategy will be implemented for the intercurrent event of the treatment discontinuation. The data collected after the patient discontinued treatment will be included in the analysis.
- Missing data for post up-dosing DBPCFC at visit 16 will be handled according to the reason for missingness as follows:
  - If a subject misses the post up-dosing DBPCFC at visit 16 due to COVID-19, the missing data will be imputed by multiple imputation (MI) method for 10 times utilizing available post up-dosing DBPCFC data at visit 16. The MI will utilize logistic regression method with treatment group and randomization stratification.
  - If a subject does not have available DBPCFC data with peanut protein at visit 16 due to reasons not related to COVID-19, this subject will be considered as a non-responder at visit 16.

Each of complete datasets after the above steps will be analyzed by the CMH test. The SAS MIANALYZE procedure will then be used to generate valid statistical inferences by combining results using Rubin's formula (Rubin, 1987).

Sensitivity analyses will include an analysis of the subset of subjects with available visit 16 DBPCFC data with peanut protein.

The supportive analyses based on FAS and PPS will be performed using primary analysis method.

5.6.2. Analysis of Secondary Efficacy Variables

Continuous Endpoints at visit 16

Change in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline at visit 16 will be analyzed using analysis of covariance (ANCOVA) with treatment as the main effect, stratification variables and baseline tolerated cumulative amount of peanut protein DBPCFC (log transformed) as covariates. If subjects do not tolerate any dose level, they will be assigned a cumulative tolerated dose of 1 mg prior to converting to the log scale. The least-squares (LS) mean for each treatment group with its corresponding standard error (SE), the LS mean difference between treatment group and its corresponding SE and 95% CI, and the p-value corresponding to the between-treatment-group difference will be reported. In addition, change the

cumulative tolerated dose of peanut protein during a DBPCFC at visit 16 will be based on a non-parametric analysis using the van Elteren test.

Missing data for post up-dosing DBPCFC at visit 16 will be handled according to the reason for missingness as follows:

- If a subject misses the post up-dosing DBPCFC at visit 16 due to COVID-19, the missing data will be imputed by MI method for 10 times utilizing available post up-dosing DBPCFC data at visit 16. The MI will utilize regression method with treatment group, randomization stratification, and baseline tolerated cumulative amount of peanut protein DBPCFC (log transformed).
- If a subject does not have an available DBPCFC at visit 16 due to reasons not related to COVID-19, the baseline value at screening DBPCFC will be used to impute the missing post up-dosing DBPCFC data at visit 16.

Each of the complete datasets after the above steps will be analyzed by the ANCOVA. The SAS MIANALYZE procedure will then be used to generate valid statistical inferences by combining results.

Two sensitivity analyses will be performed as below to assess the robustness of results:

- Completed cases will be conducted regardless the rescue medication used.
- MI method: the missing data will be imputed by MI method utilizing available post up-dosing DBPCFC data at visit 16. The MI will utilize the same regression method as the above.

Continuous secondary efficacy endpoints that are measured repeatedly over time during the 28 to 40-week treatment period, will be analyzed using ANCOVA with treatment as the main effect, stratification variables and relevant baseline. For these endpoints, missing data will be imputed by multiple imputations (MI) methods 40 times to generate 40 complete data sets by using the Statistical Analysis System (SAS) procedure MI following the 2 steps below:

Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure using seed number 68367. The monotone missing pattern means that if a subject has missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the subject.

Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with seed number 81807 and adjustment for covariates including treatment groups, randomization stratification, and relevant baseline.

Each of the 40 complete datasets will be analyzed using an ANCOVA model with treatment group being the main factor, randomization stratification and baseline value as the covariate. The SAS MIANALYZE procedure will then be used to generate valid statistical inferences by combining results from the 40 analyses.

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

Last observation carried forward (LOCF) method and worst observation carried forward (WOCF) will be employed as additional sensitivity analyses for continuous secondary efficacy endpoints that are measured repeatedly over time during the 28 to 40-week treatment period.

Percent change from baseline to visit 16 in peanut-specific IgE will be analyzed using rank-based ANCOVA with treatment as the main effect, stratification variables and baseline peanut-specific IgE level as covariates. The missing data will be imputed using MI method above. Last observation carried forward (LOCF) method will be employed as sensitivity analysis.

Binary Endpoints at visit 16

Proportion of subjects who reach 300 mg/day dose of AR101 by visit 16 will be analyzed using the Cochran-Mantel-Haenszel test adjusted by randomization stratification factors to assess the treatment difference in the proportion of subjects who reach the 300 mg/day dose of AR101 in the FAS. The proportion of subjects who reach the 300 mg/day dose of AR101 and its 95% confidence interval will be calculated for each treatment group with Clopper-Pearson confidence limits. Estimate of treatment difference, p-value, and the 2-sided 95% confidence interval using normal approximation will be provided.

Time-to-event Endpoint at visit 16

Time from randomization to the first time when subjects reach 300 mg/day dose of AR101 during the 28 to 40-week treatment period will be analyzed using the Cox proportional hazards model including treatment and randomization strata as factors. The hazards ratio, its 95% confidence interval and p-value will be reported. The Kaplan-Meier plots will be provided.

Continuous Endpoints at visit 22 and visit 25

Change in cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline to visit 22 in subjects (continuously) treated with dupilumab plus AR101 vs placebo plus AR101, and change in cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline to visit 22 in subjects (previously) treated with dupilumab plus AR101 (and re-randomized to placebo plus AR101) vs placebo plus AR101, will be assessed in a similar fashion as in visit 16 including missing data imputation and sensitivity analysis.

Percent change from baseline to visit 22 and visit 25 in peanut-specific IgE in subjects continuously treated with dupilumab + AR101 vs placebo + AR101 will be analyzed in a similar fashion as in visit 16.

Binary Endpoints at visit 22

Proportion of subjects (continuously) treated with dupilumab + AR101 vs placebo + AR10, and proportion of subjects (previously) treated with dupilumab + AR101 and re-randomized to placebo + AR101 vs placebo + AR101, who ‘pass’ a post-maintenance DBPCFC with 2044 mg cumulative peanut protein at visit 22 will be assessed the same way as for visit 16 including missing data imputation and sensitivity analysis.

5.6.3. Adjustment for Multiple Comparison

The overall Type-1 error rate of 0.05 (2-sided) will be controlled for the primary endpoint and the first secondary endpoint (i.e., change in the cumulative tolerated dose [log transformed] of peanut protein during a DBPCFC from baseline to visit 16) using a hierarchical testing procedure. Inferential conclusions about the first secondary endpoint require statistical significance at the 2-sided 0.05 significance level of the primary endpoint.

No formal hypothesis and adjustment for multiplicity will be undertaken for the maintenance phase.

5.6.4. Analysis of Exploratory Efficacy Variables

The analysis of other efficacy variables will be the same as the primary analysis described in Section 5.6.1 and Section 5.6.2 with the following exceptions. The analysis on biomarker variables will be specified in Section 5.11. The analysis on the proportion of days with allergy symptoms based on eDiary data will be specified in Section 5.12 .

5.6.5. Subgroup Analysis

Subgroup analysis for the primary endpoint and the following secondary endpoints will be performed on mFAS and FAS-maintenance. Subgroups have been defined in Section 3.6 .

- Change in cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline to visit 16 in subjects treated with dupilumab plus AR101 vs placebo plus AR101
- Proportion of subjects treated with dupilumab plus AR101 vs placebo plus AR101 who reach the 300 mg/day dose of AR101 by visit 16
- Proportion of subjects (continuously) treated with dupilumab plus AR101 vs placebo plus AR101 who “pass” a post maintenance DBPCFC with 2044 mg (cumulative) peanut protein at visit 22
- Change in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline to visit 22 in subjects (continuously) treated with dupilumab plus AR101 vs placebo plus AR101
- Proportion of subject (previously) treated with dupilumab plus AR101 (and re-randomized to placebo plus AR101) vs placebo plus AR101 who “pass” a post maintenance DBPCFC with 2044 mg (cumulative) peanut protein at visit 22
- Change in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline to visit 22 in subjects (previously) treated with dupilumab plus AR101 (and re-randomized to placebo plus AR101) vs placebo plus AR101

The analysis method for the subgroup will be the same as the primary analysis described in Section 5.6.1 and Section 5.6.2. Interactions between the subgroups and treatment groups will be tested using the logistic regression model for the binary endpoints and using the ANCOVA model for the continuous endpoints. The model will include randomization strata, treatment group, subgroup, treatment by randomization strata interaction and treatment by subgroup interaction as factors. P-values for interaction term will be reported.

Forest plots of above efficacy endpoints across subgroups will be generated.

5.7. Analysis of Safety Data

The analysis of safety and tolerability will be performed on the SAF and SAF-maintenance for each study period, as defined in Section 3.3.

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

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

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

The summary of safety results will be presented for each study period by treatment received in the corresponding period. For safety variables/summaries involving baseline values, e.g., absolute change from baseline or shift table, study period specific baselines will be used. Summaries for pre-dosing period and up-dosing period will use the study baseline (i.e., the latest available valid measurement prior to the first dose of study drug in the study). Summaries for maintenance period and follow-up period will use study baseline and visit 16 baseline (i.e., the last available valid measurement prior to the first dose of study drug in the maintenance period), respectively.

5.7.1. Adverse Events

The number and proportion of subjects reporting TEAEs will be summarized for pre-dosing period, up-dosing period, maintenance period and follow-up period separately, as described in Section 3.3.

AE incidence tables will be presented by treatment group for the SAF and SAF-maintenance as well as subgroups. Summary of TEAEs will present the number (n) and percentage (%) of subjects experiencing an TEAE by SOC, and PT, sorted by decreasing frequency of SOC and PT for the dupilumab treatment group in the pre-dosing period, dupilumab plus AR101 treatment group in the up-dosing period, and continuously on dupilumab plus AR101 treatment group in the maintenance period. Multiple occurrences of AEs of the same PT (or SOC) in the same subject will be counted only once for that PT (or SOC). For AE tables presenting severity, the worst severity will be chosen for subjects with multiple instances of the same event. The denominator for computation of percentage is the number of subjects in each treatment group for the corresponding analysis period as specified in Section 3.3.

An overall summary of TEAEs will be provided with number and proportions of subjects with any:

- TEAE
- Serious TEAE
- TEAE of special interest (AESI)

- TEAE/Serious TEAE leading to death
- TEAE/Serious TEAE leading to permanent treatment discontinuation
- TEAE/Serious TEAE of injection site reaction
- Study drug related TEAE/serious TEAE

Detailed summaries of TEAEs will include:

- TEAEs
  - TEAEs by SOC/PT
  - TEAEs by SOC/HLT/PT
  - TEAEs by PT
  - TEAEs by SOC/PT with incidence of PT ≥5% in any treatment group
  - TEAEs by severity and by SOC/PT
  - Severe TEAEs by SOC/PT
  - TEAEs related to dupilumab/placebo as assessed by the investigator by SOC/PT
  - TEAEs related to AR101 as assessed by the investigator by SOC/PT
  - Severe TEAEs related to dupilumab/placebo as assessed by the investigator by SOC/PT
  - Severe TEAEs related to AR101 as assessed by the investigator by SOC/PT
  - TEAE of special interest
- Serious TEAEs:
  - Serious TEAEs by SOC/PT
  - Serious TEAEs related to dupilumab/placebo as assessed by the investigator by SOC/PT
  - Serious TEAEs related to AR101 as assessed by the investigator by SOC/PT
- TEAEs leading to permanent discontinuation of study treatment by SOC/PT
- Death by SOC/PT

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

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

- Subject ID
- Treatment group
- Study phase

- Age/sex/race
- System Organ Class (SOC)
- High Level Term (HLT)
- Preferred Term (PT)
- Verbatim Term
- AE start date and end date/ongoing (including both calendar days and study days)
- AE duration
- Relationship of AE to dupilumab/placebo: unrelated or related
- Relationship of AE to AR101: unrelated or related
- Action taken with dupilumab/placebo: Dose not changed, Drug interrupted, Drug withdrawn, Not applicable, or Unknown
- Action taken with AR101: Dose not changed, Dose reduced, Drug interrupted, Drug withdrawn, Not applicable, or Unknown
- Severity: mild, moderate, or severe
- Outcome: Fatal, Not recovered/not resolved, Recovered/resolved, Recovered/resolved with sequelae, Recovering/resolving, or Unknown.
- Impact by COVID-19 pandemic: Yes or No

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

5.7.2. Analysis of Adverse Events of Special Interest

The adverse events of special interest (AESI) for dupilumab and AR101 will be summarized by AESI category (see Section 10.4) and HLT/PT, respectively.

The time to first AESIs (TEAE by category) or TEAE leading to permanent treatment discontinuation will be assessed by Kaplan-Meier estimates. Kaplan-Meier plots will be provided. In order to detect any safety signals, the hazard ratio (HR) will be provided together with the corresponding 95% confidence interval (CI) for the selected adverse events. Hazard ratios will be calculated using a Cox model including factors of treatment group, and randomization strata. The time is defined as the date of first event – the date of first dose + 1. Subjects without an event will be censored at the end of each study period. Graphs of cumulative incidence rate over time will be presented by treatment group.

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

5.7.3. Clinical Laboratory Measurements

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

- Descriptive statistics of laboratory result and change from baseline by visit
- The number (n) and percentage (%) of subjects with treatment-emergent PCSVs. This summary will be provided based on all subjects in the SAF as well as in the subgroup of SAF subjects who did not meet the PCSV criterion at baseline
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listing of all laboratory parameters normal range, abnormal flag, treatment-emergent PCSV by subject, visit and the status of impact by COVID-19 pandemic will be provided.

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

5.7.4. Analysis of Vital Signs

Summaries of vital sign variables excluding post-dose measurements at AR101 up-dosing visit and measurements at DBPCFCs will include:

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

Summaries of vital sign variables at DBPCFCs of peanut protein will include:

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

Listings of vital sign will be provided with flags indicating the treatment-emergent PCSVs and the status of impact by COVID-19 pandemic.

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

5.7.5. Physical Exams

Shift tables based on baseline normal/abnormal status will be provided for assessments of each physical exam category and presented by visit.

5.7.6. Spirometry and Peak Expiratory Flow (PEF)

Summaries of spirometry and PEF variables at visits without DBPCFCs performed will include:

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

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

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

5.8. Analysis of Pharmacokinetic Data

The following analyses will be conducted:

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

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

5.9. Analysis of Immunogenicity Data

5.9.1. Analysis of ADA Data

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

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

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

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

5.9.2. Analysis of Neutralizing Antibodies (NAb) Data

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

5.10. Association of Immunogenicity with Exposure, Safety and Efficacy

5.10.1. Immunogenicity and Exposure

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

5.10.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

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

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

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

- ADA positive subjects, that is subjects with treatment-emergent or treatment-boosted response.

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

5.11. Analysis of Biomarker Data

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

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

For up-dosing period, exploratory analyses for the difference between dupilumab + AR101 group and placebo + AR101 group on the change from baseline and percent change from baseline values will be performed using a rank-based ANCOVA model with treatment group and randomization stratification factors as fixed factors, and the relevant baseline values as covariate. Missing value will be imputed by LOCF method using available post-baseline data for visits up to visit 16. P-value for difference between dupilumab +AR101 and placebo + AR101 will be provided.

For maintenance period, exploratory analyses for the difference between continuously on dupilumab + AR101 group and continuously on placebo + AR101 group on the change from baseline and percent change from baseline values will be performed using a rank-based ANCOVA model with treatment group and randomization stratification factors as fixed factors, and the relevant baseline values as covariate. Missing value will be imputed by LOCF method using available post-baseline data for visits up to visit 22. P-value for difference between continuously on dupilumab + AR101 and continuously on placebo + AR101 will be provided.

Correlation of baseline serum peanut sIgE, sIgG, sIgG4, total IgE, absolute change or percent change at visit 16, 22 and 25 from baseline in these biomarkers; baseline Ara h1 sIgE, Ara h1 sIgG4, Ara h2 sIgE, Ara h2 sIgG4, Ara h3 sIgE, Ara h3 sIgG4, absolute change or percent change at visit 16 in these biomarkers; baseline in basophil sensitivity to peanut allergen stimulation measured by EC50, frequency of peanut specific T-cell subsets (e.g. Th2A cells), and absolute change or percent change at visit 16 in these biomarkers with the following continuous clinical endpoints will be explored using the Spearman's rho test. Both Spearman correlation coefficients and p-value will be reported. The correlation between post-baseline biomarkers and clinical outcomes will only be evaluated at the same visit.

- Change in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline to visit 16 in subjects treated with dupilumab plus AR101 vs placebo plus AR101
- Change in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline to visit 22 in subjects (continuously) treated with dupilumab plus AR101 vs placebo plus AR101
- Change in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline to visit 25 in subjects (continuously) treated with dupilumab plus AR101 vs placebo plus AR101
- Change in the normalized wheal size of titrated skin prick test from baseline to visit 16 in subjects treated with dupilumab plus AR101 vs placebo plus AR101
- Change in the normalized wheal size of titrated skin prick test from baseline to visit 22 in subjects (continuously) treated with dupilumab plus AR101 vs placebo plus AR101
- Change in the normalized wheal size of titrated skin prick test from baseline to visit 25 in subjects (continuously) treated with dupilumab plus AR101 vs placebo plus AR101
- Change in the FeNO from baseline to visit 16 in subjects treated with dupilumab plus AR101 vs placebo plus AR101
- Change in the FeNO from baseline to visit 22 in subjects (continuously) treated with dupilumab plus AR101 vs placebo plus AR101
- Change in the FeNO from baseline to visit 25 in subjects (continuously) treated with dupilumab plus AR101 vs placebo plus AR101

Correlation of baseline serum peanut sIgE, sIgG, sIgG4, total IgE, basophil sensitivity to peanut allergen stimulation, and Th2A cell frequency with the following binary clinical endpoints will also be explored using logistic model. The model will include the responder/non-responder of below clinical endpoint as the dependent variable, with randomization stratification factors, treatment group, baseline biomarker value, and treatment by baseline biomarker interaction as the predictor variables. Model coefficients and P-value will be provided to indicate significance of the correlation/association.

- Subjects treated with dupilumab plus AR101 vs placebo plus AR101 who "pass" 2044 mg (cumulative) peanut protein at visit 16

- Subjects treated with dupilumab plus AR101 vs placebo plus AR101 who "pass" 1044 mg (cumulative) peanut protein at visit 16
- Subjects treated with dupilumab plus AR101 vs placebo plus AR101 who "pass" 444 mg (cumulative) peanut protein at visit 16

5.12. Analysis of Daily Allergy Symptom Diary Data

The daily allergy symptom diary analyses during up-dosing period will be performed on the mFAS and FAS using all observed data, respectively.

The continuous variables of the proportion of days with one or more allergy symptoms and with one or more severe allergy symptoms will be analyzed descriptively by treatment group during up-dosing period, separately. Similarly, the proportion of days with one or more allergy symptoms will be summarized descriptively for each symptom category defined in Section 4.5.3 .

5.13. Analysis of Pediatric Eosinophilic Esophagitis Symptom Score

Listings of pediatric eosinophilic esophagitis symptom scores from parent report age 2-18 years and self-report age 8-18 years will be provided, respectively.

6. DATA CONVENTIONS

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

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the study baseline assessment for all measurements will be the latest available valid measurement taken prior to the first administration of study drug. If any randomized subjects are not treated, the baseline will be the last value on or prior to the randomization. In addition, maintenance period baseline is defined as the last available valid measurement taken prior to the first administration of dupilumab/placebo during the maintenance period.

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

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

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

6.2. General Data Handling Conventions

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

6.3. Data Handling Convention for Missing Data

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

Adverse event

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

Adverse event start date

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

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

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

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

Adverse event end date

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

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

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

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

Prior or concomitant medication

Medication start and end date missing

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

Prior medication start date

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

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

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

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

Prior medication end date

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

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

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

Concomitant medication start date

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

Concomitant medication end date

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

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

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

Medication coding

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

PCSV

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

6.4. Visit Windows

Data analyzed by-visit-analysis (including efficacy, laboratory data, vital sign and spirometry/PEF) will be summarized by the study scheduled visits described in the study protocol and SAP, "Schedule of Event". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits and early termination (ET) visit have the potential to be summarized.

No analysis visit windows will be applied for the study scheduled visits.

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

Visit	Target Day (TD)	Analysis Time Window Based on Study Day[a]
Screening 1	-113 to -17	-113 to -17
Screening 1a	-57 to -15	-57 to -15
Baseline	1	1
Visit 3 (Week 2)	15	[2, 22]
Visit 4 (Week 4)	29	[23, 36]
Visit 5 (Week 6)	43	[37, 50]
Visit 6 (Week 8)	57	[51, 64]
Visit 7 (Week 10)	71	[65, 78]
Visit 8 (Week 12)	85	[79, 92]
Visit 9 (Week 14)	99	[93, 106]
Visit 10 (Week 16)	113	[107, 120]
Visit 11 (Week 18)	127	[121, 134]
Visit 12 (Week 20)	141	[135, 148]
Visit 13 (Week 22)	155	[149, 162]
Visit 14 (Week 24)	169	[163, 176]
Visit 15 (Week 26)	183	[177, 190]
Following visit 15a – 15f are optional visits[b] during up-dosing period		
Visit 15a (Week 28)	197	[191, 204]
Visit 15b (Week 30)	211	[205, 218]
Visit 15c (Week 32)	225	[219, 232]
Visit 15d (Week 34)	239	[233, 246]
Visit 15e (Week 36)	253	[247, 260]
Visit 15f (Week 38)	267	[261, 274]
Following windows only apply to subjects who entered double-blind maintenance period		
Visit 16 (Week 28 to 40)	Target Day (TD) at last visit during up-dosing period[c] + 14 days	[Visit 16 TD[d] - 8 days, Visit 16 TD + 30 days]
Visit 17 (V16 + 4 weeks)	Visit 16 TD + 28 days	[Visit 17 TD – 13 days, Visit 17 TD + 14 days]

Visit 18 (V16 + 8 weeks)	Visit 16 TD + 56 days	[Visit 18 TD – 13 days, Visit 18 TD + 14 days]
Visit 19 (V16 + 12 weeks)	Visit 16 TD + 84 days	[Visit 19 TD – 13 days, Visit 19 TD + 14 days]
Visit 20 (V16 + 16 weeks)	Visit 16 TD + 112 days	[Visit 20 TD – 13 days, Visit 20 TD + 14 days]
Visit 21 (V16 + 20 weeks)	Visit 16 TD + 140 days	[Visit 21 TD – 13 days, Visit 21 TD + 14 days]
Visit 22 (Week 52 to 64, V16 + 24 weeks)	Visit 16 TD + 168 days	[Visit 22 TD – 13 days, Visit 22 TD + 14 days]
Following windows apply to subjects who entered follow-up period		
Visit 23 (V16 + 28 weeks)	Target Day (TD) at last visit in pre-dosing/up-dosing/maintenance period [e] + 28 days	[Visit 23 TD – 13 days, Visit 23 TD + 14 days]
Visit 24 (V16 + 32 weeks)	Target Day (TD) at last visit in pre-dosing/up-dosing/maintenance period + 56 days	[Visit 24 TD – 13 days, Visit 24 TD + 14 days]
Visit 25 (Week 64 to 76, V16 + 36 weeks)	Target Day (TD) at last visit in pre-dosing/up-dosing/maintenance period + 84 days	≥ Visit 24 TD + 14 days

[a] Study day is calculated relative to the date of first study drug injection.
[b] Visit 15a – 15f are optional visits in order to reach 300 mg/day AR101 for at least two weeks. Subjects may reach 300 mg/day AR101 for at least two weeks at any of the optional visits.
[c] The last visit during up-dosing period could be any of visit 15, 15a, 15b, 15c, 15d, 15e, or 15f.
[d] Visit 16 target day (TD) is defined as target day at last visit during up-dosing period + 14 days.
[e] The target day at last visit in pre-dosing/up-dosing/maintenance period could be any of the following visit: 1) visit 15 during up-dosing period; 2) ET visit during up-dosing period; 3) visit 22 during maintenance period; 4) ET visit during maintenance period.

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

4. Scheduled visit
5. ET or end of study (EOS), whichever comes first if scheduled visit not available
6. Unscheduled visit if both scheduled visit and ET/EOT/EOS are not available

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

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

7. INTERIM ANALYSIS

No interim analysis is planned.

An unblinded primary analysis will be performed once all subjects in the study have completed the 28 to 40-week treatment period (visit 16 or earlier for those subjects who are withdrawn prematurely from the study). If performed, the primary analysis will be considered the final analysis for the primary endpoint and secondary efficacy endpoints up to visit 16.

8. SOFTWARE

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

9. REFERENCES

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10. APPENDIX

10.1. Summary of Statistical Analyses

Efficacy Analysis:

Endpoints	Analysis Population	Primary Statistical Method	Supportive/Sensitivity Statistical Method	Subgroup Analysis	Other Analyses
Primary Endpoint					
Proportion of subjects treated with dupilumab plus AR101 vs placebo plus AR101 who "pass" a post up-dosing DBPCFC with 2044 mg (cumulative) peanut protein at visit 16	mFAS, FAS	Cochran-Mantel-Haenszel test/ MI for missing due to COVID-19, otherwise missing data as non-responder	Cochran-Mantel-Haenszel test with available visit 16 DBPCFC data	Yes	Bar chart
Secondary Endpoint					
Change in cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline to visit 16	mFAS, FAS	ANCOVA model/ MI for missing due to COVID-19, otherwise missing data imputed by BOCF method	ANCOVA model with available visit 16 DBPCFC data; MI method; van Elteren test with LOCF method/with available visit 16 DBPCFC data for change in cumulative tolerated dose	Yes	Bar chart
Proportion of subjects treated with dupilumab plus AR101 vs placebo plus AR101 who reach 300 mg/day dose of AR101 by visit 16	mFAS, FAS	Cochran-Mantel-Haenszel test	No	Yes	Bar chart
Time from randomization to the first-time subjects reach the 300 mg/day dose of AR101 during up-dosing treatment phase (up to visit 16)	mFAS, FAS	Kaplan-Meier estimates; Cox regression model	No	No	Kaplan-Meier plot

Endpoints	Analysis Population	Primary Statistical Method	Supportive/Sensitivity Statistical Method	Subgroup Analysis	Other Analyses
Proportion of subjects (continuously) treated with dupilumab plus AR101 vs placebo plus AR101 who 'pass' a DBPCFC with 2044 mg (cumulative) peanut protein at visit 22	FAS-maintenance	Cochran-Mantel-Haenszel test/ MI for missing due to COVID-19, otherwise missing data as non-responder	Cochran-Mantel-Haenszel test with available visit 22 DBPCFC data	Yes	Bar chart
Change in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline to visit 22 in subjects (continuously) treated with dupilumab plus AR101 vs placebo plus AR101	FAS-maintenance	ANCOVA model/ MI for missing due to COVID-19, otherwise missing data imputed by BOCF method	ANCOVA model with available visit 22 DBPCFC data; MI method; van Elteren test with LOCF method/with available visit 22 DBPCFC data	Yes	Line plot
Proportion of subjects (previously) treated with dupilumab plus AR101 vs placebo plus AR101 who 'pass' a DBPCFC with 2044 mg (cumulative) peanut protein at visit 22	FAS-maintenance	Cochran-Mantel-Haenszel test/ MI for missing due to COVID-19, otherwise missing data as non-responder	Cochran-Mantel-Haenszel test with available visit 22 DBPCFC data	Yes	Bar chart
Change in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline to visit 22 in subjects (previously) treated with dupilumab plus AR101 vs placebo plus AR101	FAS-maintenance	ANCOVA model/ MI for missing due to COVID-19, otherwise missing data imputed by BOCF method	ANCOVA model with available visit 22 DBPCFC data; MI method; van Elteren test with LOCF method/with available visit 22 DBPCFC data	Yes	Line plot
Percent change from baseline to visit 16 in peanut-specific IgE in subjects treated with dupilumab plus AR101 vs subjects treated with placebo plus AR101	mFAS, FAS	Rank-based ANCOVA model, missing data imputed by MI method	ANCOVA model with LOCF method	No	Line plot
Percent change from baseline to visit 22 in peanut-specific IgE in subjects (continuously) treated with dupilumab plus AR101 vs subjects treated with placebo plus AR101	FAS-maintenance	Rank-based ANCOVA model, missing data imputed by MI method	ANCOVA model with LOCF method	No	Line plot

Endpoints	Analysis Population	Primary Statistical Method	Supportive/Sensitivity Statistical Method	Subgroup Analysis	Other Analyses
Percent change from baseline to visit 25 in peanut-specific IgE in subjects (continuously) treated with dupilumab plus AR101 vs subjects treated with placebo plus AR101	FAS-maintenance	Rank-based ANCOVA model, missing data imputed by MI method	ANCOVA model with LOCF method	No	Line plot

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse events	SAF, SAF-maintenance	Descriptive statistics	No	Yes, for selected AE summary	No
Laboratory measures	SAF, SAF-maintenance	Descriptive statistics	No	No	No
Vital sign	SAF, SAF-maintenance	Descriptive statistics	No	No	No
Spirometry	SAF, SAF-maintenance	Descriptive statistics	No	No	No
Daily allergy symptom diary during up-dosing period	mFAS, FAS	Descriptive statistics	No	No	No

10.2. Schedule of Time and Events

Table 2: Schedule of Events – Screening, Baseline, Double-Blind Treatment Period

Study Procedure	**Screening**		**Baseline**	**Double-Blind Treatment Period**												
			Study Drug Pretreatment		**Study Drug Concomitant Treatment AR101 Up-Dosing**											
Visit (V)	**V1**[12]	**V1a**[13]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week (W)[14]	**-113**	**before**	**D1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**
Day (D)[14]	**to -17**	**-15**	1	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**
Visit Window (d)				±3d	±3d	±3d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d
Screening/Baseline:																
Informed Consent/Assent	X															
ICF for optional assessments	X															
Inclusion/Exclusion	X		X													
Medical History/ Demographics	X															
Randomization			X													
Training on Daily Allergy Symptom Diary					X											
Training on Study Drug Administration		X	X	X												
Treatment:																
Blinded Study Drug SC Q2W Administration[1]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject Study Drug Injection Log[1]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
AR101 Daily Administration[2]					X **IDED**	X	X	X	X	X	X	X	X	X	X	X
Daily subject AR101 Dosing Diary[2]					X	X	X	X	X	X	X	X	X	X	X	X
AR101 Dispensation/Account[3]					X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	**Screening**		**Baseline**	**Double-Blind Treatment Period**												
			Study Drug Pretreatment	**Study Drug Concomitant Treatment AR101 Up-Dosing**												
Visit (V)	**V1**[12]	**V1a**[13]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week (W)[14]	**-113 to -17**	**before -15**	**D1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**
Day (D)[14]			1	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**
Visit Window (d)				±3d	±3d	±3d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d
Epinephrine Autoinjector Training		X	X	X	X											
Con Meds/Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy[4]**:**																
DBPCFC[5]		X														
Peanut Skin Prick Test (SPT)[6]	X															
Peanut SPT titrated[6]			X		X											
EASI for AD, ACQ-5 asthma		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Daily Allergy Symptom Diary[7]					X	X	X	X	X	X	X	X	X	X	X	X
FAQL Questionnaire			X													
Safety[4]**:**																
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X															
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X														
Spirometry/Peak Flow[9, 9.a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[4]**:**																
HIV ab, HBsAg, HBcAb, Hep C Ab	X															
Hematology, Chemistry	X		X		X				X				X			
FeNO Test[9, 9a]		X	X		X		X		X		X		X		X	
Urinalysis	X		X		X				X			X	X	X		X

Study Procedure	**Screening**		**Baseline**	**Double-Blind Treatment Period**												
			Study Drug Pretreatment	**Study Drug Concomitant Treatment AR101 Up-Dosing**												
Visit (V)	**V1**[12]	**V1a**[13]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week (W)[14]	**-113 to -17**	**before -15**	**D1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**
Day (D)[14]			1	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**
Visit Window (d)				±3d	±3d	±3d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d
Pregnancy Test (WOCBP only)	S		U	U	U	U	U	U	U	U	U	U	U	U	U	U
Total IgE	X		X		X				X				X			
sIgE, sIgG4, sIgG Against Peanut Extract and Peanut Allergen Components	X		X		X				X				X			
Future Biomedical Research Sample (Optional)			X		X				X				X		X	
Optional blood samples for additional exploratory research (eg, TruCulture, Basophil sensitivity, PBMC, allergen-specific T-cell profiling)[10]			X		X											
DNA sample (Optional)[11]			X													
PK/Drug Concentration and ADA Samples[4]:																
Functional dupilumab PK sample			X	X			X		X		X		X		X	
Anti-dupilumab antibody sample			X								X					

Abbreviations: S, serum; U, urine; FAQL, Food Allergy Quality of Life; FeNO, fractional exhaled nitric oxide; WOCBP, women of child bearing potential; PBMC, peripheral blood mononuclear cell; PK, pharmacokinetic

Study Procedure	**Double-Blind Treatment Period**					
	Study Drug Concomitant Treatment AR101 Up-Dosing (if applicable)					
Visit (V)	**V15a**	**V15b**	**V15c**	**V15d**	**V15e**	**V15f**
Week (W)[14]	**W28**	**W30**	**W32**	**W34**	**W36**	**W38**
Day (D)[14]	**197**	**211**	**225**	**239**	**253**	**267**
Visit Window (d)	±2d	±2d	±2d	±2d	±2d	±2d
Screening/Baseline:						
Informed Consent/Assent						
ICF for optional assessments						
Inclusion/Exclusion						
Medical History/ Demographics						
Randomization						
Training on Daily Allergy Symptom Diary						
Training on Study Drug Administration						
Treatment:						
Blinded Study Drug SC Q2W Administration[1, 15]	X	X	X	X	X	X
Subject Study Drug Injection Log[1]	X	X	X	X	X	X
AR101 Daily Administration[2]	X	X	X	X	X	X
Daily subject AR101 Dosing Diary[2]	X	X	X	X	X	X
AR101 Dispensation/Account[3]	X	X	X	X	X	X
Epinephrine Autoinjector Training						
Con Meds/Procedures	X	X	X	X	X	X
Efficacy[4]**:**						
DBPCFC[5]						
Peanut Skin Prick Test (SPT)[6]						
Peanut SPT titrated[6]						
EASI for AD, ACQ-5 asthma	X	X	X	X	X	X
Daily Allergy Symptom Diary[7]	X	X	X	X	X	X
FAQL Questionnaire						
Safety[4]**:**						

Study Procedure	**Double-Blind Treatment Period**					
	Study Drug Concomitant Treatment AR101 Up-Dosing (if applicable)					
Visit (V)	**V15a**	**V15b**	**V15c**	**V15d**	**V15e**	**V15f**
Week (W)[14]	**W28**	**W30**	**W32**	**W34**	**W36**	**W38**
Day (D)[14]	**197**	**211**	**225**	**239**	**253**	**267**
Visit Window (d)	±2d	±2d	±2d	±2d	±2d	±2d
Weight	X	X	X	X	X	X
Height						
Vital Signs[8]	X	X	X	X	X	X
Physical Examination						
Spirometry/Peak Flow[9, 9a]	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X
Laboratory Testing[4]:						
HIV ab, HBsAg, HBcAb, Hep C Ab						
Hematology, Chemistry	X				X	
FeNO Test[9,9a]	X		X		X	
Urinalysis	X			X	X	X
Pregnancy Test (WOCBP only)	U	U	U	U	U	U
Total IgE	X				X	
sIgE, sIgG4, sIgG Against Peanut Extract and Peanut Allergen Components	X				X	
Future Biomedical Research Sample (Optional)	X				X	
Optional blood samples for additional exploratory research (eg, TruCulture, Basophil sensitivity, PBMC, allergen-specific T-cell profiling)[10]						
DNA sample (Optional)[11]						
Functional dupilumab PK sample		X		X		X
Anti-dupilumab antibody sample						

Abbreviations: S, serum; U, urine; FAQL, Food Allergy Quality of Life; FeNO, fractional exhaled nitric oxide; WOCBP, women of child bearing potential; PBMC, peripheral blood mononuclear cell; PK, pharmacokinetic

Table 3: Schedule of Events – Maintenance Period and Follow-Up Period

Study Procedure	**Maintenance Period**[12]							**Post-Treatment Follow-up Period**			**Unscheduled Visit** (if applicable)	**ET Visit** (if applicable)
								Study drug and AR101 Withdrawal				
Visit (V)	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25 EOS**		
Week (W)[13]	**W28 - 40**	**V16+ 4wk**	**V16+ 8wk**	**V16+ 12wk**	**V16+ 16wk**	**V16+ 20wk**	**W52 - 64, Vtar16 + 24wk**	**V16+ 28 wk**	**V16+ 32wk**	**W64 – 76, V16 + 36wk**		
Visit Window (d)	-7/+30 d[14]	±3d	±3d	±3d	±3d	±3d	-7/+30 d[14]	±3d	±3d	-7/+30 d[14]		
Treatment:												
Blinded Study Drug Q2W SC Administration [1]	X	X	X	X	X	X					X[15]	
Subject Study Drug Injection Log[1]	X	X	X	X	X	X						
AR101 Daily Administration[2]	X	X	X	X	X	X						
Daily Subject AR101 Dosing Diary [2]	X	X	X	X	X	X	X					
AR101 Dispensation/Account[3]	X	X	X	X	X	X	X					X
Concomitant medications/Procedures	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[4]												
DBPCFC[5, 14]	X						X			X		
Peanut SPT titrated[6]	X						X			X		X
EASI for AD, ACQ-5 for asthma	X	X	X	X	X	X	X	X	X	X		X
Daily Allergy Symptom Diary[7]	X	X	X	X	X	X	X				X	X
FAQL Questionnaire	X						X			X		
Safety: [4]												
Weight	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X						X			X		X
Spirometry/Peak Flow[9,9a]	X			X			X			X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
PEESS Questionnaire[10]											X	X
Laboratory Testing: [4]												
HIV ab, HBsAg, HBcAb, Hep C Ab												
Hematology, Chemistry	X			X			X			X		X
FeNO Test[9, 9a]	X			X			X			X		X

Urinalysis	X			X			X			X		X
Pregnancy Test (WOCBP only)	U	U	U	U	U	U	U			S		U

Study Procedure	**Maintenance Period**							**Post-Treatment Follow-up Period**			**Unscheduled Visit** (if applicable)	**ET Visit** (if applicable)
								Study drug and AR101 Withdrawal				
Visit (V)	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25 EOS**		
Week (W)[13]	**W28 - 40**	**V16+ 4wk**	**V16+ 8wk**	**V16+ 12wk**	**V16+ 16wk**	**V16+ 20wk**	**W52 - 64, V16+ 24wk**	**V16 + 28 wk**	**V16+ 32wk**	**W64 – 76, V16 + 36wk**		
Visit Window (d)	-7/+30 d[14]	±3d	±3d	±3d	±3d	±3d	-7/+30 d[14]	±3d	±3d	-7/+30 d[14]		
Total IgE	X			X			X			X		X
sIgE, sIgG4, sIgG Against Peanut Extract and Peanut Allergen Components	X			X			X			X		X
Future Biomedical Research sample (Optional)	X			X			X			X		X
Optional blood samples for additional exploratory research (eg, TruCulture, Basophil sensitivity, PBMC)[11]	X						X			X		X
PK/Drug Concentration and ADA Samples:[4]												
Functional dupilumab PK sample	X	X	X	X	X		X			X	X	X
Anti-dupilumab antibody sample	X			X			X			X	X	X

Abbreviations: EOS = End of study; ET = Early termination; WOCBP = Women of child bearing potential

Footnotes for the Schedule of Events Table 2

1. The subject/legal guardian will administer SC study drug as scheduled on dosing days. Subject/legal guardian will complete an injection log (e-diary) to document compliance with injection of study drug. On days when both dupilumab/placebo study drug and AR101 are administered, the study drug will be administered at least 8 hours apart from the AR101 and at least 24 hours after the start of in-clinic dosing.

2. The subject/legal guardian will administer AR101 during the days in which no in-clinic visit is scheduled. Subject/legal guardian will complete a dosing diary to document compliance with AR101. On the day following in-clinic up-dosing, the site is to make telephone contact to inquire if any AEs occurred and report appropriately.
3. Starting at visit 4 (week 4), AR101 will be dispensed at the site to the subject/caregiver for the doses that will be administered before the next clinic visit.
4. Assessments will be performed before the administration of study drug.
5. Subject will be observed for a minimum of 2 hours after the final administered dose and discharged only when deemed clinically stable by a study doctor. On the day following a food challenge, the site must make telephone contact to inquire if the subject experienced any AEs and report appropriately. Before each challenge, the subject will have a physical assessment performed by a trained physician's assistant, registered nurse, nurse practitioner, and/or physician of the study team who is blinded to the testing material. Eczema Area and Severity Index and ACQ only needed be completed once during day 1 of the food challenge.
6. Subjects should not take anti-histamines for at least 5 days prior to the SPT.
7. Site should confirm subject compliance at each clinic visit.
8. During DBPCFC, vital signs will be collected every 15 to 30 minutes. During maintenance phase for in-clinic office visits, the post-dose observation may be shortened to 30 minutes.
9. Spirometry will be performed in-clinic on the same day whenever FeNO measurement is scheduled; however, spirometry will also be performed at other visits when FeNO is not collected. FeNO should be done prior to spirometry. If the DBPCFC is scheduled on the day of the visit, then both FeNO measurement and spirometry will be performed twice before the subject goes home: once before DBPCFC, once after DBPCFC.
    a. During the COVID-19 pandemic, measurements of FeNO no longer need to be completed while on study (although FeNO is still required at screening). Additionally, if spirometry cannot be completed after enrollment, peak flow may be performed instead at the discretion of the investigator (although spirometry is still required at screening).
10. On the day of the DBPCFCs, blood draws for optional exploratory research-will be performed before the DBPCFC is performed. For the day 1 exploratory research sample, the last DBPCFC must be ≥15 days before to ensure washout of peanut allergen.
11. One optional DNA sample for the genomics analyses (buccal swab) can be collected on day 1 (visit 2) or any other visit.
12. Must complete all visit 1 assessments and confirm eligibility before visit 1a.
13. Visit 1a must occur at least 15 days before visit 2 to allow a 2-week washout after the peanut screening DBPCFC.

14. The time points listed in this table correspond with the bi-weekly up-dosing schedule. These time points may no longer be accurate following adjustments to the planned up-dosing period. As of Amendment 3, the up-dosing period has been permitted to be extended to accommodate COVID-19 restrictions of in-clinic visits, as well as dose reductions and re-escalation, if necessary. This extension permits a maximum up-dosing period of 40 weeks, while 28 weeks is ideal (consisting of 4 weeks pretreatment, 22 to 34 weeks of up-dosing, and at least 2 weeks at the maximum dose.)
15. Study drug administration at unscheduled and/or optional visits 15a-f is to be documented in the unscheduled visits folder.

Footnotes for the Schedule of Events Table 3

1. The subject/legal guardian will administer SC study drug as scheduled on dosing days. Subject/ legal guardian will complete an injection log (e-diary) to document compliance with injection of study drug. On days when both dupilumab/placebo study drug and AR101 are administered, the study drug will be administered at least 8 hours apart from the AR101 and at least 24 hours after the start of in-clinic dosing. Both days of the post up-dosing DBPCFC at visit 16 should be completed before starting the visit 16 SC study drug as part of the maintenance phase.
2. The subject/legal guardian will administer AR101 during the days in which no clinic visit is scheduled. Subject/caregiver will complete a dosing diary to document compliance with AR101.
3. Starting at visit 4 (week 4), AR101 that is dispensed at the site to the subject/legal guardian will be accounted for.
4. Assessments will be performed before the administration of study drug.
5. 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 SC study drug. Subject 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. On the day following a food challenge, the site must make a telephone contact to inquire if the subject experienced any AEs and report appropriately. Before each challenge, the subject will have a physical assessment performed by a trained physician's assistant, registered nurse, nurse practitioner, and/or physician of the study team who is blinded to the testing material. Eczema Area and Severity Index and ACQ only needed be completed once during day 1 of the food challenge.
6. Subjects should not take anti-histamines for at least 5 days prior to the SPT.
7. Site should confirm subject compliance at each clinic visit.
8. During DBPCFC, vital signs will be collected every 15 to 30 minutes.

9. Spirometry will be performed in-clinic on the same day whenever FeNO measurement is scheduled; however, spirometry will also be performed at other visits when FeNO is not collected. FeNO should be done prior to spirometry. If the DBPCFC is scheduled on the day of the visit, then both FeNO measurement and spirometry will be performed twice before the subject goes home: once before DBPCFC, once after DBPCFC.
    a. During the COVID-19 pandemic, measurements of FeNO no longer need to be completed while on study (although FeNO is still required at screening). Additionally, if spirometry cannot be completed after enrollment, peak flow may be performed instead at the discretion of the investigator (although spirometry is still required at screening).
10. Only for patients who discontinue for GI AEs. If applicable, after week 64 PEESS will be collected by phone.
11. On the day of the DBPCFCs, blood draws for optional exploratory research-will be performed before the DBPCFC is performed.
12. Clinic visits are monthly. However, SC study drug administration is Q2W and dosing diaries for AR101 and allergic symptoms are done daily.
13. The time points listed in this table correspond with the bi-weekly up-dosing schedule. These time points may no longer be accurate following adjustments to the planned up-dosing period. As of Amendment 3, the up-dosing period has been permitted to be extended to accommodate COVID-19 restrictions of in-clinic visits, as well as dose reductions and re-escalation, if necessary. This extension permits a maximum up-dosing period of 40 weeks, while 28 weeks is ideal (consisting of 4 weeks pretreatment, 22 to 34 weeks of up-dosing, and at least 2 weeks at the maximum dose.)
14. If subjects are not able to go into the clinic for the DBPCFC within the target time frame, the DBPCFC can be started up to 7 days before and 30 days after the target date for visit 22 and/or visit 25.
15. Study drug administration at unscheduled and/or optional visits 15a-f is to be documented in the unscheduled visits folder.

10.3. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	Treatment Emergent PCSV	Comments
Clinical Chemistry		
Alanine Aminotransferase (ALT)	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently.
Aspartate Aminotransferase (AST)	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently.
Alkaline Phosphatase (ALP)	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.
Bilirubin (BILI)	>1.3 ULN and baseline ≤ 1.3 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Based on normal range: <1 mg/dL, CF = mg x 1.7 = µmol Concept paper on DILI – FDA draft Guidance Oct 2007. Based on normal ranges: <6 mg/dL (Term 0-1 day), <8 mg/dL (Term 1-2 days), <12 mg/dL (Term 3-5 days), <1 mg/dL (Term >5 days)
Conjugated Bilirubin	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin ≥1.3 ULN) and (Direct Bilirubin ≤35% Total Bilirubin or Total Bilirubin ≤1.3 ULN) at baseline	Conjugated bilirubin will be measured when the total Bilirubin is above the ULN Based on normal range: 0 to 0.4 mg/dL
(ALT or AST) and Bilirubin (BILI)	((ALT > 3 ULN or AST >3 ULN)) and BILI >2 ULN) and baseline ((ALT ≤3 ULN or AST ≤3 ULN) or BILI ≤2 ULN)	Concept paper on DILI – FDA draft Guidance Oct 2007.
Creatine Kinase (CK)	>5 ULN and baseline ≤5 ULN >10 ULN and baseline ≤10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative.

Creatinine (CREAT)	>=30% increase from individual subject baseline >=60% increase from individual subject baseline	Benichou C., 1994. 2 independent criteria
Urate (URATE) Hyperuricemia Hypouricemia	>=30% increase from individual subject baseline >=60% increase from individual subject baseline	Harrison- Principles of internal Medicine 17th Ed., 2008. Two independent criteria
Urea Nitrogen (UREAN)	>=30% increase from individual subject baseline >=60% increase from individual subject baseline	
Chloride (CL) Hypochloremia Hyperchloremia	<80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	Two independent criteria
Sodium (SODIUM) Hyponatremia Hypernatremia	<129 mmol/L and baseline ≥129 mmol/L >150 mmol/L and baseline ≤ 150 mmol/L	Two independent criteria
Potassium (K) Hypokalemia Hyperkalemia	<3.5 mmol/L and baseline ≥ 3.5 mmol/L >5.0 mmol/L and baseline ≤ 5.0 mmol/L	FDA Feb 2005. Two independent criteria
Cholesterol (Cholesterol)	>6.20 mmol/L and ≤ 6.20 mmol/L at baseline	
Triglycerides (TRIG)	> 5.64 mmol/L and ≤ 5.64 mmol/L at baseline	Threshold for therapeutic intervention with pharmacotherapy in children. (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; 2011). CF = g x 1.14 = mmol
Glucose (GLUC) Hypoglycaemia Hyperglycaemia	≤ 2.7 mmol/L ≥10 mmol/L	
Albumin (ALB)	<25 g/L and ≥25 g/L at baseline	
Calcium (CA)	<2 mmol/L and baseline ≥2 mmol/L >2.9 mmol/L and baseline ≤2.9 mmol/L	

LDL Cholesterol (LDL)	>4.91 mmol/Land ≤4.91 mmol/L at baseline	Threshold for therapeutic intervention with pharmacotherapy in children (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; 2011).
Hematology		
Leukocytes (WBC)	<4.0 Giga/L and ≥4.0 Giga/L at baseline >13.5 Giga/L and ≤13.5 Giga/L at baseline	
Lymphocytes (LYM)	<0.6 Giga/L and ≥0.6 Giga/L at baseline >6.0 Giga/L and ≤6.0 Giga/L at baseline	
Neutrophils (NEUT)	<1.2 Giga/L and ≥1.2 Giga/L at baseline >ULN and baseline ≤ ULN	
Monocytes (MONO)	>1.2 Giga/L and ≤ 1.2 Giga/L at baseline	
Basophils (BASO)	>0.2 Giga/L	
Eosinophils (EOS)	(>0.5 Giga/L and >ULN) and (≤ 0.5 Giga/L or ≤ ULN at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin (HGB)	<100 g/L and ≥100 g/L at baseline or any decrease ≥ 20 g/L >200 g/L and ≤200 g/L at baseline	Two criteria are independent
Hematocrit (HCT)	<0.37 v/v and ≥ 0.37 v/v at baseline for Male; <0.33 v/v and ≥0.33 v/v at baseline for Female >0.52 v/v and ≤0.52 v/v at baseline for Male; >0.47 v/v and ≤0.47 v/v at baseline for Female	Two criteria are independent
Platelets (PLAT)	<100 Giga/L and ≥100 Giga/L at baseline >700 Giga/L and ≤700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria
Urinalysis		
pH (PH)	<5 or >7	
Ketones (KETONES) Ketonuria	Presence and absence at baseline	Semi-quantitative methods

Glucose (GLUC) Glycosuria	Presence and absence at baseline	Semi-quantitative methods
Erythrocytes (RBC) Microscopic Hematuria	> 5 RBCs/ HPF and ≤5 RBCs/ HPF at baseline	Semi-quantitative methods
Protein (PROT) Proteinuria	≥ 1+ and <1 at baseline	Semi-quantitative methods, ≥ 1+ means concentration ≥30 mg/dL
Vital Signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤90 mmHg and decrease from baseline ≥20mmHg ≥119 mmHg and increase from baseline ≥20 mmHg.	
DBP	≤54 mmHg and decrease from baseline ≥10 mmHg ≥78 mmHg and increase from baseline ≥10 mmHg	
Temperature	Rectal, Tympanic: >100.4 °F/38.0 °C Oral: >99.5 °F/37.5 °C Axillary or skink infrared (temporal): >37.2 °C	
Respiratory rate	< 12 per minute and ≥12 per minute at baseline >20 per minute and ≤20 per minute at baseline	
Weight	≥5 % weight loss from baseline ≥5 % weight gain from baseline	Based on identification of trends in the child's growth with a series of visits WHO Multicentre Reference Study Group, 2006; Center for Disease Control. Growth chart 2007.

10.4. Search Criteria for TEAE of Special Interest for Dupilumab

AESI	**Search Criteria**
Anaphylactic reactions	SMQ narrow "Anaphylactic Reactions"
Systemic or severe hypersensitivity reactions	Hypersensitivity: Narrow SMQ for hypersensitivity excluding preferred term equal to dermatitis atopic or eczema Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock

Helminthic infections[2]	-HLT = Cestode infections -HLT = Helminthic infections NEC -HLT = Nematode infections -HLT = Trematode infections
Any type of conjunctivitis or blepharitis (severe or serious)	Broad CMQ conjunctivitis (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Ocular hyperaemia, Conjunctival hyperaemia, Xerophthalmia) Blepharitis PTs (Blepharitis, blepharitis allergic) **AND** Serious AE= "Yes" OR Severity= "severe" Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock.
Keratitis	Any of the following PTs: a. Keratitis b. Allergic keratitis c. Ulcerative keratitis d. Atopic keratoconjunctivitis e. Herpes ophthalmic f. Ophthalmic herpes simplex Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock.

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

10.5. Search Criteria for TEAE of Special Interest for AR101

AESI	Search Criteria
Anaphylactic reactions	SMQ narrow "Anaphylactic reactions"
Gastrointestinal AEs resulting in prolonged disruption of dosing	Disruption of AR101 dosing ≥7 consecutive days AND Any PT under SOC "Gastrointestinal disorders"

10.6. Important Protocol Deviations

*Note: This is a preliminary list and the final list will be generated prior to database lock.

Category	Description of Protocol Deviation	Notes
Entered study even though entry criteria was not satisfied	Male or female Aged 6 to 17 years (inclusive)	
Entered study even though entry criteria was not satisfied	Subject has a clinical history of allergy to peanuts or peanut containing foods (symptom[s] of reaction due to exposure).	
Entered study even though entry criteria was not satisfied	Experience dose-limiting symptoms at or before the 100 mg challenge dose (<=144 mg cumulative) of peanut protein on screening DBPCFC and not experiencing dose-limiting symptoms to placebo or Missing	
Entered study even though entry criteria was not satisfied	Serum IgE to peanut of >=24 kUA/L and/or a SPT to peanut >=10 mm compared to a negative control or missing value (up to PA1)	
Entered study even though entry criteria was not satisfied	Subjects/legal guardians must be trained on the proper use of the epinephrine autoinjector device to be allowed to enroll in the study	
Entered study even though entry criteria was not satisfied	Subjects 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	
Entered study even though entry criteria was not satisfied	Willing and able to comply with all clinic visits and study-related procedures	
Entered study even though entry criteria was not satisfied	Written informed consent from parent/guardian for minor subjects	
Entered study even though entry criteria was not satisfied	Written assent from minor subjects as appropriate (e.g. above the age of 6 years or the applicable age per local regulatory requirements)	
Entered study even though entry criteria was not satisfied	Any previous exposure to marketed dupilumab or dupilumab in a clinical trial	
Entered study even though entry criteria was not satisfied	Member of the clinical site study team or his/her immediate family	
Entered study even though entry criteria was not satisfied	History of other chronic disease (other than asthma, AD, or allergic rhinitis) requiring therapy (eg, heart disease, diabetes, hypertension)	
Entered study even though entry criteria was not satisfied	History of frequent or recent severe, life-threatening episode of anaphylaxis or anaphylactic shock as defined by more than 3 episodes of anaphylaxis	
Entered study even though entry criteria was not satisfied	History of eosinophilic GI disease	
Entered study even though entry criteria was not satisfied	Current participation or participation within 6 months prior to screening in any other interventional study	

Category	Description of Protocol Deviation	Notes
Entered study even though entry criteria was not satisfied	Severe unstable asthma at time of enrollment with FEV1 <80% of predicted, ACQ >1.5 or missing value (Original protocol and accessed at visit 1)	
Entered study even though entry criteria was not satisfied	Use of systemic corticosteroids within 2 months prior to screening	
Entered study even though entry criteria was not satisfied	Use of omalizumab within 6 months prior to screening	
Entered study even though entry criteria was not satisfied	Use of other forms of allergen immunotherapy or immunomodulatory therapy within 3 months prior to screening	
Entered study even though entry criteria was not satisfied	Use of any agents known or likely to interact with epinephrine within 3 weeks prior to screening	
Entered study even though entry criteria was not satisfied	Allergy to oat (placebo in DBPCFC)	
Entered study even though entry criteria was not satisfied	Hypersensitivity to epinephrine and any of the excipients in the epinephrine product	
Entered study even though entry criteria was not satisfied	History of a mast cell disorder, including mastocytosis, urticarial pigmentosa, and hereditary or idiopathic angioedema	
Entered study even though entry criteria was not satisfied	Treatment with a live (attenuated) vaccine within 3 months prior to screening and during the study	
Entered study even though entry criteria was not satisfied	Active chronic or acute infection requiring systemic treatment with antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks prior to the baseline visit	
Entered study even though entry criteria was not satisfied	History of malignancy within 5 years before the screening visit	
Entered study even though entry criteria was not satisfied	Established diagnosis of a primary immunodeficiency disorder or secondary immunodeficiency	
Entered study even though entry criteria was not satisfied	Known history of human immunodeficiency virus (HIV) infection or HIV seropositivity at the screening visit	
Entered study even though entry criteria was not satisfied	With an established diagnosis of hepatitis B viral infection at the time of screening or is positive for hepatitis B surface antigen or hepatitis B core antibody at the time of screening	
Entered study even though entry criteria was not satisfied	Body weight <=17 kg or missing for screening V1	

Category	Description of Protocol Deviation	Notes
Entered study even though entry criteria was not satisfied	Pregnant or breastfeeding women, women planning to become pregnant or breastfeed during the study	
Entered study even though entry criteria was not satisfied	Girls at or beyond menarche who are not sexually abstinent and are unwilling to practice highly effective contraception	
Entered study even though entry criteria was not satisfied	Serum IgE to peanut of >=10 kUA/L and/or a SPT to peanut >=8 mm compared to a negative control (after PA2)	
Entered study even though entry criteria was not satisfied	Use of anti-histamines within 5 days prior to screening and within 5 days prior to SPTs and day 1 of DBPCFCs (SCR only)	
Entered study even though entry criteria was not satisfied	Asthma at time of enrollment with any of the following: FEV1<80% or predicted, or ratio of FEV1 to forced vital capacity (FEV1/FVC) <75% of predicted (PA1 and after)	
Entered study even though entry criteria was not satisfied	Asthma at time of enrollment with inhaled corticosteroids dosing of > 500 ug daily fluticasone. (PA1 and after)	
Entered study even though entry criteria was not satisfied	Asthma at time of enrollment with one hospitalization in the past year for asthma or Emergency room visit for asthma within 6 months prior to screening. (PA1 and after)	
Inadequate Informed Consent administration	Subject did not sign an ICF (main study, pharmacogenomics, photography, imaging, etc…) and study procedures initiated (never signed ICF or signed after procedure)	
Inadequate Informed Consent administration	Sub-study laboratory sample was collected without signed sub-study consent	
Inadequate Informed Consent administration	Subject did not sign an amended ICF and study procedures initiated	
Inadequate Informed Consent administration	Subject confidentiality not maintained	
Inadequate Informed Consent administration	ICF is not in subject's language	
Inadequate Informed Consent administration	Study Procedures performed after patient withdraws full consent	
Other Treatment compliance	Subject poor treatment compliance to SC study drug (define as underdose of 80% of planned doses overall) that significantly impacts efficacy outcome	
Other Treatment compliance	Subject poor treatment compliance to SC study drug (define as overdose of 110% of planned doses) that significantly impacts efficacy outcome	
Other Treatment compliance	Subject poor treatment compliance to AR101 study drug (define as underdose of 95% of cumulative planned doses) that significantly impacts efficacy outcome during updosing phase	
Other Treatment compliance	Subject poor treatment compliance to AR101 study drug (define as underdose of 90% of cumulative planned doses) that significantly impacts efficacy outcome during maintenance phase	
Other Treatment compliance	Site staff were unblinded to the food challenge exposure (oat/peanut days) at DBPCFC at visit V16, V22 or V25.	

Category	Description of Protocol Deviation	Notes
Procedure not performed	Demographics were not collected at Screening V1	
Procedure not performed	Vital Signs were not collected at Screening V1, V1A, V16, V22, V25	
Procedure not performed	Physical Examination was not collected at Screening V1	
Procedure not performed	Pregnancy Test (serum) was not collected at Screening V1 for WOCBP.	
Procedure not performed	Peanut sIgE was not collected at Screening V1	
Procedure not performed	Spirometry was not collected at Screening V1a	
Procedure not performed	Randomization was not collected at Baseline V2	
Procedure not performed	2 or more Blinded Study Drug SC Q2W Administration was not collected at Baseline V2, V3, V4, V5, V6, V7, V8, V9, V10, V11, V12, V13, V14, V15, V16, V17, V18, V19, V20 or V21 (up to PA2)	
Procedure not performed	Pregnancy Test (urine) was not collected at Baseline V2, V3, V4, V5, V6, V7, V8, V9, V10, V11, V12, V13, V14, V15, V16, V17, V18, V19, V20, V21, V22 or Early Termination Visit for wOCBP	
Procedure not performed	Pregnancy Test (serum) was not collected at V25 EOS for WOCBP	
Procedure not performed	Randomization was not collected at V16	
Procedure not performed	DBPCFC was not collected at V16	
Procedure not performed	DBPCFC was not collected at V22	
Procedure not performed	2 or more Blinded Study Drug SC Q2W Administration was not collected at Baseline V2, V3, V4, V5, V6, V7, V8, V9, V10, V11, V12, V13, V14, V15, V15a, V15b, V15c, V15d, V15e, V15f, V16, V17, V18, V19, V20 or V21 or in USCHED (PA3 and after)	
Procedure not performed	Pregnancy Test (urine) was not collected at V15a, V15b, V15c, V15d, V15e, V15f for WOCBP (PA3)	
Procedure not performed	Weight was not collected at Baseline V2	
Procedure performed outside of window	Food challenges were not performed either on different day, more than 1 day apart or less than 7-days apart during DBPCFC at on-study visit V16, V22 or V25 EOS	
Randomization Error	Stratification error	
Randomization Error	Subject randomized twice	
Received an excluded concomitant treatment	Subject received prohibited medication impacting safety or efficacy parameters and assessments treatment with a live (attenuated) vaccine per protocol	
Received an excluded concomitant treatment	Treatment with an investigational drug (other than dupilumab)	

Category	Description of Protocol Deviation	Notes
Received an excluded concomitant treatment	Treatment with immunomodulating biologics agents, including anti-IgE and anti-IL-5	
Received an excluded concomitant treatment	Treatment with allergen immunotherapy other than AR101	
Received an excluded concomitant treatment	Treatment with systemic corticosteroids (up to PA1)	
Received an excluded concomitant treatment	Treatment with any agents known or likely to interact with epinephrine (eg, betablockers, ACE-inhibitors, tri-cyclic antidepressants, or other drugs)	
Received an excluded concomitant treatment	Treatment with antihistamines within 5 days- prior to SPTs and Day 1 DBPCFCs (post randomization)	
Received an excluded concomitant treatment	Major elective surgical procedures	
Received an excluded concomitant treatment	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 (PA2 and after)	
Received wrong treatment or incorrect dose	Subject given study drug but subject not randomized	
Received wrong treatment or incorrect dose	Subject received incorrect treatment (wrong kit given, kit dispensed without IVRS/IWRS transaction at re-supply visit, wrong order)	
Received wrong treatment or incorrect dose	Subject received incorrect treatment or unacceptable IP (expired or temperature excursion deemed unacceptable) that would impact safety or efficacy	
Received wrong treatment or incorrect dose	Site level treatment unblinded (to for example Investigator, patient or medical monitor) where patient care, decision making, data analysis and reporting impacted	
Subject developed withdrawal criteria but were not withdrawn	Missing >2 consecutive doses of study drug (dupilumab or placebo)	
Subject developed withdrawal criteria but were not withdrawn	Missing >7 consecutive days of AR101 therapy (eg, concurrent illness such as gastroenteritis)	
Subject developed withdrawal criteria but were not withdrawn	Anaphylaxis resulting in severe hypotension (Appendix 3), neurological compromise, or mechanical ventilation secondary to OIT dosing or any food challenge.	
Subject developed withdrawal criteria but were not withdrawn	Subject develops biopsy-documented EoE or other eosinophilic GI disease	
Subject developed withdrawal criteria but were not withdrawn	Any subject deemed to have a severe allergic reaction or has a life-threatening reaction at any time but continues study treatment	
Subject developed withdrawal criteria but were not withdrawn	Other circumstances such as poor control or persistent secondary atopic disease or started beta blockers	

Category	Description of Protocol Deviation	Notes
Subject developed withdrawal criteria but were not withdrawn	Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immuno-compromised status	
Subject developed withdrawal criteria but were not withdrawn	Severe laboratory abnormalities that are deemed to be related to dupilumab	
Subject developed withdrawal criteria but were not withdrawn	Diagnosis of a malignancy during the study	
Subject developed withdrawal criteria but were not withdrawn	Evidence of pregnancy	
Subject developed withdrawal criteria but were not withdrawn	Treatment with any prohibited concomitant medication or procedure but continued to take study drug	
Visit not performed	Visit 16 was not performed	
Visit not performed	Week 52 Visit 22 (D365) was not performed	
Visit not performed	Week 64 Visit 25 EOS (D449) was not performed	
Visit not performed	Screening visit 1 (D-113 to D-17) was not performed	
Visit not performed	Screening visit 1A (D1 to D-15) was not performed	
Visit performed out of window	Screening V1 (Day -57 to Day -17) was not performed -57 days of Baseline visit 2 (D1) (up to PA2)	
Visit performed out of window	Visit 1A was not performed 15 days before visit 2	
Visit performed out of window	Week 28 Visit 16 (D197) was not performed within 196 days (+/- 3 days) of Baseline V2 (D1) (PA2 and earlier)	
Visit performed out of window	Visit 16 was not performed within 189-309 days of Baseline V2 (D1) (PA4)	

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