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Clinical Study Protocol

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
Clinical Phase:	2
Protocol Number:	R668-ALG-16114
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AMENDMENT HISTORY

Amendment 4

The purpose of this amendment is to define the primary efficacy analysis based on approximately 122 subjects who up-dosed AR101 per the original protocol's 24-week up-dosing schedule (pre-COVID-19 restrictions) and to define a modified analysis set to differentiate these subjects. Changes were also made to clarify: rescue and prohibited medications, biomarker variables, visit windows, and adverse events of special interest (AESIs). The following table outlines changes made to the protocol and the rationale.

Description of Change	Rationale	Section Changed
Updated sample size for the primary analysis such that approximately 122 subjects who undergo the post up-dosing double-blind placebo-controlled food challenge (DBPCFC) at week 28 (visit 16) or discontinue from study prior to week 28 (visit 16) will be included in the primary efficacy analysis. Added a new analysis set to the statistical plan to clarify that these subjects who up-dosed AR101 per the original protocol plan will be analyzed in a modified full analysis set (mFAS), separate from the full analysis set (FAS), which includes all randomized subjects.	To differentiate the analysis of subjects who up-dosed AR101 per the original protocol plan from those subjects who attended optional visits 15a-f (added in amendment 3 to accommodate COVID-19 restrictions), which extended up-dosing by up to 12 weeks. Subjects who attend optional visits will have increased duration of exposure to AR101 and dupilumab.	Clinical Study Protocol Synopsis: Statistical Plan Section 11.2 Justification of Sample Size Section 11.3.1 Efficacy Analysis Sets Section 11.4.1 Subject Disposition Section 11.4.3 Efficacy Analyses Section 11.4.3.1 Primary Efficacy Analysis
Clarified that several treatments listed in prohibited medications are also considered rescue treatments and should result in study discontinuation, whereas acute treatment with epinephrine and certain other medications is permitted for the treatment of allergic reactions.	For clarification that certain rescue medications will lead to study drug discontinuation as they may affect study outcome.	Section 8.2 Rescue Treatment Section 8.3.2.1 Reasons for Permanent Discontinuation of Study Drug Section 8.7 Concomitant Medications Section 8.7.1 Prohibited Medications and Procedures
Updated biomarker variables to include sIgE, sIgG4, and sIgG against main peanut protein allergen components such as Ara h1, Ara h2, and Ara h3.	To align with emerging data in food allergy research that suggest IgE-mediated allergic reactions to main peanut allergen components (eg, Ara h1, h2, h3) may correlate with clinical sensitivity to peanut exposure and the outcome of DBPCFC. It is important to understand how dupilumab as an adjunct to AR101 could modulate the IgE, IgG, and IgG4 levels against different peanut	Section 5.6 Pharmacodynamic and Biomarker Variables Table 3 Schedule of Events – Screening, Baseline, Double-Blind Treatment Period Table 4 Schedule of Events – Maintenance Period and Follow-Up Period Section 9.2.5 Pharmacodynamic and Biomarker Procedures

Description of Change	Rationale	Section Changed
	allergen components during oral immunotherapy (OIT).	
Extended the visit window for the DBPCFCs at visit 16, 22, and 25 to up to 7 days before and 30 days after the target date for all subjects.	To address the difficulty subjects have encountered in scheduling the DBPCFCs within the -3 day visit window. (In amendment 3, the visit window was extended to -3/+30 days due to COVID-19).	Table 4 Schedule of Events – Maintenance Period and Follow-Up Period Section 9.1.2 Footnotes for the Schedule of Events Table 4, footnote #14
Updated the list of AESIs to remove malignancy and suicide-related events.	For program consistency based on regulatory authority feedback.	Section 10.4.3 Other Events that Require Accelerated Reporting to Sponsor
Corrected the language pertaining to a secondary endpoint for the daily symptom e-diary.	The e-diary uses a numeric rather than categorical scale to rate symptom severity.	Clinical Study Protocol Synopsis: Endpoints Section 4.2 Secondary Endpoints
Specified that study drug administration will be recorded in the unscheduled visit folder for unscheduled and optional visits.	For clarification.	Table 3 Schedule of Events – Screening, Baseline, Double-Blind Treatment Period Table 4 Schedule of Events – Maintenance Period and Follow-Up Period Section 9.1.1 Footnotes for the Schedule of Events Table 3, footnote #15 Section 9.1.2 Footnotes for the Schedule of Events Table 4, footnote # 15
Clarified procedures in the peanut skin prick test (SPT) and Eczema Area and Severity Index (EASI).	For clarification.	Section 9.2.2.3 Peanut Skin Prick Test Section 9.2.2.4 Eczema and Severity Index
Clarified that subjects who do not achieve 300 mg/day will still enter the 12-week follow-up.	For clarification.	Section 6.1 Study Description and Duration
Minor editorial corrections and clarifications.	For clarification.	Throughout the protocol.

Amendment 3

The purpose of this protocol amendment is to protect subject safety and data integrity during the COVID-19 pandemic by extending the screening and up-dosing periods, and by modifying requirements for FeNO (fractional exhaled nitric oxide) and spirometry assessments. All mechanisms utilized and deviations from planned study procedures are to be documented as being related to COVID-19 where applicable and will remain in effect for the duration of the public health emergency. The following table outlines the changes made to the protocol and the rationale.

Description of Change	Rationale	Section Changed
The up-dosing period for AR101 peanut protein was permitted to be extended an additional 12 weeks for subjects impacted by the COVID-19 pandemic, such that the up-dosing period is ideally 28 weeks but may be extended to a maximum of 40 weeks (4 weeks pretreatment, 22 to 34 weeks up-dosing, and 2 weeks at maximum dose). These changes are reflected in the Schedule of Events such that all subjects will complete up to visit 15, then visits 15a-f will be optional to reach 300 mg/day AR101 for a minimum of 2 weeks. Subsequently, the on-study double-blind placebo-controlled food challenges (DBPCFCs) were re-named to reference milestones rather than time points for operational consideration: • **Screening DBPCFC** (name unchanged) • **Post up-dosing DBPCFC at visit 16** (formerly week 28) is the first on-study food challenge after the up-dosing period (week 28 to week 40). This will be considered visit 16 regardless of whether a subject completes optional visits 15a-f. • **Post maintenance DBPCFC at visit 22** (formerly week 52) is the second on-study food challenge at the end of the maintenance period (week 52 to week 64), 24 weeks	The AR101 up-dosing period was extended to allow for in-clinic visit flexibility and thereby protect subject safety and data integrity in the context of the COVID-19 pandemic. The DBPCFCs were subsequently re-named for clarification, as the time points may differ for subjects affected by COVID-19.	Clinical Study Protocol Synopsis: Objective(s), Study Design, Study Duration, Treatment(s), Endpoints, Procedures and Assessments, Statistical Plan Section 2.1 Primary Objective Section 2.2 Secondary Objectives Section 3.2.2 Rationale for Study Design Section 3.2.3.2 Dose and Regimen for AR101 Oral Immunotherapy Section 4.1 Primary Endpoint Section 4.2 Secondary Endpoint Section 6.1 Study Description and Duration Figure 1 Schematic of Study Design Considerations Section 6.1.1.2 AR101 Up-Dosing Regimen Starting at Week 6 Table 2 AR101: Bi-Weekly Up-Dosing Regimen Starting at Week 6 Section 6.1.3 Study Design Safety Considerations for DBPCFC Section 6.2 Planned Interim Analysis Section 8.5 Method of Treatment Assignment Table 3 Schedule of Events – Screening, Baseline, Double-Blind Treatment Period Table 4 Schedule of Events – Maintenance Period and Follow-Up Period Section 9.1.1 Footnotes for the Schedule of Events Table 3, footnote #14 Section 9.1.2 Footnotes for the Schedule of Events Table 4, footnote #13 Section 9.1.3 Early Termination Visit Section 10.4.1 Adverse Events Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Section 11.4 Statistical Methods Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis

Description of Change	Rationale	Section Changed
after the post up-dosing DBPCFC • **End of study DBPCFC at visit 25** (formerly week 64) is the end of study food challenge (week 64 to week 76), 12 weeks after the post maintenance DBPCFC		Section 11.4.3.3 Multiplicity Considerations Section 11.4.3.4 Timing of Analyses Section 11.4.4.1 Adverse Events Appendix 1 Peanut DBPCFC Schedule of Dosing Performed at Screening, Visits 16, 22, and 25 Appendix 5 Schematic for Subsequent AR101 Dose Escalation Days Performed In-Clinic at Weeks 6 Through End of Up-Dosing (week 28 to 40)
While screening and enrollment have been halted for new subjects during COVID-19, the screening period duration was extended from 8 weeks to 16 weeks for current subjects in screening. Screening was previously day -57 to day -17 and is now day -113 to day -17.	The screening period was extended to allow for in-clinic visit flexibility and thereby protect subject safety and data integrity in the context of the COVID-19 pandemic.	Clinical Study Protocol Synopsis: Study Design Section 6.1 Study Description and Duration Table 3 Schedule of Events – Screening, Baseline, Double-Blind Treatment Period
Modifications were made to the requirements for FeNO (not required at screening or on-study during COVID-19, at the discretion of the investigator) and spirometry (may be replaced with peak flow while on-study during COVID-19 at the discretion of the investigator, but still required at screening).	FeNO and spirometry requirements were modified to minimize aerosolized exposure concerns and thereby protect both site staff and subject safety during the COVID-19 pandemic.	Section 5.6 Pharmacodynamic and Biomarker Variables Table 3 Schedule of Events –Screening, Baseline, Double-Blind Treatment Period Table 4 Schedule of Events – Maintenance Period and Follow-Up Period Section 9.1.1 Footnotes for the Schedule of Events Table 3, footnote #9.a Section 9.1.2 Footnotes for the Schedule of Events Table 4, footnote #9.a Section 9.2.2.2 Fractional Exhaled Nitrous Oxide Section 9.2.3.3 Spirometry
Added language to clarify general changes in study conduct in the context of the COVID-19 pandemic.	For clarification.	Section 3.3 Safety Considerations (Risk-Benefit) Section 8.1 Investigational and Reference Treatments Section 9.1 Schedule of Events Section 9.1.2 Footnotes for the Schedule of Events Table 4, footnote #14 Section 11 Statistical Plan Section 13.1 Monitoring of Study Sites
Provided updated language regarding AR101, which is now approved in the US as a monotherapy for peanut allergy (previously listed as investigational).	For clarification.	Section 1 Introduction Section 3.2.1 Rationale for Study Section 3.3.2 Risk-Benefit for Peanut Protein Section 23 References
Minor editorial corrections.	For clarification.	Throughout the protocol.

Amendment 2

The following table shows the changes made to the protocol and the sections affected.

Change	Section Changed
Decreased the level of serum peanut specific IgE required for inclusion from ≥24 kUA/L to ≥10 kUA/L and/or Skin Prick Test (SPT) to peanut of ≥10 mm to ≥8 mm, compared to SPT negative control, to expand the pool of subjects who may be eligible for the study. The previous criteria were too restrictive compared to similar oral immunotherapy (OIT) studies and the change will still enroll only severely allergic subjects who react to screening double-blind peanut challenge at ≤144 mg (cumulative).	Section 7.2.1 Inclusion Criteria, #4
Changed prohibited use to allow use of systemic (oral, intravenous [IV], intramuscular [IM], subcutaneous [SC]) corticosteroids during the study for no more than 5 continuous days, no more than 15 days in total, or within 2 days prior to double-blind placebo-controlled food challenges (DBPCFCs) to align with standard of care.	Section 8.7.1 Prohibited Medications and Procedures
Modified windows for visits W8 to W26 from +/- 1 day to +/- 2 days to allow greater flexibility for subject scheduling consistent with expected clinical practice and other OIT studies.	Table 3 Schedule of Events – Screening, Baseline, Double-Blind Treatment Period
The timing of administration of AR101 was changed from at least 8 hours before SC study drug administration to at least 8 hours apart from SC study drug administration to allow greater dosing flexibility.	Clinical Study Protocol Synopsis – Study Design Section 3.2.3.1 Dose and Regimen for Dupilumab Section 6.1 Study Description and Duration Section 6.1.2 Study Design Safety Considerations for AR101 Section 9.1.1 Footnotes for the Schedule of Events Table 3, #1 Section 9.1.2 Footnotes for the Schedule of Events Table 4, #1

Change	Section Changed
Removed the time restriction of daily dosing in the evening with AR101 to align with Aimmune Protocol ARC003 and anticipated clinical use of AR101. Daily dosing in the evening is recommended but provision for dosing at other times were clarified. A statement was added that subjects should be monitored for at least 2 hours afterwards.	Clinical Study Protocol Synopsis – Study Design Section 3.2.3.1 Dose and Regimen for Dupilumab Section 6.1 Study Description and Duration Section 6.1.1.1 AR101 Initial Dose Escalation Day at Week 4 Section 6.1.2.1 Guidance for Home Dosing Section 8.1.1 AR101 for Oral Immunotherapy and IDED Section 9.1.1 Footnotes for the Schedule of Events Table 3, #1 and #2 Section 9.1.2 Footnotes for the Schedule of Events Table 4, #1 and #2
A positive SPT result determined by averaging maximal perpendicular wheal diameters 15 minutes after applying lancet was modified from ≥5 to ≥3 mm to be consistent with standard guidelines.	Section 9.2.2.3 Peanut Skin Prick Test
The start of the 2-week washout period after food challenge was revised from the last DBPCFC to after the peanut screening DBPCFC day to reduce time to randomization.	Section 6.1 Study Description and Duration Section 9.1.1 Footnotes for the Schedule of Events Table 3, #13
Revision was made to clarify that all subjects who undergo a DBPCFC at week 28 and week 52 for assessment of desensitization, dosing with AR101 should continue on the days between the 2 parts of the DBPCFC.	Clinical Study Protocol Synopsis – Study Design Section 6.1 Study Description and Duration
Limited the post-dose observation period to 30 minutes during the maintenance phase in clinic to align with Aimmune Protocol ARC003 and anticipated clinical practice.	Section 6.1 Study Description and Duration Section 9.1.1 Footnotes for the Schedule of Events Table 3, #8
Modified vital sign collection time interval at DBPCFC, initial dose escalation days, and up-dosing visits from every 15 minutes to every 15 to 30 minutes to align with other OIT studies. Also added that only pulse and blood pressure need to be taken for post-dose monitoring.	Clinical Study Protocol Synopsis – Study Design Section 6.1 Study Description and Duration Section 6.1.1.2 AR101 Up-Dosing Regimen Starting at Week 6 Section 9.1.1 Footnotes for the Schedule of Events Table 3, #8 Section 9.1.2 Footnotes for the Schedule of Events Table 4, #8 Section 9.2.3.1 Vital Signs

Change	Section Changed
Added some background information on pharmacodynamic and biomarker variables of Serum Peanut-Specific Antibody Assays and Peanut-Reactive Th2A Cells	Section 5.6 Pharmacodynamic and Biomarker Variables
Clarified that blood samples collected for exploratory research will be kept for up to 15 years for studying the allergen response ex-vivo.	Section 5.7 Other Exploratory Research (Optional)
Clarified that DNA sample is recommended to be collected on any day after day 1.	Section 9.1.1 Footnotes for the Schedule of Events Table 3, #11 Section 9.2.6.1 Genomics Analysis (Optional)
Clarified that subjects who exhibit moderate symptoms may have their dose reduced by 1 dose level per visit until the dose is tolerated with no or mild symptoms.	Section 6.1.1.2 AR101 Up-Dosing Regimen Starting at Week 6
Clarified that visit windows should be adhered to strictly as per the schedule of assessment.	Section 6.1 Study Description and Duration
Clarified that maintenance dose can continue to be taken at home on in-clinic maintenance period.	Section 6.1 Study Description and Duration
Cumulative column of Table 1 (AR101 Initial Dose Escalation Day at Week 4) was removed for clarity.	Table 1 AR101 Initial Dose Escalation Day at Week 4
Clarified that subjects in the dupilumab treatment group being re-randomized 1:1 to placebo or dupilumab are from the up-dosing phase. Also, that subjects will have an interactive web response system transaction to maintain the blind.	Section 6.1 Study Description and Duration
Added ‘symptom(s) of reaction due to exposure’ in parentheses for clarity.	Section 7.2.1 Inclusion Criteria, #2
Deleted ‘investigational’ from the following sentence for clarity: Use of other investigational forms of allergen immunotherapy (eg, oral, subcutaneous, patch, or sublingual) or immunomodulatory therapy (not including corticosteroids) within 3 months prior to screening.	Section 7.2.2 Exclusion Criteria, #10
Corrected the list of biomarkers to be investigated.	Section 9.2.5 Pharmacodynamic and Other Biomarker Procedures
Clarified that additional samples will be collected as detailed in the schedule of assessments for Future Biomedical Research.	Section 9.2.6 Future Biomedical Research (Optional)
Removed CODIT as part of descriptor for AR101 Figure 1.	Figure 1 Schematic of Study Design
Minor editorial revisions for clarification, consistency, corrections, and completeness.	Throughout

Amendment 1

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

Change	Section Changed
Provided greater detail in exclusion criterion for asthma per regulatory authority recommendation and added relevant references.	Section 7.2.2 Exclusion Criteria, #7 Section 23 References
Specified that subjects should receive all vaccinations for measles, mumps, rubella, and varicella at least 3 months prior to enrollment into the study, per regulatory authority recommendation.	Section 7.2.2 Exclusion Criteria, #16 Section 8.7.1 Prohibited Medications and Procedures
Corrected numeric errors about assumptions in the justification of sample size per regulatory authority request. No change has been made to sample size.	Clinical Study Protocol Synopsis – Statistical Plan Section 11.2 Justification of Sample Size
Expanded monitoring plan for eosinophilic esophagitis (EoE) and other gastrointestinal (GI) symptoms per regulatory authority request and added Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) v2.0 at Early Termination visit.	Section 6.1.2.5 Gastrointestinal Adverse Events and Disruption of Dosing Table 4 Schedule of Events – Maintenance Period and Follow-up Period Section 9.1.2 Footnotes for the Schedule of Events Table 4 (footnote #10)
Modified window for screening visits to allow greater flexibility and specified that a 2-week washout period is required after the screening Double-blind, placebo-controlled food challenge (DBPCFC), before visit 2 (randomization visit). Added footnote to schedule of events table to clarify modified screening window and clarified footnote #10.	Clinical Study Protocol Synopsis – Study Design Section 6.1 Study Description and Duration Table 3 Schedule of Events – Screening, Baseline, Double-Blind Treatment Period Section 9.1.1 Footnotes for Schedule of Events Table 3 (footnote #10, #12, #13)
Added that subjects must meet all eligibility for screening visit 1 before proceeding with the DBPCFC in visit 1a.	Section 6.1 Study Description and Duration Section 9.1.1 Footnotes for Schedule of Events Table 3 (footnote #12)
Modified Guidance for Home Dosing to clarify that moderate or severe symptoms should be confirmed by the investigator.	Section 6.1.2.1 Guidance for Home Dosing
Clarified that escalation during the initial dose escalation day is to 6 mg single dose	Section 6.1.2 Study Design Considerations for AR101
Clarified that the injection log in the e-diary will only document compliance with injection of study drug and not injection site reactions or concomitant medications, which will be collected in the case report form (CRF). Also, that the	Section 9.1.1 Footnotes for the Schedule of Events Table 3 (footnote #1, #2) Section 9.1.2 Footnotes for the Schedule of Events Table 4 (footnotes #1, #2)

Change	Section Changed
dosing diary will document only compliance with AR101, not concomitant medications as these are collected in the CRF.	
Added a statement to schedule of events footnotes from the study design that subjects will have a physical assessment before each DBPCFC and added a physical examination at visit 1a	Table 3 Schedule of Events – Screening, Baseline, Double-Blind Treatment Period Section 9.1.1 Footnotes for the Schedule of Events Table 3 (footnote #5) Section 9.1.2 Footnotes for the Schedule of Events Table 4 (footnote #5)
Added a paragraph regarding the use of the fractional exhaled nitric oxide (FeNO) device in subjects aged 6 years, which resulted in the addition of two references.	Section 9.2.2.2 Fractional Exhaled Nitric Oxide Section 23 References
Included the asthma control questionnaire-interviewer administered (ACQ-IA) for children aged 6 to 10 years and added a statement regarding validation of the asthma control questionnaire (ACQ).	Section 9.2.2.5 Juniper Asthma Control Questionnaire
Specified that subjects with moderate reaction at 6 mg single dose will be discontinued. In addition, the statement "Subjects to return for dosing at 6 mg" was removed from the initial dose escalation day (IDED) schematic.	Section 6.1.1.1 AR101 Initial Dose Escalation Day at Week 4 Appendix 4 Schematic for AR101 Initial Dose Escalation Day Performed in-Clinic at Week 4.
Clarified that subjects who experience severe allergic reactions in dose escalation of AR101 will discontinue from study.	Section 6.1.1.2 AR101 Up-Dosing Regimen Starting at Week 6 Section 6.1.2 Study Design Safety Considerations for AR101 Appendix 5 Schematic for Subsequent AR101 Dose Escalation Days Performed In-clinic at Weeks 6 through 28
Specified that biomedical research samples and the DNA sample are optional and added a paragraph regarding consent.	Table 3 Schedule of Events – Screening, Baseline, Double-Blind Treatment Period Table 4 Schedule of Events – Maintenance Period and Follow-up Period Section 9.2.6 Future Biomedical Research (Optional) Section 9.2.6.1 Genomic Analysis (Optional)
Removed CODIT as part of descriptor for AR101.	Throughout (including title)
Corrections: • Added "with e-diary" to daily allergy symptoms • Removed FeNO as a safety variable	Section 5.2 Efficacy Variables Section 5.3 Safety Variables Section 5.5 Anti-Drug Antibody Variables

Change	Section Changed
• Updated ADA variables by removing neutralizing antibody status • Abbreviation for peak expiratory flow was updated • Removed "single day" and "blinded" in IDED • Stopping rule #5 now reads (a severe allergic reaction or" instead of "and" • Clarified that dose-limiting symptoms should be evaluated by the same physician for all DBPCFCs. • Removed Daily Allergy Symptom Diary at visits 2 and 3 in schedule of events. • Footnote #2 in schedule of events tables was revised to include "subject/caregiver" instead of "subjects" • Corrected description of skin prick test (SPT) • Reference added for spirometry measurements • Removed the statement that "no formal statistical analysis will be performed" for drug concentration data. • Corrections made to analysis of anti-drug antibody data by adding "treatment-boosted"	Section 6.1.1.1 AR101 Initial Dose Escalation Day at Week 4 Section 6.1.2.3 Individual Subject Stopping Rules Section 8.5.1 Blinding Table 3 Schedule of Events – Screening, Baseline, Double-Blind Treatment Period Section 9.1.1 Footnotes for the Schedule of Events Table 3 (footnote #2) Section 9.1.2 Footnotes for the Schedule of Events Table 4 (footnote #2) Section 9.2.2.3 Peanut Skin Prick Test Section 9.2.3.3 Spirometry Section 11.4.5 Analysis of Drug Concentration Data Section 11.4.6 Analysis of Anti-Drug Antibody Data Section 23 References Appendix 3 Criteria for Suspected Diagnosis and Severity Grading of Anaphylaxis
Minor editorial corrections	Throughout

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	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)
Site Locations	Approximately 25 sites in the US
Principal Investigator	To be determined
Objectives	Primary objective: • To assess whether dupilumab as adjunct to AR101 compared to placebo improves desensitization at the completion of up-dosing, defined as an increase in the proportion of subjects who pass a post up-dosing double-blind placebo-controlled food challenge (DBPCFC) at visit 16 Secondary objectives: • To assess whether dupilumab as adjunct to AR101 compared to placebo 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 immunoglobulin E (sIgE), immunoglobulin G (IgG), immunoglobulin G4 (IgG4), and peanut-specific IgG4/IgE ratio • To assess if dupilumab increases the tolerability of AR101 as measured by the daily symptoms (electronic diary [e-diary]) during the up-dosing phase

Study Design

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 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 to reach 300 mg/day (ideally 28 weeks in duration, including pretreatment, but may be extended to a maximum of 40 weeks to accommodate dose reductions and re-escalation as well as COVID-19 restrictions of in-clinic visits; a 24-week maintenance phase with 300 mg/day AR101 in combination with 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. Total duration is between 64 and 76 weeks, excluding the screening period.

After obtaining informed consent/assent, subjects will be assessed for eligibility during a 2-part screening period. 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.

During screening visit 1a (must be before day -15), under direct study investigator monitoring, subjects will undergo a DBPCFC to confirm peanut allergy. This will consist of 5 doses (1, 3, 10, 30 and 100 mg) of peanut protein given every 15 to 30 minutes in increasing amounts up to a cumulative total of 144 mg of peanut protein. Vital signs will be assessed every 15 to 30 minutes. If the study team suspects a reaction may be developing, they may exercise their clinical judgement to separate doses by up to an additional 30 minutes (1-hour maximum between doses). The matching placebo challenge will consist of placebo material (oat protein) given also in 5 doses. The food challenges will be performed on different days (1-day placebo [oat] protein, 1-day peanut protein, with order determined at random) at least 24 hours apart. After the last dose of the DBPCFC, the subject will be monitored for 2 hours and then discharged from the clinic. Subjects will be considered to have tolerated the DBPCFC if they do not experience any objective Grade 1 (mild) reaction on the peanut protein days based on the Consortium of Food Allergy Research (CoFAR) grading system and will be excluded from the study.

Double-Blind Treatment Period (28 to 40 weeks duration)

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 (n=52 for placebo and n=104 for dupilumab). 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 of pretreatment, 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 dose reductions and re-escalation as well as COVID-19 restrictions of in-clinic visits. 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). After ingestion of AR101, subjects should be monitored for 2 hours for allergic reaction. All subjects will complete up to visit 15. Visits 15a-f will be optional in order to reach 300 mg/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.

Placebo Group
At day 1: Placebo (weight-based dose) Q2W SC for 28 to 40 weeks.

At week 4: 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/day AR101 for the next 2 weeks until up-dosing) followed by bi-weekly (Q2W) 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 (visits 15a-f, as needed) to accommodate dose reductions and re-escalation as well as COVID-19 restrictions of in-clinic visits. 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).

Dupilumab Group
At day 1: Dupilumab (weight-based or dose) Q2W SC for 28 to 40 weeks.

At week 4: AR101 using a standardized regimen of single 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/day AR101 for the next 2 weeks until up-dosing) followed by Q2W 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 (visits 15a-f, as needed) to accommodate dose reductions and re-escalation as well as COVID-19 restrictions of in-clinic visits. 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).

Double-Blind Maintenance Phase (Only for Subjects Who Reach 300 mg/Day AR101)
Subjects who achieve 300 mg/day AR101 for at least 2 weeks during the up-dosing period will enter a 24-week maintenance phase in which all subjects will continue to receive AR101 300 mg/day at home. Subjects in the dupilumab treatment group will be re-randomized (1:1) to receive dupilumab or placebo. Subjects who received placebo during the up-dosing phase will continue to receive placebo in the maintenance phase. After 24 weeks of AR101 and dupilumab or placebo, subjects will undergo a post maintenance DBPCFC to assess the level of peanut protein sensitivity at visit 22. Dosing with AR101 should continue on the days between the two parts of the DBPCFC.

Subjects who do not achieve 300 mg/day AR101 for at least 2 weeks at visit 16 are not permitted to enter the maintenance phase and will enter a 12-week follow-up period.

Double-Blind, Placebo-Controlled Food Challenge
At visit 16, all subjects who achieve 300 mg/day AR101 for at least 2 weeks in the up-dosing phase 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 mg (cumulative) peanut protein or placebo to assess desensitization. Dosing with AR101 should continue on the days between the two parts of the DBPCFC. The subject's sensitivity to peanut allergen is defined as the dose at which the subject experiences allergic reactions. The DBPCFC will consist of 8 doses (peanut protein or placebo), separated 15 to 30-minute time intervals: 1, 3, 10, 30, 100, 300,

	600, 1000 mg resulting in a total challenge of up to 2044 mg peanut protein (cumulative). Both peanut and oat protein will be concealed in a food that masks the taste. The food challenges will be performed on different days (1-day placebo [oat] protein, 1-day peanut protein, with order determined at random) at least 24 hours, but not more than 7 days, apart and not within 24 hours of a dose of study drug. After the last dose of the DBPCFC, the subject will be monitored for 2 hours and then discharged from the clinic. Subjects will be considered to have passed the DBPCFC if they do not experience any objective mild (Grade 1) reaction by CoFAR grading system. 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. **Post-Treatment Follow-Up Period (12 weeks)** 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) post maintenance DBPCFC at visit 22 will be eligible to undergo a final end of study DBPCFC (up to 2044 mg cumulative) under intensive monitoring, at visit 25 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.
Study Duration	The duration of the study for a subject is approximately 64 to 76 weeks, excluding the screening period.
Population	
Sample Size:	Approximately 156 subjects, 104 and 52 for the dupilumab and placebo treatment groups, respectively, with a history of confirmed peanut allergy will be enrolled at approximately 25 sites in the US.
Target Population:	Male and female subjects aged 6 to 17 years inclusive with a history of peanut allergy confirmed by peanut SPT, peanut-specific IgE and by the level of peanut protein safely ingested during a peanut DPBCFC.
Treatments	
Study Drug Dose/Route/Schedule:	Dupilumab SC (prefilled syringe): 100 mg Q2W for subjects <30 kg following a loading dose of 200 mg on day 1, 200 mg Q2W for subjects ≥30 to <60 kg following a loading dose of 400 mg on day 1, and 300 mg Q2W for subjects ≥60 kg following a loading dose of 600 mg on day 1.
Placebo Route/Schedule:	Dupilumab matching placebo SC Q2W following a loading dose on day 1.
Background Treatment Dose/Route/Schedule:	AR101 (peanut oral immunotherapy). Initial dose escalation day at week 4: 0.5, 1, 1.5, 3, and 6 mg (12 mg cumulative) over 5 hours. Then 3 mg/day

orally for the next 14 days prior to up-dosing to 300 mg daily over the next 22 to 34 weeks. The on-study DBPCFCs 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).

Endpoints

Primary:

- 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

Secondary:

- 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

  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 up-dosing 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 subjects (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 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 placebo plus AR101 • Percent change from baseline to the end of the study visit 25 in peanut-specific IgE in subjects (continuously) treated with dupilumab plus AR101 vs subjects treated placebo plus AR101 • 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)
Procedures and Assessments	The efficacy of dupilumab will be assessed by 3 DBPCFCs to occur after the initial screening DBPCFC: • Post up-dosing DBPCFC at visit 16 (after reaching 300 mg/day of AR101 for at least 2 weeks; week 28 to 40) • Post maintenance DBPCFC at visit 22 (24 weeks after the up-dosing DBPCFC; week 52 to 64) • End of study DBPCFC at visit 25 (12 weeks after the maintenance DBPCFC; week 64 to 76) Overall safety will be assessed by monitoring/evaluation of treatment-emergent adverse events (TEAEs), physical examinations, vital signs, and clinical safety laboratory tests at prespecified time points.
Statistical Plan	**Sample Size** 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 the placebo plus AR101 arm will be 40%, based on the Aimmune presentation at the 2018 American Academy of Allergy, Asthma & Immunology–World Allergy Organization Joint Congress with the proportion of subjects in the 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 a treatment difference of 25% between placebo plus AR101 and dupilumab plus AR101 at the 2-sided Fisher exact test with 5% significance level (the minimum significant difference is approximately 17.8%). Approximately 122 subjects who undergo the post up-dosing DBPCFC at week 28 (visit 16 with a window of -7/+30 days) 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 the placebo plus AR101 treatment effect is 40% at the 2-sided Fisher exact test with 5% significance level.

Efficacy Analysis Set

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

The modified full analysis set (mFAS) includes all FAS subjects who undergo the post up-dosing DBPCFC at week 28 (visit 16 with a window of -7/+30 days) or discontinue from study prior to week 28 (visit 16 with a window of -7/+30 days).

The mFAS will be used for primary analysis for all efficacy endpoints. Analysis of the FAS will also be done for supportive analyses.

Safety Analysis Set

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

Primary Efficacy Analysis

The primary endpoint will be analyzed using the Cochran-Mantel-Haenszel test adjusted by randomization stratification factors to assess the treatment difference in the proportion of responders (ie, those who "pass" a post up-dosing DBPCFC with 2044 mg [cumulative] peanut protein at visit 16 [week 28 with a window of -7/+30 days]) in the mFAS. In addition, the primary efficacy endpoint will be performed on the FAS as a supportive analysis.

If a subject does not have available post up-dosing DBPCFC data at visit 16, the subject will be considered as a non-responder regardless of reasons for missing data.

Sensitivity analyses of the primary endpoint will include an analysis of the subset of subjects with available visit 16 post up-dosing DBPCFC.

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

Secondary Efficacy Analysis

All secondary endpoints will be analyzed descriptively at given visits.

Change in the cumulative tolerated dose (log transformed) of peanut protein during a DBPCFC from baseline to the end of the up-dosing period 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 as covariates. In addition, a non-parametric analysis using the Van Elteren test will be conducted as a sensitivity analysis. **Safety Analysis** Safety analysis will be based on the SAF. This includes reported TEAEs and other safety data (ie, clinical laboratory evaluations and vital signs results). A descriptive summary of safety results will be presented by treatment group.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACIP	Advisory Committee on Immunization Practices
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AD	Atopic Dermatitis
ADA	Anti-Drug Antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR101	Investigational oral biologic drug for use as oral immunotherapy in peanut-allergic individuals
AST	Aspartate aminotransferase
BAT	Basophil Activation Test
BUN	Blood urea nitrogen
CoFAR	Consortium, of Food Allergy Research
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CSR	Clinical study report
DBPCFC	Double-blind, placebo-controlled food challenge
DLT	Dose-limiting toxicity
EAACI	European Academy of Allergy and Clinical Immunology
EASI	Eczema Area and Severity Index
EDC	Electronic data capture
e-diary	Electronic diary
EoE	Eosinophilic Esophagitis
EU	European Union
FAQLQ	Food Allergy Quality of Life Questionnaire
FAS	Full analysis set
FDA	Food and Drug Administration
FeNO	Fractional Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume 1 Second
GCP	Good Clinical Practice
GI	Gastrointestinal
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen

Hep C Ab	Hepatitis C Antibody
HDL	High-density lipoprotein
HIV	Human Immunodeficiency Virus
HPMC	Hydroxypropyl methylcellulose
ICF	Informed consent form
ICH	International Council for Harmonisation
IDED	Initial dose escalation day
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IM	Intramuscular
IL	Interleukin4
IL-4Rα	Interleukin-4 Receptor Alpha
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified full analysis set
OIT	Oral immunotherapy
PCSV	Potentially clinically significant value
PEESS	Pediatric Eosinophilic Esophagitis Symptom Score
PK	Pharmacokinetic
PEF	Peak expiratory flow
PT	Preferred term
QW	Every week
Q2W	Every 2 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous

SOC	System organ class
SPT	Skin prick test
TEAE	Treatment-emergent adverse event
Th1	Type 1 T-helper cell
Th2	Type 2 T-helper cell
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential

1. INTRODUCTION

Food allergy is a potentially life-threatening condition that affects up to 8% of young children and 3% to 5% of the entire United States (US) population (Gupta, 2011) (Sicherer, 2010). 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. The aim of OIT is to induce desensitization and increase the threshold for peanut ingestion and reduce the risks of allergic reactions after accidental ingestion. However, many subjects in OIT trials continue to have side effects that can hinder their compliance and the overall efficacy of OIT, which is a concern as is the re-sensitization upon cessation of peanut intake. 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. 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 (oral biologic drug) in subjects with significant allergy to peanuts.

The immune system in the gut actively induces an immune tolerant state to the proteins that are normally consumed. Food allergy occurs when the body has a break in this tolerance, which results in an abnormal immune reaction to food. 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 (ie, 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 interleukin (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. Inhibiting both IL-4 and IL-13 signaling with dupilumab has demonstrated clinical efficacy in moderate-to-severe atopic dermatitis (AD), persistent, uncontrolled asthma, nasal polyposis, and is currently being investigated in eosinophilic esophagitis (EoE). It is known that oral allergen up-dosing during OIT induces up-regulation of IL-4 and IL-13 as well as other Type 2 inflammatory cytokines and pathway activity, which contribute to dose-limiting side effects of OIT such as GI (nausea, vomiting, diarrhea and abdominal pain), respiratory (wheezing and shortness of breath), and skin (generalized rash, pruritus, and angioedema) symptoms. In addition, IL-4 and IL-13 induce isotype class switching to IgE and production of allergen-specific IgE.

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. In addition, the study will evaluate whether dupilumab influences known biomarkers important in the allergic response such as a reduction in allergen-specific immunoglobulin sub-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.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To assess whether dupilumab as adjunct to AR101 compared to placebo 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 double-blind placebo-controlled food challenge (DBPCFC) at visit 16

2.2. Secondary Objectives

- To assess whether dupilumab as adjunct to AR101 compared to placebo 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, and peanut-specific IgG4/IgE ratio
- To assess if dupilumab increases the tolerability of AR101 as measured by the daily symptoms (electronic diary [e-diary]) during the up-dosing phase

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

Treatment with dupilumab will improve the efficacy of OIT.

3.2. Rationale

3.2.1. Rationale for Study

This study will investigate whether addition of dupilumab, a fully human monoclonal antibody directed against IL-4Rα, will improve OIT in subjects with peanut allergy. This study will seek to demonstrate that addition of dupilumab to AR101 will enhance the safety, tolerability, and efficacy of OIT. This will be determined by assessing whether treatment with dupilumab provides an enhanced ability to tolerate a higher cumulative dose of peanut protein during a food challenge after 6 months of treatment compared to placebo, when given concomitantly with AR101, and whether treatment with dupilumab allows for more rapid up-dosing of peanut during desensitization. The differences in safety and tolerability will be assessed through an evaluation of treatment differences in AEs and study drop-out rates.

Oral immunotherapy has demonstrated efficacy in desensitizing food-allergic subjects by promoting physiologic changes, which suppress an allergic response to the ingested food antigen. Desensitization is defined as the ability to tolerate a higher threshold of food allergen without an allergic reaction, while consuming the food regularly. The first open-label clinical trial of peanut protein OIT showed that OIT could successfully induce desensitization in peanut-allergic subjects, with a favorable side-effect profile and low rates of anaphylaxis (Jones 2009). A 20-fold or greater improvement in DBPCFC-tolerated peanut dose compared to baseline after up-dosing to 800 mg per day over 6 months was demonstrated with minimal responses in placebo-treated subjects (Anagnostou 2014). A high proportion of individuals who achieve desensitization develop clinical reactivity within 3 months if peanut treatment is stopped (Vickery, 2014) (Syed, 2014). Persistent adverse reactions, primarily GI related, lead to OIT termination in 20% of subjects (Narisety, 2015) (Virkud, 2016). Three hundred mg/day of peanut protein can be safely ingested by 20 to 34 weeks and 1200 mg/day by 30 to 58 weeks. Most AEs occur in the first 12 weeks (76% GI, 7% respiratory, and 14% skin) delaying up-dosing to 300 mg/day in these subjects for 12 weeks. Peanut antigen-specific Th2 cells express the highest levels of IL-4 and IL-13 in subjects with the highest rate of allergic AEs (Syed, 2014).

AR101 (Aimmune) is an immunotherapy that consists of an oral peanut protein formulation that was evaluated in a double-blind placebo-controlled phase 2 study in 55 pediatric and adult subjects who were highly reactive to peanut. Subjects were started on an oral peanut dose of 3 mg on a single day and were then escalated to a maintenance dose of 300 mg/day by approximately week 22. After 22 weeks of treatment, 23 of the 29 subjects (79%, intent-to-treat [ITT]) assigned to OIT (6 dropped out because of GI side effects) tolerated 443 mg (cumulative) (equivalent to approximately 1.5 peanut kernels) of peanut protein, and 18 of the 29 subjects (62%, ITT) were able to tolerate 1043 mg (cumulative) (equivalent to 4 peanut kernels). Among the 26 subjects in the placebo group, only 5 (19%, ITT) could tolerate 443 mg of peanut protein, and none was able to reach the 1043 mg challenge dose (Bird 2015).

The open-label follow on study ARC002 evaluated the safety and efficacy of AR101 OIT in 47 eligible peanut-allergic subjects who participated in the ARC001 originating study. Former placebo-treated subjects began AR101 up-dosing to 300 mg/day, followed by 2 weeks of daily dosing at 300 mg/day, and a post up-dosing DBPCFC. At the post up-dosing DBPCFC, former placebo-treated subjects exhibited a high rate of desensitization, with 20 of 21 subjects (95%) tolerating the 443 mg cumulative dose of peanut protein. No moderate or severe AEs were reported, and no subject required epinephrine. These findings are consistent with those of the originating study exit DBPCFC in AR101-treated subjects. A total of 40 subjects overall, in both the former placebo-treated and AR101-treated groups, entered a 12-week maintenance period at 300 mg/day, followed by a post maintenance DBPCFC. After 9 months of AR101 treatment (6 months up-dosing, 3 additional months of 300 mg/day of maintenance), 73% of subjects (ITT) tolerated 443 mg (cumulative), 65% tolerated 1043 mg (cumulative) and 44% tolerated 2043 mg (cumulative) peanut protein DBPCFC. Moderate or severe AEs were reported in a minority of subjects at the 2 highest doses. Two subjects each required a single dose of epinephrine (AR101 Investigator Brochure).

A retrospective cohort analysis was also performed to evaluate the safety and efficacy profile of AR101 in relation to baseline peanut-specific IgE. Subjects were grouped by peanut-specific IgE levels of ≤100 kUA/L or >100 kUA/L. All subjects in both groups tolerated at least 443 mg cumulative of peanut protein. However, the 2 groups had different tolerance to higher doses of peanut-specific protein: 1043 mg of cumulative peanut protein was tolerated by 21 subjects (91%) in the ≤100 kUA/L group and 15 subjects (88%) in the >100 kUA/L group; 2043 mg of cumulative peanut protein was tolerated by 17 subjects (74%) in the ≤100 kUA/L group and 7 subjects (17%) in the >100 kUA/L group (Wang 2016).

In the phase 3 AR101 study (PALISADE) in which the prespecified primary analysis was children aged 4 to 17 years (n=496) with peanut allergy, subjects were started on an oral peanut dose of 3 mg on a single day and were then escalated to a maintenance dose of 300 mg/day during an up-dosing period of approximately 6 months, which was followed by a 6 month double-blind maintenance phase. The primary endpoint was the proportion of subjects tolerating 1043 mg (cumulative) peanut protein in the exit DBPCFC; 67.2% of the 372 subjects (ITT) treated with peanut OIT tolerated 1043 mg (cumulative) peanut protein compared to 4.0% of the 124 subjects treated with placebo. Those tolerating 2043 mg (cumulative) peanut protein, a key secondary efficacy endpoint, were 50.3% and 2.4% for peanut OIT and placebo, respectively. Of the AR101-treated subjects, a total of 76 (20.4%) discontinued, with 46 (12.4%) related to AEs. Treatment with AR101 was associated with a marked reduction in the IgE/IgG4 ratio from approximately 100 to <10, whereas an increase was noted in the subjects treated with placebo. Similarly, wheal size in the skin prick test (SPT) was reduced compared to placebo by AR101 treatment (PALISADE Group of Clinical Investigators, 2018).

Other investigator-initiated studies have also demonstrated the safety and efficacy of peanut protein OIT. These studies suggest that higher levels of peanut protein tolerated at a maintenance dose provide a greater protection in a DBPCFC. For example, a prospective cohort study of peanut OIT, in which 22 children received a maintenance dosing of 800 mg/day of peanut protein for 32 weeks demonstrated a significant increase in peanut challenge threshold, with 86% of subjects tolerating up-dosing and 14/22 (64%) tolerating 6600 mg (cumulative) of peanut protein at the completion of treatment (Anagnostou 2011).

The mechanisms by which OIT leads to clinical protection may include mast cell and basophil exhaustion or suppression, development of food-specific IgA and IgG4 blocking antibodies, increase in the peanut-specific IgG4/IgE ratio, up-regulation and expansion of Treg cells, a skewing from a Th2 to a Type 1 T-helper cell (Th1) profile, and the development of anergy and/or exhaustion in Th2 antigen-specific cells (Syed, 2014) (Vickery, 2013) (Gorelik, 2015) (Santos, 2015).

The use of omalizumab (monoclonal anti-IgE antibody) as an adjunct therapy to peanut protein OIT has been shown to significantly increase the threshold of reactivity in peanut-allergic subjects (MacGinnitie 2016). Omalizumab decreased the allergic response by binding to free circulating IgE molecules and reducing IgE-mediated mast cell and basophil degranulation on allergen exposure. Omalizumab allows more rapid desensitization to higher doses of peanut but does not affect long-term efficacy (MacGinnitie 2016). Therefore, there is an unmet need for a safer, more rapid, and more reliable adjunct to OIT treatment of peanut allergy that provides lasting protection.

3.2.2. Rationale for Study Design

AR101, with and without dupilumab, will be tested in a 2-arm, double-blind, randomized, parallel-group study in subjects with confirmed peanut allergy. Pediatric subjects will be enrolled as children represent the majority of subjects with peanut allergy and are a greater risk for accidental ingestion of peanut. Dupilumab/placebo treatment for 28 to 40 weeks as an adjunct to 24 to 36 weeks of daily AR101 treatment will be evaluated, followed by maintenance period of 24 weeks of daily AR101 treatment with concomitant dupilumab or placebo. Two treatment groups are required to provide informative controls and minimize bias on clinical endpoints: dupilumab plus AR101 and placebo plus AR101. Subjects will be treated for 28 to 40 weeks with either Q2W subcutaneous (SC) dupilumab or placebo. After the first 4 weeks of pretreatment, subjects will begin a 24 to 36 week up-dosing regimen of daily oral AR101. The study will assess an up-dosing regimen up to a maximum of 300 mg/day over the following 24 to 36 weeks of the study. If the scheduled bi-weekly up-dosing is not possible, the up-dosing period may be extended by up to 12 weeks (optional visits 15a-f) if necessary to accommodate dose reductions and re-escalation as well as COVID-19 restrictions of in-clinic visits. 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).

Subjects who achieve 300 mg daily dose of AR101 for at least 2 weeks at visit 16 (ie, the end of the up-dosing period, week 28 to 40) will enter a 24-week maintenance period. Subjects treated with dupilumab during the up-dosing period and who achieve 300 mg/day AR101 for at least 2 weeks will be re-randomized to 2 groups, AR101 plus dupilumab (indefinite [continuously]) and AR101 plus placebo (limited [previously]); this will allow an assessment of a lasting or limited effect of dupilumab. Subjects treated with placebo during the up-dosing period and who achieve 300 mg daily AR101 for at least 2 weeks will continue to be treated with placebo plus AR101 during the maintenance period.

This design allows for a direct comparison between adjunct dupilumab plus AR101 to placebo plus AR101 during the 28 to 40 week double-blind treatment period. It will also evaluate the effect of dupilumab in maintaining the response to AR101, defined as an increase in the proportion of subjects who pass a DBPCFC.

3.2.3. Rationale for Dose Selection

3.2.3.1. Dose and Regimen for Dupilumab

The approved dosing regimen in the treatment of AD in adults is 300 mg SC Q2W. The doses selected for this study are consistent with the approved AD pediatric study plan doses for this age group and the doses being tested in the ongoing AD pediatric study, R668-AD-1652 (6 to <12 years of age).

In study R668-AD-1412, 78 children aged 6 to 17 years received doses up to 4 mg/kg SC every week (QW) for 4 doses, where exposures similar to those in adults receiving 300 mg SC Q2W were achieved. Significant improvements in measures of AD were noted in these children, with an acceptable safety profile. As with many monoclonal antibodies, weight is the most significant covariate affecting dupilumab pharmacokinetics. The weight-based doses chosen for treatment in this study are chosen such that subjects should achieve similar dupilumab exposure in serum to that observed at the Food and Drug Administration (FDA)-approved adult dose for moderate-severe AD (300 mg SC Q2W), based on pharmacokinetic modeling of the data from study R668-AD-1412. The dupilumab SC dose will be 300 mg Q2W in children >60 kg following a loading dose of 600 mg on day 1. Children who weigh 30 kg or more but less than 60 kg, will receive 200 mg Q2W following a loading dose of 400 mg on day 1. Children weighing less than 30 kg will receive 100 mg SC Q2W following a loading dose of 200 mg on day 1. Regardless of subject weight gain or loss, the dupilumab dosing regimen assigned at randomization on day 1 will be maintained throughout the study.

Subcutaneous study drug will be dosed at home by the subject or by their legal guardian after adequate training (for subjects under 12 years old, legal guardian injections will be required) and at least 8 hours apart from the AR101 daily dose in order to allow for an accurate attribution of AE relatedness to study drug or AR101. In addition, dupilumab/placebo must be given at least 24 hours after in-clinic AR101 up-dosing.

The administration of the loading dose of dupilumab will allow systemic concentrations to reach steady-state faster. Rapid attainment of target-saturating concentrations may yield a rapid clinical response within a 4-week period of dupilumab pretreatment by suppressing Type 2 effector cell function, which is believed to be responsible for the allergic GI side effects of OIT. Dupilumab blockade of IL4/IL13 in AD, an immune-driven disease, reduced skin lesions and suppressed at 4 weeks the mRNA expression of genes related to T-cells, dendritic cells, eosinophils, inflammatory pathways, and Th2-inducing chemokines, whereas increases or insignificant decreases were observed with placebo. The correlation between these mechanistic changes and rapid improvement in clinical measures of disease activity in adults with AD, including Eczema Area and Severity Index (EASI) and SCORing AD, support an AR101 study design with only 4 weeks of dupilumab SC pretreatment (Hamilton, 2014). Rapid improvements in forced expiratory volume in the first second (FEV1) and FeNO have also been observed within 4 weeks in dupilumab studies in adults with asthma (Wenzel, 2013) (Wenzel 2016). The results in other indications suggest 4 weeks of dupilumab treatment significantly suppresses Type 2-mediated responses.

3.2.3.2. Dose and Regimen for AR101 Oral Immunotherapy

Concurrent with dupilumab dosing, subjects in the placebo plus AR101 and the dupilumab plus AR101 groups will begin at week 4, with Q2W up-dosing of AR101 beginning at 3 mg/day up to a maximum of 300 mg/day over 24 to 36 weeks (Baumert 2017). This 300 mg/day maintenance dosing regimen has previously been shown to provide significant clinical efficacy and consistent kinetics of the sIgG4 and sIgE response (Bird 2015). The AR101 regimen target of 300 mg/day may be clinically effective for desensitization for accidental peanut exposure. The majority of allergic side effects (GI) occur during bi-weekly up-dosing at a peanut dose less than 100 mg/day (Nadeau et al, POISED Peanut OIT Study; unpublished data).

3.3. Safety Considerations (Risk-Benefit)

Unlike many other childhood allergies, peanut allergy typically persists into adulthood and is associated with a higher incidence of severe anaphylaxis as compared with other food allergies (Dyer 2015). Although recent progress has been made in the treatment of food allergy through allergen-specific OIT, side effects often limit its full efficacy in many subjects and there is an unmet need for a new therapy in food allergy. It is known that allergic response to food is an IgE-mediated event; however, recent data suggest that the role of IL-4 and IL-13 may also play a significant role in food allergy pathogenesis. Consequently, dupilumab treatment, either alone or as an adjunct treatment to OIT, would be expected to provide benefit by blocking the activity of IL-4 and IL-13 and decreasing Type 2 responses, decreasing production of peanut-specific IgE, and potentially increasing the peanut-specific IgG4 response.

Note: Recognizing that the "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the sponsor does not intend to screen any subjects in this study until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and subjects can safely participate in this study.

3.3.1. Risk-Benefit for Dupilumab

At the time of writing this protocol, dupilumab 300 mg SC Q2W had been approved in the US, the European Union (EU), and several countries ex-US including Japan for the treatment of adults with moderate-to-severe AD. Marketing applications are under review in additional countries. Fourteen clinical studies (phases 1 through 3) of repeated-doses of dupilumab in AD patients have been completed. Dupilumab has demonstrated robust and consistent efficacy in completed clinical trials, across a variety of clinical outcomes, reflecting clinically meaningful and statistically significant improvement in AD signs, symptoms, and quality of life, with sustained efficacy demonstrated to 52 weeks.

Short term (4 weeks), 12- and 16-week treatment with repeated QW doses of SC dupilumab (75, 150, or 300 mg) monotherapy was well tolerated in adult patients with moderate-to-severe AD not adequately controlled with topical medications. Similar results were observed with dupilumab 300 mg SC QW administered concomitantly with topical corticosteroid in study R668-AD-1121.

Dupilumab's efficacy in adult patients with moderate-to-severe uncontrolled asthma has also been demonstrated at doses of 200 mg or 300 mg SC Q2W for 24 weeks (study DRI12544) and 52 weeks (study EFC13579). Asthma is a common comorbidity of allergy and asthma

exacerbations are an important safety concern for immunotherapy. In these studies, treatment with dupilumab at all doses tested was generally well tolerated with a favorable safety profile.

The first clinical study of dupilumab in pediatric patients aged 6 years to <18 years old with AD has been completed. Data generated from this study showed that dupilumab administered as single and repeated weekly doses was generally well tolerated and had an acceptable safety profile similar to that for adults in both pediatric age groups included in this study (6 to 11 years and 12 to <18 years). There were no new safety signals detected with dupilumab in this pediatric population. Most of the AEs reported were mild in intensity, transient in nature, and not related to the study drug. Both SC dose regimens of dupilumab evaluated (2 mg/kg and 4 mg/kg) showed significant clinical benefit in both pediatric age groups.

As of March 2018, approximately 600 pediatric AD (n=407) and asthma (n=196) patients have been exposed to dupilumab in completed and ongoing clinical studies.

3.3.2. Risk-Benefit for Peanut Protein

AR101 has been approved in the US as a monotherapy for peanut allergy. Based on previously published studies, approximately 80%, 15%, and <1% of the subjects are expected to have a reversible mild, moderate, or severe allergic symptom, respectively, during dosing with peanut. Allergic symptoms may include sneezing, rhinorrhea, urticaria, angioedema, flushing, flares of eczema, ocular, nasal, oral and/or throat pruritus, nausea, vomiting, abdominal discomfort, stridor/laryngeal edema, cough, wheezing, and/or shortness of breath in addition to severe anaphylaxis.

The only major atypical AE reported in the literature related to OIT has been several reported cases of EoE. In adult patients with EoE, treatment with dupilumab has shown clinical improvement of dysphagia symptoms and histology.

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

The potential benefit of peanut oral immunotherapy to desensitize peanut allergic subjects is outlined in Section 3.2.1.

4. STUDY ENDPOINTS

4.1. 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

4.2. Secondary Endpoints

- 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

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

- 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)

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

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

5.2. Efficacy Variables

Efficacy variables will include the DBPCFC, the peanut SPT, EASI for subjects with AD, asthma control questionnaire (ACQ-5 or Juniper ACQ) for subjects with asthma, daily allergy symptoms (recorded in an e-diary), and food allergy quality of life questionnaires.

5.3. Safety Variables

Safety variables will include vital signs, spirometry (FEV1 and/or peak expiratory flow [PEF]), hematology and chemistry, urinalysis, and AEs.

5.4. Pharmacokinetic Variables

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

5.5. Anti-Drug Antibody Variables

Anti-drug antibody (ADA) variables include ADA status,-titer, NAb status, and-time point/visit.

5.6. Pharmacodynamic and Biomarker Variables

Pharmacodynamic and biomarker variables are:

Serum Total IgE: Serum total IgE is a marker of Type 2 activity. Dupilumab significantly suppressed total IgE in studies of adult AD, nasal polyposis, and asthma patients.

Serum Peanut-Specific Antibody Assays (IgE, IgG, IgG4 against peanut extract and peanut protein allergen components): The induction of peanut allergen specific IgG4 during OIT has been reported in multiple studies. In a 5-year peanut OIT study of 39 peanut-allergic children, increases in total peanut-specific IgG levels were reported during the 12-month up-dosing period (Vickery 2014). In an open-label study of 29 peanut-allergic children, peanut-specific IgG4 increased steadily during the first year of treatment, reaching 3.5-fold increase over baseline after 3 months of OIT and roughly 10-fold increase at the end of first year (Jones 2009). In the same study, peanut allergen specific IgE was seen to increase by ~3-fold after 3 months of OIT and gradually return to baseline at one year.

In study R668-AD-1307 and other dupilumab studies in adults, dupilumab suppressed both total and allergen-specific IgEs. In general, dupilumab suppresses total IgE by ~50% with 12 to 16 weeks of treatment.

Fractional Exhaled Nitric Oxide: Asthma is a common comorbidity in peanut allergic children, reported to be between 40%-60% by different groups. While peanut allergic children often outgrow co-existing asthma symptoms, eosinophilic airway inflammation usually persists and is directly associated with anaphylactic reactions to peanut. Fractional exhaled nitric oxide is a non-invasive marker that has been shown to correlate with allergic airway inflammation and IgE sensitization. In a study of 94 peanut-allergic children, elevated FeNO levels (>35 ppb) were found in over 75% of the subjects (Hughes, 2010). Additionally, baseline FeNO level (pre-OFC) has been reported to be comparable to peanut SPT at predicting clinical outcomes in oral food challenge to peanut (Preece, 2014). In a 12-month study enrolling 56 subjects with peanut allergy, FeNO measurement demonstrated superior reproducibility (Intra-class Correlation Coefficient =0.73) in comparison to peanut SPT (Intra-class Correlation Coefficient =0.51) (Percival, 2016). In this study, we aim to use FeNO (pre-DBPCFC) as a measure of persistent airway eosinophilic inflammation in peanut-allergic children. In past asthma studies, dupilumab significantly lowered FeNO levels in adult and adolescent asthma patients, thus we hypothesize that dupilumab treatment will suppress FeNO levels in peanut allergic children. It is highly likely that peanut exposure during peanut DBPCFC in these subjects may trigger an increase in FeNO levels and asthmatic symptoms. Therefore, on the day of DBPCFC, FeNO levels will be measured both before and after the oral challenge to assess whether dupilumab may suppress the airway inflammation associated with DBPCFC, as reflected by induction of FeNO after the oral challenge. During the COVID-19 pandemic, measurements of FeNO no longer need to be completed (at the discretion of the investigator).

Basophil Sensitivity Test (optional): Basophils are one cell type involved in acute allergic reaction. CD203c and CD63 have been shown to be increased in basophils from peanut-allergic subjects compared to non-allergic healthy controls. The utility of the Basophil Activation Test (BAT) was assessed for diagnosing peanut allergy in a well-characterized population of peanut-allergic, peanut-sensitized, and non-sensitized children. The BAT showed high accuracy (97%) in diagnosing peanut allergy. In a study of omalizumab (anti-IgE) in peanut allergic subjects, CD203c expression in the BAT decreased during treatment and returned to pretreatment levels after cessation of treatment (Gernez, 2011). However, as a flow cytometry-based test, the CD203c or CD63 median fluorescence intensity reading is intrinsically highly variable. As an improvement to the traditional BAT, the basophil sensitivity test measures the minimum amount of peanut extract required to activate basophils in subject whole blood, as measured by up-regulation of CD203c and CD63. Basophil sensitivity to other allergens may also be tested. The results of these exploratory tests will not be presented in the clinical study report (CSR).

Peanut-reactive Th2A cells (Optional): One important area of investigation is to determine the effect of dupilumab on allergic T-cell responses as an adjunct during AR101 treatment. At week 4 (300 mg QW or Q2W) dupilumab effectively reduced CD3+ T-cells in AD skin lesions and suppressed Th2 inflammatory pathway genes (eg CCL13, CCL17 and CCL18), as shown by past studies in atopic dermatitis (Hamilton, 2014; Guttman-Yassky, 2019). These data indicate that dupilumab has direct suppressive effect on Th2 cells. However, due to the extreme low frequency of allergen-specific T-cells in circulation, conventional immunophenotyping of Th2 cells has not been successful in capturing changes in allergen-specific T-cells during specific immunotherapy. Th2A cells are allergen-specific Th2 cells with characteristic surface marker signatures (CRTH2+, CD27-, CD154+, CD161+, CD45RB- and CD49d+) (Wambre, 2017). Using these markers,

Wambre et al showed a reduction in the frequency of pro-allergic Th2A cell subsets from subjects receiving AR101, but not in the placebo group in Aimmune's Phase II study. Th2A subset of T-cells were also shown to be secreting higher levels of IL-4, IL-5, and IL-9, and were thus postulated to be a key pathogenic driver of allergic-T cell response. Therefore, monitoring peanut-reactive Th2A cells may reveal important mechanistic insight into the amelioration of allergic symptoms by dupilumab as an adjunct to AR101 (peanut oral immunotherapy).

5.7. Other Exploratory Research (Optional)

Blood may be obtained for additional exploratory tests such as whole blood stimulation with CD3/CD28 in the TruCulture® system and flow cytometry-based immune-phenotyping on type-2 allergic T-cells. Blood samples collected for exploratory research will be kept for up to 15 years for studying the allergen response ex-vivo. In subjects who consent/assent, peripheral blood mononuclear cells may be collected for RNA sequencing and RNA expression studies. The results of these exploratory tests will not be presented in the CSR.

6. STUDY DESIGN

6.1. Study Description and Duration

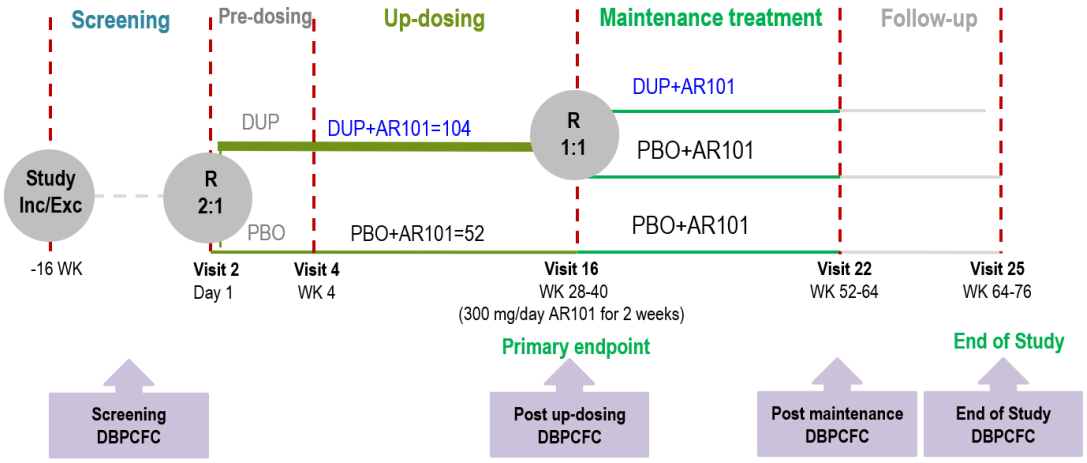
This is a phase 2, multicenter, randomized, double-blind, parallel-group, 2-arm study in subjects aged 6 to 17 years inclusive who are allergic to peanut. The study consists of a screening period of up to 16 weeks; a 28 to 40 week double-blind treatment period, which includes 4 weeks of pretreatment 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. Visit windows should be adhered to as per the schedule of events, which contains flexibility in the screening and up-dosing periods to accommodate dose reductions and re-escalation as well as COVID-19 restrictions of in-clinic visits.

All AR101 dose escalation will need to be done in-clinic. If the scheduled bi-weekly up-dosing is not possible, the up-dosing period may be extended by up to 12 weeks (optional visits 15a-f) if necessary to accommodate dose reductions and re-escalation as well as COVID-19 restrictions of in-clinic visits. If necessary, subjects may continue on a dose beyond the planned 2-week duration during the up-dosing period. If a temporary hold on up-dosing of AR101 is needed (current dose maintained), the investigator should follow up with the subjects via telephone call to evaluate safety and administration at current dose.

The duration of the study is approximately 64 to 76 weeks, excluding the screening period, for subjects who enter the maintenance period, and 40 to 52 weeks, excluding the screening period, 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 will enter a 12-week follow-up



Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; DUP, dupilumab; Exc, exclusion; Inc, inclusion; PBO, placebo

Screening

After obtaining informed consent/assent, subjects will be assessed for eligibility during a 2-part screening period. During screening visit 1 (day -113 to day -17), subjects will undergo a medical history, physical examination, spirometry, peanut 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.

During screening visit 1a (must be before day -15), under direct study-investigator monitoring, subjects will undergo a screening DBPCFC to confirm current peanut allergy. This will consist of 5 doses of peanut protein given every 15 to 30 minutes in increasing amounts up to a cumulative total of 144 mg of peanut protein. Vital signs will be assessed every 15 to 30 minutes. If the study team suspects a reaction may be developing, they may exercise their clinical judgement to separate doses by up to an additional 30 minutes (1-hour maximum between doses). The matching placebo challenge will consist of placebo material (oat protein) given also in 5 doses. The food challenges will be performed on different days (1-day placebo [oat] protein, 1-day peanut protein, with order determined at random) at least 24 hours apart. The doses will be 1, 3, 10, 30 and 100 mg of peanut protein (or placebo). Both food challenge days (placebo and peanut) must be done. Any subject who is assessed to have had dose-limiting symptoms to the placebo part, or both parts, of the screening DBPCFC (ie, to oat flour as well as peanut flour) will be considered a screen failure and will not be randomized. Investigator/site personnel will be unblinded only to the results of the screening food challenge upon completion of the second part of the challenge to assess eligibility. All other food challenges in the study will remain blinded.

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

Reactions will be scored using the Consortium of Food Allergy Research (CoFAR) grading system (see Appendix 2). The DBPCFC will be stopped when the blinded assessor finds symptoms and/or signs that indicate a definite objective allergic reaction (CoFAR grading system [see Appendix 2]) has occurred based on clinically significant changes in reported symptoms, physical findings, or vital signs that the subject is experiencing to the challenge material. The 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. All food challenges will be performed under physician supervision. If the subject has no symptoms related to allergic reactions to the peanut ingestion with the DBPCFC ≤144 mg (cumulative) peanut protein or if he/she experiences any symptoms at any dose of placebo, he/she will not be enrolled in the study. A 2-week washout period is needed after the peanut screening DBPCFC day, before subject can proceed with randomization visit.

Double-Blind Treatment Period (28 to 40 Weeks Duration)

Subjects with a history of confirmed peanut allergy signs and symptoms 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 1 of 2 treatment arms

(n=52 for placebo and 104 for dupilumab). A minimum of 15 subjects for each weight group will be enrolled.

Dupilumab and placebo will be dosed 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 Q2W following a loading dose of 200 mg on day 1 or matching placebo Q2W (including doubling the amount on day 1)
- subjects weighing ≥30 kg and <60 kg will receive dupilumab 200 mg Q2W following a loading dose of 400 mg on day 1 or matching placebo Q2W (including doubling the amount on day 1)
- subjects weighing ≥60 kg will receive dupilumab 300 mg Q2W following a loading dose of 600 mg on day 1 or matching placebo Q2W (including doubling the amount on day 1)

After the first 4 weeks of pretreatment, 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 dose reductions and re-escalation as well as COVID-19 restrictions of in-clinic visits. Thus, the 28 to 40 week 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). After ingestion of AR101, subject should be monitored for 2 hours for allergic reaction. All subjects will complete up to visit 15 of the up-dosing period. Visits 15a-f will be conducted as needed in order to achieve 300 mg/day AR101 for 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 2 parts of the DBPCFC.

Placebo Group

At day 1: Placebo (weight-based dose) Q2W SC for 28 to 40 weeks.

At week 4: AR101 using a standardized initial dose escalation day (IDED) regimen of doses of 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/day peanut protein for the next 2 weeks until up-dosing) (Table 1) followed by bi-weekly (every 2 weeks) 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 dose reductions and re-escalation as well as COVID-19 restrictions of in-clinic visits. 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).

Dupilumab Group

At day 1: Dupilumab (weight-based dose) Q2W SC for 28 to 40 weeks.

At week 4: AR101 using a standardized IDED regimen of doses of 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/day peanut protein 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 dose reductions and re-escalation as well as COVID-19 restrictions of in-clinic visits. 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

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

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

See Section 6.1.1 for details on peanut protein dose escalation.

After 28 to 40 weeks of dupilumab treatment and 24 to 36 weeks of AR101, subjects who achieve 300 mg/day of AR101 for at least 2 weeks will undergo a DBPCFC to assess the level of peanut sensitivity.

Re-Randomization at Week 28 to 40 for Dupilumab Group

Subjects in the dupilumab treatment group from the up-dosing phase will be re-randomized 1:1 placebo or dupilumab regardless of whether they achieve 300 mg/day AR101 for at least 2 weeks at visit 16 or discontinue. However, only those subjects who achieve 300 mg/day AR101 at visit 16 will be eligible to enter the maintenance phase. Subjects who do not achieve 300 mg/day AR101 for at least 2 weeks will enter a 12-week follow-up period. All subjects will have an interactive web response system (IWRS) transaction to maintain the blind.

Double-Blind Maintenance Phase (Only for Subjects Who Reach 300 mg/Day AR101)

Subjects who achieve 300 mg/day AR101 for at least 2 weeks during the up-dosing period will be eligible to enter a 24-week maintenance phase in which all subjects will continue to receive AR101 300 mg/day at home. The 24-week maintenance duration will start from when the subject has their day 1 of their post up-dosing DBPCFC at visit 16. (Safety analysis of the maintenance period starts after the second day of the visit 16 post up-dosing DBPCFC.) Subjects will have a monthly clinic visit. If the on-site clinic visit cannot occur, phone visits can take place as long as there are no changes to the subject's AR101 dose. Subjects in the dupilumab treatment group will be randomly assigned to either continue dupilumab at the same dose as administered during the up-dosing

period or to receive placebo. Subjects who received placebo during the up-dosing phase will continue to receive placebo in the maintenance phase. After 24 weeks of AR101 and 24 weeks of dupilumab or placebo, subjects will undergo a post maintenance DBPCFC to assess the level of peanut sensitivity at the end of the maintenance period.

Subjects who do not achieve 300 mg/day AR101 for at least 2 weeks at visit 16 and are not permitted to enter the maintenance phase, will enter a 12-week follow-up period (see below). The procedure for monitoring subjects for safety after in-clinic dosing is the same as for the up-dosing visits except that the initial period required for post-dose observation may be shortened to 30 minutes.

Double-Blind, Placebo-Controlled Food Challenge

At visit 16 (the end of up-dosing) 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 (see Appendix 1) to assess desensitization. At visit 22 (the end of maintenance period), all subjects who maintain 300 mg/day AR101 will undergo a post maintenance DBPCFC up to 2044 mg (cumulative) peanut protein or placebo to assess desensitization. Dosing with AR101 should continue on the days between the 2 parts of the DBPCFC. 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) (see Appendix 2). Up-dosing during the DBPCFC will be stopped when the blinded assessor finds symptoms and/or signs that indicate a definite objective (Grade 1 [mild]) allergic reaction (CoFAR grading system [see Appendix 2]) has occurred based on clinically significant changes in reported symptoms, physical findings, or vital signs that the 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 resulting in a total challenge of up to 2044 mg (cumulative) peanut protein. Both peanut and oat protein will be concealed in a food that masks the taste. The food challenges will be performed on different days (1-day placebo [oat] protein, 1-day peanut protein, with order determined at random) at least 24 hours, but not more than 7 days, apart, and not within 24 hours of a dose of study drug. Subjects will be considered to have passed the DBPCFC if they do not experience any objective Grade 1 (mild) reaction by CoFAR grading system (see Appendix 2). 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 a study physician. Symptom severity will be adjudicated by an independent, blinded assessor who is not involved in subject study visit conduct. 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. The determination of tolerability must be made on the basis of clinical judgement. The following are presented as guidelines for determining whether a dose associated with the emergence of a mild subjective

symptom or symptoms was tolerated. A dose eliciting only mild subjective symptoms may be considered to be tolerated if the symptoms are:

- Isolated to a single organ system except for airway (including tongue) or respiratory system
- Resolve with no pharmaceutical intervention or with a single oral administration of an H1 antihistamine
- Do not require administration of epinephrine
- Are not worsening in intensity or distribution over time
- Resolve, or shows definite signs of resolving, in under 1 hour

On the day following DBPCFC, the site is to make telephone contact with the subject/subject's parent or guardian to inquire if any AEs (including allergic symptoms) occurred subsequent to the subject leaving the clinic, and to provide assistance in the recording of any such events.

Post-Treatment Follow-Up Period (12 Weeks)

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

The duration of the 12-week follow-up period is based on the time expected for drug levels to fall below the lower limit of quantification after the last dose of dupilumab. At the end of the 12-week follow-up period, subjects who passed a 444 mg (cumulative) peanut protein DBPCFC at visit 22 (the end of the 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.

Subjects who do not achieve 300 mg/day peanut protein at visit 16, (ideally week 28, and up to a maximum of week 40) will enter a 12 week follow-up period.

6.1.1. Description of AR101 Dose Escalation, and Study Stopping Rules

6.1.1.1. AR101 Initial Dose Escalation Day at Week 4

The IDED will be done in-clinic at week 4 and consist of AR101 dosing, beginning at 0.5 mg of AR101 with graduated doses every 30 minutes up to 6 mg (cumulative 12 mg) over 5 hours (see Table 1 and Appendix 4). Subjects must be stable, with stable lung function, FEV1 >80% predicted, without evidence of wheezing on exam, or active allergic symptoms such as AD or symptoms of allergic rhinitis or any other symptoms that in the clinical judgement of the study physician contradicts initial dosing.

Trained clinical staff will be present at all times during all of the in-clinic AR101 dosing visits and will be available to respond within minutes to any allergic reaction. Allergic events (Appendix 2) will be monitored for at least 2 hours after the last dose or for at least 2 hours after resolution of symptoms prior to discharge from the clinic. Subjects tolerating the escalation dose will continue to administer a 3 mg/day dose at home for the next 14 days. Subjects who do not tolerate the 6 mg single dose (12 mg cumulative) during IDED, due to moderate or severe allergic reactions

(Appendix 4), will be considered treatment failures and will not initiate home AR101 dosing and should be early terminated from the study.

6.1.1.2. AR101 Up-Dosing Regimen Starting at Week 6

Subjects in the placebo and dupilumab treatment groups will have bi-weekly in-clinic visits with bi-weekly dose increases of the daily oral home AR101 dose from 3 mg/day up to a maximum of 300 mg/day by week 24 to 36 (see Table 2) depending on safety (see Appendix 5). Subjects who exhibit moderate symptoms (Appendix 2) may have the dose reduced by 1 dose level per visit (ie, go back to the previous dose prior to new up-dose) until dose tolerated with no or mild symptoms (see Appendix 5). A dose reduction, at the investigator's discretion, may also be implemented for an intercurrent adverse event. Subjects who exhibit severe allergic symptoms (Appendix 2) must be discontinued from study drug (see Appendix 5).

> Note: As of Amendment 3, the up-dosing period has been extended to accommodate dose reductions and re-escalation as well as COVID-19 restrictions of in-clinic visits. 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.)

For chronic or recurrent GI symptoms, especially upper GI symptoms, investigators are advised to establish a low threshold for instituting a dose reduction and for considering early discontinuation of affected subjects from the study due to the potential for EoE (see Section 6.1.2.5) following discussion with the medical monitor.

Each AR101 dosing increase will be administered in-clinic and monitored for adverse allergic events for at least 2 hours prior to discharge. If the current dose is maintained (ie, subject remains at the same dose and not escalated to the new dose during the clinic visit), then the observation period can be shortened to 1 hour with subject being discharged if deemed clinically stable. Vital signs will be monitored every 15 to 30 minutes. Subjects/legal guardians will be instructed not to exceed the specifically assigned doses at home. They will also be instructed not to introduce any new foods to the diet and to avoid accidental ingestions. Subjects/legal guardians will be supplied with epinephrine autoinjectors for treatment of allergic reactions and 24-hour access to an emergency contact telephone number.

On the day following in-clinic AR101 up-dosing, the site is to make telephone contact with the subject/subject's parent or guardian to inquire if any AEs (including allergic symptoms) occurred subsequent to the subject leaving the clinic, and to provide assistance in the recording of any such events in the diary.

Table 2: AR101: Bi-Weekly Up-Dosing Regimen Starting at Week 6

	Dupilumab/Placebo + AR101 protein
Planned Study Week	**Dose protein (mg)**
6	6
7	6
8	12
9	12

	Dupilumab/Placebo + AR101 protein
Planned Study Week	**Dose protein (mg)**
10	20
11	20
12	40
13	40
14	80
15	80
16	120
17	120
18	160
19	160
20	200
21	200
22	240
23	240
24	300
25	300
26	300
27	300
28 (up to week 40)	**DBPCFC**

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge.
Note: As of Amendment 3, the up-dosing period is ideally 28 weeks but may be extended up to 40 weeks if needed to accommodate dose reductions and re-escalation as well as COVID-19 restrictions of in-clinic visits.

6.1.2. Study Design Safety Considerations for AR101

- All up-dosing visits will be supervised in an in-clinic setting where trained study physicians are available. Subjects who exhibit moderate allergic symptoms (Appendix 2 for grading and treatment) may have the dose reduced to the previous dose (see Appendix 5). For chronic or recurrent GI symptoms, especially upper GI symptoms, investigators are advised to establish a low threshold for instituting a dose reduction and for considering early discontinuation of affected subjects from the study due to the potential for EoE.
- Standing orders from a study physician will be provided for all clinical study personnel to immediately (ie, prior to study physician notification) initiate treatment of reactions, including IM administration of epinephrine, based on their own clinical judgement.
- A crash cart with pediatric equipment will be available in close proximity (within 50 feet) of all subject clinic rooms.
- A code team will be available.
- Will only escalate to a maximum 6 mg AR101 single dose during the IDED, which has been determined in Aimmune phase 2 and 3 peanut protein OIT trials to be a level safely achieved in most subjects.

- Subjects will be dosed bi-weekly SC at home with dupilumab or placebo on separate days (at least 24 hours) from the in-clinic AR101 dose escalation and at least 8 hours apart from ingesting their daily oral AR101 dose.
- Dosing allergic symptoms and AEs will be captured throughout the study.
- Subjects will be prescribed an epinephrine autoinjector (if not prescribed by a treating clinician previous to study entry) and all subjects/legal guardian will be trained in its use. Subjects will be advised to carry the autoinjector with them at all times.
- Subjects/legal guardians will be cautioned against consuming any peanuts or peanut-containing foods other than study-supplied food allergen while on study.
- Subjects/legal guardians will be cautioned against vigorous exercise or hot showers/baths within 1 hour prior to and 3 hours after AR101.
- During the in-clinic dosing days, home dosing of AR101 should not occur.
- An independent data monitoring committee (IDMC) will have oversight of subject safety (see Section 6.3.1 for more details).

6.1.2.1. Guidance for Home Dosing

The subject should take the AR101 at approximately the same time each day and it should be taken as part of a meal. Dosing at evening meal is recommended to permit children to be observed and supervised in the home setting by their parents or guardian for several hours after dosing. Subjects are to be cautioned against activities likely to increase allergic reactivity (eg, exercising or taking hot showers or baths within 3 hours after dosing). Dosing should not occur within 2 hours of bedtime. If dosing cannot be done in the evening, then it can be done with other meals as long as the subject can be observed for 2 hours for allergic reaction. Additionally, if a subject has been engaged in strenuous exercise prior to dosing, dosing should be delayed until signs of a hypermetabolic state (eg, flushing, sweating, rapid breathing and/or rapid heart rate) have abated. No attempt should be made to make up a missed dose if greater than 6 hours has elapsed from the usual time of dosing.

If moderate or severe allergic symptoms (Appendix 2) occur during home dosing, the subject or parent/legal guardian should call the study site and the subject should immediately stop home dosing and return to the clinic the next day. Upon confirmation by the investigator of moderate symptoms, the next dose will be administered under medical supervision. Upon confirmation by the investigator of severe symptoms, subject will discontinue all study drugs (Appendix 5) and return to the clinic for follow-up.

6.1.2.2. Missed Doses AR101

No attempt should be made to make up a missed dose if greater than 6 hours has elapsed from the usual time of dosing and the subject should continue with the next scheduled dose, which may be at home. If 2 consecutive doses are missed, the subject should continue with the next scheduled dose, which may be at home. If 3 to 7 consecutive doses are missed, the subject should return to the clinic for the next dose.

6.1.2.3. Individual Subject Stopping Rules

1. Missing >2 consecutive doses of study drug (dupilumab or placebo)
2. Missing >7 consecutive days of AR101 therapy (eg, concurrent illness such as gastroenteritis).
3. Anaphylaxis resulting in severe hypotension (Appendix 3), neurological compromise, or mechanical ventilation secondary to OIT dosing or any food challenge.
4. Subject develops biopsy-documented EoE or other eosinophilic GI disease.
5. Any subject deemed to have a severe allergic reaction or has a life-threatening reaction at any time will be discontinued from further therapy.
6. Other circumstances including, but not limited to, the following:
    a. Poor control or persistent severe activation of secondary atopic disease (eg, AD, asthma)
    b. Started on beta-blockers-with no alternative medications available per the prescribing physician
    c. Pregnancy

6.1.2.4. Anaphylaxis

The definition of anaphylaxis that has been adopted for this study is from the 2014 position paper by the European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy and Anaphylaxis Guidelines Group (Muraro, 2007), that in turn was based on the publications of Simons (2011) and Johansson (2004), and is consistent with the recently published "International consensus on (ICON) anaphylaxis" (Simons, 2014). Accordingly, anaphylaxis is defined as a severe, potentially life-threatening systemic hypersensitivity reaction, characterized by being rapid in onset with life-threatening airway, breathing, or circulatory problems that is usually, though not always, associated with skin and mucosal changes.

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

6.1.2.5. 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 (see Section 8.3.2).

Subjects that discontinue because of GI AEs will be asked to complete the Pediatric Eosinophilic Esophagitis Symptom Score (PEESS™) v2.0 questionnaire (Franciosi, 2011), with the assistance of a parent or guardian, as appropriate, every month for 6 months.

If a subject with chronic/recurrent GI AEs has not experienced complete resolution of symptoms within 6 weeks of discontinuation of dosing with the investigational product (peanut), the subject should be referred to a (pediatric) gastroenterologist.

Subjects who discontinue dosing prematurely due to chronic/recurrent GI AEs are to be requested to return to the clinic for evaluation monthly for at least 6 months (if the subject is asymptomatic), telephone follow-up with a physician investigator may be substituted for an in-clinic visit, at the investigator's discretion. If chronic/recurrent GI AEs persist beyond 6 months, subjects are to continue to be followed with monthly clinic visits until the symptoms have resolved or are assessed to have stabilized with optimal medical management.

If a subject is seen by a pediatric gastroenterologist, the investigational site is to procure records of the visit, as well as any test results, including those from endoscopy and endoscopic biopsy, if performed. These are to be retained with the subject's source documentation.

6.1.3. Study Design Safety Considerations for DBPCFC

The DBPCFC during screening and precautions taken are described in Section 6.1 (Screening). Similarly, the DBPCFCs at visits 16, 22, and 25, and as the stopping rules are described in Section 6.1 (Double-Blind, Placebo-Controlled, Food Challenge). Oral food challenges may induce an allergic response. Allergic reactions can be severe, including life-threatening allergic reactions; however, the risk of an allergic reaction is reduced by initiating the challenge with a very small amount of the food, gradually increasing the dose, and stopping the challenge at the first sign of a reaction. If subjects have an allergic reaction during the challenges, they may need oral, IM, or IV medications. Subjects will have an IV catheter placed before the food challenges if they have a medically documented history of anaphylaxis with hypotension requiring IV fluid resuscitation. Additionally, IV catheters may be placed, at physician discretion for any visit, based on factors such as previous reactions, recent clinical history, and clinical status observed at the visit. Trained personnel, including a study physician, as well as medications and equipment, will be immediately available to treat any reaction. The anticipated rate of life-threatening anaphylactic reactions is <0.1%.

6.1.4. End of Study Definition

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

6.2. Planned Interim Analysis

No interim analysis is planned. An unblinded primary analysis may be performed once all subjects in the study have completed the 28 to 40 week up-dosing treatment period as specified in the protocol (visit 16 or earlier for those subjects who are withdrawn prematurely from the study). If performed, this primary analysis will be considered the final analysis for the primary endpoint and secondary efficacy endpoints up to the end of the up-dosing period at visit 16 (week 28 to 40). A description of the statistical methods to be employed and blinding implications are in Section 11.4.3.

6.3. Study Committees

6.3.1. Independent Data Monitoring Committee

The dupilumab clinical development program in food allergy IDMC, composed of members who are independent from the sponsor and the study investigators, will provide oversight of subject safety by conducting formal reviews of accumulated safety data that will be blinded by treatment group; if requested, the IDMC may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment. The IDMC will provide Regeneron and Sanofi with appropriate recommendations on the conduct of the food allergy clinical studies to ensure the protection and safety of the subjects enrolled in these studies.

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

6.3.2. Adjudication Committee

The Adjudication Committee will review reports of specific serious adverse events (SAEs) and adverse events of special interest (AESI) to verify appropriate diagnosis as per protocol definitions (eg, anaphylaxis) and appropriate determination of event seriousness, severity, and causality. The Adjudication Committee will provide a complete assessment of the selected cases to help independently validate these reports. Adjudication Committee assessments will be reported in addition to the investigator's assessments.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF SUBJECTS

7.1. Number of Subjects Planned

Approximately 156 subjects, 104 in the dupilumab treatment arm and 52 in the placebo arm, with a history of confirmed peanut allergy will be enrolled at approximately 25 sites in the US.

7.2. Study Population

Male and female subjects ages 6 to 17 years inclusive with a history of peanut allergy confirmed by peanut SPT, peanut-specific IgE and by the level of peanut protein safely ingested during a peanut DPBCFC.

7.2.1. Inclusion Criteria

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

1. Age 6 to 17 years (inclusive).
2. Subject has a clinical history of allergy to peanuts or peanut-containing foods (symptom[s] of reaction due to exposure).
3. Experience dose-limiting symptoms at or before the 100 mg challenge dose (≤144 mg cumulative) of peanut protein (measured as 200 mg of peanut flour) on screening DBPCFC conducted in accordance with PRACTALL (Practical Issues in Allergology, Joint United States/European Union Initiative) guidelines. And not experiencing dose-limiting symptoms to placebo.
4. Serum IgE to peanut of ≥10 kUA/L and/or a SPT to peanut ≥8 mm compared to a negative control.
5. Subjects/legal guardians must be trained on the proper use of the epinephrine autoinjector device to be allowed to enroll in the study.
6. 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.
7. Willing and able to comply with all clinic visits and study-related procedures.
8. Written informed consent from parent/guardian for minor subjects.
9. Written assent from minor subjects as appropriate (eg, above the age of 6 years or the applicable age per local regulatory requirements).

7.2.2. Exclusion Criteria

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

1. Any previous exposure to marketed dupilumab or dupilumab in a clinical trial
2. Member of the clinical site study team or his/her immediate family
3. History of other chronic disease (other than asthma, AD, or allergic rhinitis) requiring therapy (eg, heart disease, diabetes, hypertension) that, in the opinion of the principal investigator, would represent a risk to the subject's health or safety in this study or the subject's ability to comply with the study protocol
4. History of frequent or recent severe, life-threatening episode of anaphylaxis or anaphylactic shock as defined by more than 3 episodes of anaphylaxis within the past year and/or an episode of anaphylaxis within 60 days of screening DBPCFC
5. History of eosinophilic GI disease
6. Current participation or participation within 6 months prior to screening in any other interventional study.
7. Asthma at time of enrollment with any of the following:
    1. FEV1 <80% of predicted, or ratio of FEV1 to forced vital capacity (FEV1/FVC) <75% of predicted with or without controller medications (only for age 6 or greater and able to do spirometry; 6 to 8 year old [Wang 1993], 8 to 18 years old [Third National Health and Nutrition Examination Survey or NHANES III -see Hankinson, 1999]) or
    2. Inhaled corticosteroids (ICS) dosing of >500 µg daily fluticasone (or equivalent ICS based on National Heart, Lung, and Blood Institute dosing chart) or
    3. one hospitalization in the past year for asthma or
    4. Emergency room visit for asthma within 6 months prior to screening.
8. Use of systemic corticosteroids within 2 months prior to screening.
9. Use of omalizumab within 6 months prior to screening.
10. Use of other forms of allergen immunotherapy (eg, oral, SC, patch, or sublingual) or immunomodulatory therapy (not including corticosteroids) within 3 months prior to screening.
11. Use of anti-histamines within 5 days prior to screening and within 5 days prior to SPTs and day 1 of DBPCFCs.
12. Use of any agents known or likely to interact with epinephrine (eg, beta-blockers, angiotensin converting enzyme-inhibitors, tri-cyclic antidepressants, or other drugs), within 3 weeks prior to screening.
13. Allergy to oat (placebo in DBPCFC).
14. Hypersensitivity to epinephrine and any of the excipients in the epinephrine product.

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

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

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

7.3. Premature Withdrawal from the Study

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

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

Subjects who are withdrawn prematurely from the study will be asked to complete study assessments, as described in Section 13.

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

7.4. Replacement of Subjects

Subjects prematurely discontinued from study will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

Dupilumab 150 mg/mL: Each 2.25 mL single-use, prefilled glass syringe with snap-off cap delivers 300 mg of study drug (2.0 mL of a 150 mg/mL solution)

Dupilumab 175 mg/mL: Each 1.14 mL single-use, prefilled glass syringe with snap-off cap delivers 200 mg of study drug (1.14 mL of a 175 mg/mL solution).

Dupilumab 150 mg/ml: Each 0.67 mL single-use, prefilled glass syringe with snap-off cap delivers 100 mg study drug (0.67 mL of a 150 mg/mL solution).

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

1. 2 mL placebo matching 300 mg dupilumab formulation
2. 1.14 mL placebo matching 200 mg dupilumab formulation
3. 0.67 mL placebo matching 100 mg dupilumab formulation

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

Instructions on dose preparation are provided in the pharmacy manual. Direct-to-subject shipment of study medication may be possible if clinic visits cannot take place, as long as it is for the subject's current dose of AR101 and SC study drug.

8.1.1. AR101 for Oral Immunotherapy and IDED

AR101 is characterized peanut allergen in the form of peanut flour, formulated with a bulking agent (maize starch, microcrystalline cellulose, and other excipients to prevent clumping) and a flow agent in premeasured graduated doses. The AR101 drug product is encapsulated in hydroxypropyl methylcellulose (HPMC) capsules. The capsules used in the Initial Escalation Period and Up-dosing Period of this study currently include the following strengths: 0.5, 1, 10, 20, and 100 mg each of peanut protein. AR101 is characterized by high performance liquid chromatography and by specific enzyme-linked immunosorbent assay for key allergenic proteins to demonstrate stability and lot-to-lot consistency.

AR101 0.5 mg: each opaque white HPMC capsule delivers 0.5 mg peanut protein

AR101 1 mg: each opaque red HPMC capsule (with white bars) delivers 1 mg peanut protein

AR101 10 mg: each opaque blue HPMC capsule delivers 10 mg peanut protein

AR101 20 mg: each opaque white HPMC capsule (with grey bars) delivers 20 mg peanut protein

AR101 100 mg: each opaque Swedish orange HPMC capsule (with grey and black bars) delivers 100 mg peanut protein

AR101 capsules will be provided in prepackaged thermoform blister wallet cards with features to allow access to each dose in dosing kits. Appropriate combinations of capsules are used to provide the required AR101 doses (eg, one 20 mg capsule and one 100 mg capsule to provide a 120 mg dose). For the escalation periods, each individual kit will contain 21 daily doses at a given dose level, enough to supply 2 weeks of dosing plus 7-day coverage to accommodate potential visit scheduling issues.

For the maintenance period dosing, a 300 mg AR101 dose will be provided in sealed, foil-laminate sachets (1 sachet/day). Sachets will be provided in kits containing 35 individual doses.

All AR101 will be packaged and labeled at the central packaging facility, then inventoried for distribution from a drug depot for shipment to the clinical sites. AR101 will be dispensed, according to subject identification number using an IWRS according to site-specific institutional policies. AR101 will then be distributed to each subject or parent(s)/guardian(s) by study site personnel.

After 4 full weeks of either dupilumab or placebo treatment, subjects start using a standardized regimen of single IDED AR101 (0.5 mg to a maximum of 6 mg, 12 mg cumulative) over approximately 5 to 6 hours. Subjects will begin a 3 mg/day oral dose at home for the next 14 days followed by bi-weekly up-dosing to a maximum of 300 mg/day AR101 at home.

AR101 will be stored in a secure location at each study site and kept refrigerated between 2°C and 8°C. Study site personnel will maintain temperature logs for all refrigerators storing study drug for the duration of the study.

8.1.2. Peanut for Food Challenges

For the DBPCFC, peanut flour mixture (containing ~50% peanut protein) or a placebo (oat) flour mixture, mixed in a vehicle food, will be used. The placebo flour mixture will be supplied pre-mixed with a small amount of artificial peanut flavor to provide a reasonable degree of taste-matching of the final placebo/vehicle food mixture to the peanut/vehicle food mixture. Investigational sites will be provided with standardized recipes for preparation of the DBPCFC in a separate manual of procedures.

8.2. Rescue Treatment

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

8.3. Dose Modification and Study Treatment Discontinuation Rules

8.3.1. Dose Modification

Dose modification of dupilumab for an individual subject is not allowed.

8.3.2. Study Drug Discontinuation

Subjects who permanently discontinue from study drug and who do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule. If dupilumab study drug is permanently discontinued, subject will also discontinue AR101 and vice versa.

Subjects who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 13.

8.3.2.1. Reasons for Permanent Discontinuation of Study Drug

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

- Anaphylactic reaction or other severe systemic reaction to dupilumab
- Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immuno-compromised status
- Severe laboratory abnormalities that are deemed to be related to dupilumab:
  - Neutrophil count $\leq 0.5 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$
  - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values greater than 3 × upper limit of normal (ULN) with total bilirubin >2 × ULN (unless elevated bilirubin is related to confirmed Gilbert's Syndrome)
  - Confirmed AST and/or ALT >5 × ULN (for more than 2 weeks)
- Diagnosis of a malignancy during the study
- Evidence of pregnancy
- Treatment with certain rescue medications, as specified in Section 8.2
- Missing >2 consecutive doses of study drug (dupilumab or placebo)

8.3.2.2. Reasons for Temporary Discontinuation of SC Study Drug

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

- Clinically important laboratory abnormalities such as:

  - Neutrophil count <1.5 x 10^3/µL but >0.5 x 10^3/µL
  - ALT or AST 3 × ULN but ≤5 × ULN
  - Platelet count ≤100 × 10^3/µL but >50 × 10^3/µL
  - Creatinine phosphokinase (CPK) >2.5 x ULN
  - Serum creatinine >1.5 x ULN
  - Eosinophils >5000/ µL
- Severe laboratory abnormalities (as noted in Section 8.3.2.1) where a causal relationship to dupilumab can be reasonably excluded (ie, an alternative cause is evident). In these cases, study treatment will be discontinued while the clinical circumstances are being assessed but it may be resumed when the laboratory parameters normalize sufficiently. A decision to resume treatment will be made jointly by the investigator and medical monitor
- Other intercurrent illnesses or major surgery
- An infection that requires parenteral treatment with antibiotic, antifungal, antiviral, antiparasitic, or antiprotozoal agents, or requires oral treatment with such agents for longer than 2 weeks

After the condition leading to suspension of dosing normalizes sufficiently, study treatment may resume at the discretion of the principal investigator in consultation with the medical monitor. A decision to discontinue study drug and/or to reinstitute study treatment should be discussed with the medical monitor. Note that dosing may NOT be resumed if subject met conditions for permanently discontinuing study drug described in Section 8.3. The investigator may suspend study treatment at any time, even without consultation with the medical monitor, if the urgency of the situation requires immediate action and if this is determined to be in the subject's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation. Resumption of study treatment after temporary discontinuation should always be discussed with the medical monitor.

8.4. Management of Acute Reactions

8.4.1. Acute Injection Reactions

8.4.1.1. Systemic Injection Reactions

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

8.5. Method of Treatment Assignment

28 to 40 Week Treatment Phase

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) described in Section 6.1 according to a central randomization scheme provided by an IWRS to the designated

study pharmacist (or qualified designee). Randomization will be stratified by screening peanut-specific IgE level (≤100 kUA/L or >100 kUA/L) and body weight (<30, ≥30 kg and <60 kg, or ≥60 kg) at randomization. A minimum of 15 subjects for each weight group will be enrolled.

Maintenance Treatment Phase

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). For subjects not achieving 300 mg/day AR101 for at least 2 weeks at visit 16 or early discontinued from study before visit 16, the re-randomization is used to determine their hypothetical assigned treatment for the maintenance phase in order to include them in the intent-to-treatment analysis of visit 22 endpoints. The 24-week maintenance period will start from day 1 of the post up-dosing DBPCFC at visit 16.

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. To maintain the blinding of treatment assignment, an IWRS randomization call needs to take place for these subjects.

8.5.1. Blinding

With the exception of the IDMC members and the provisions in Section 8.5.2, this study will remain blinded to all individuals until the prespecified unblinding to conduct the primary analyses. All study staff and study team will be blinded to all post-screening food challenge results until the end of the study (once all subjects study-wide have completed the study and the sites receive permission to unblind from the sponsor).

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

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

An unblinded pharmacist or designee will mix the peanut protein or oat protein in the food selected for masking taste for administration in the DBPCFC. For each subject, a "blinded" evaluating physician (Blinded Assessor) is to be designated to assess the tolerability of the challenge doses presented in the DBPCFC. The blinded evaluating physician is not to be involved directly in the oversight of study product dosing (neither initial escalation, nor up-dosing, nor maintenance phase), nor the assessment or management of AEs (for details refer to the Study Manual). The principal investigator or sub-investigator involved in subject care should not perform the post-screening food challenges as this may result in bias.

8.5.2. Emergency Unblinding

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

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

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

8.6. Treatment Logistics and Accountability

8.6.1. Packaging, Labeling, and Storage

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

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

8.6.2. Supply and Disposition of Treatments

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

8.6.3. Treatment Accountability

All drug accountability records must be kept current.

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

- dispensed to each subject/legal guardian,
- returned from each subject/legal guardian (if applicable), and

- disposed of at the site or returned to the sponsor or designee.

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

8.6.4. Treatment Compliance

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

8.7. Concomitant Medications

Any treatment administered from the time of the first dose of study drug to the final study visit will be considered concomitant medication. This includes medications that were started before the first dose of study drug and are ongoing during the study. This section considers concomitant medications that are not considered rescue treatment. See Section 8.2 for a discussion of rescue treatments.

8.7.1. Prohibited Medications and Procedures

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

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

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

NOTE: All subjects must have received all vaccinations per ACIP or local guidelines for measles, mumps, rubella, and varicella at least 3 months prior to enrollment in the study.

- Treatment with any agents known or likely to interact with epinephrine (eg, beta blockers, ACE-inhibitors, tri-cyclic antidepressants, or other drugs)
- Treatment with anti-histamines within 5 days prior to screening and within 5 days prior to SPTs and day 1 of the DBPCFCs

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures

NOTE: If a subject requires a prohibited medication or procedure at any time during the study, the principal investigator should contact the Regeneron medical monitor (except for illness requiring prompt treatment). Based on the discussions, study treatment may be continued or temporarily or permanently discontinued.

8.7.2. Permitted Medications

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

Medications used to treat chronic disease other than those listed in Section 8.7.1 are also permitted. If there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the medical monitor.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 3 and Table 4.

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19, are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Table 3: 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												
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
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															

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
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, 9a]	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
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,			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
allergen-specific T-cell profiling)[10]																
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						

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
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]:						
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]:						

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
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 4: Schedule of Events – Maintenance Period and Follow-Up Period

Study Procedure	**Maintenance Period[12]**							**Post-Treatment Follow-up Period**			**Un-scheduled 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/ +30d[14]	±3d	±3d	±3d	±3d	±3d	-7/ +30d[14]	±3d	±3d	-7/ +30d[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[1]	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

Study Procedure	**Maintenance Period[12]**							**Post-Treatment Follow-up Period**			**Un-scheduled 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/ +30d[14]	±3d	±3d	±3d	±3d	±3d	-7/ +30d[14]	±3d	±3d	-7/ +30d[14]		
Urinalysis	X			X			X			X		X
Pregnancy Test (WOCBP only)	U	U	U	U	U	U	U			S		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)[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

9.1.1. 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.
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/legal guardian 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. Fractional exhaled nitric oxide 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 (at the discretion of the investigator). 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 peanut day for the 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 (Table 2). 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 dose reductions and re-escalation as well as COVID-19 restrictions of in-clinic visits. 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.

9.1.2. Footnotes for the Schedule of Events Table 4

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 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/legal guardian will complete a dosing diary to document compliance with AR101.
3. Starting at visit 4 (week 4), site will account for the AR101 that is dispense to the subject/legal guardian.
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. Fractional exhaled nitric oxide 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 (at the discretion of the investigator). 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 subjects 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 (Table 2). 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 dose reductions and re-escalation as well as COVID-19 restrictions of in-clinic visits. 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 16, 22, and/or 25.
15. Study drug administration at unscheduled and/or optional visits 15a-f is to be documented in the unscheduled visits folder.

9.1.3. Early Termination Visit

Subjects who are withdrawn from the study before the primary endpoint visit (week 28 to 40) will be asked to return to the clinic for an early termination visit consisting of study assessments described in Table 4. Subjects who are withdrawn from the study after the primary endpoint visit will be asked to return to the clinic for early termination assessments only but the DBPCFC will not be required.

9.1.4. Unscheduled Visits

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

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

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

9.2.2. Efficacy Procedures

9.2.2.1. Double-Blind Placebo-Controlled Food Challenge

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 (see Appendix 2). Up-dosing during the DBPCFC will be stopped when the principal investigator (or designee) finds symptoms and/or signs that indicate a definite objective allergic reaction (CoFAR grading system [see Appendix 2]) has occurred based on clinically significant changes in reported symptoms, physical findings, or vital signs that the subject is experiencing to the challenge material. The challenge 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 challenges will be performed on different days (1-day placebo [oat] protein, 1-day peanut protein, with order determined at random) at least 24 hours, but not more than 7 days apart, and not within 24 hours of a dose of study drug. After the last dose of the DBPCFC, the subject will be monitored for at least 2 hours and then discharged from the clinic. Subjects will be considered to have tolerated the DBPCFC and passed if they do not experience any objective Grade 1 (mild) reaction by CoFAR grading system (see Appendix 2). If the subject experiences reactions, they will be treated with the necessary rescue medications. Symptom severity will be adjudicated by an independent, blinded assessor who is not involved in performing the baseline food challenge.

9.2.2.2. Fractional Exhaled Nitric Oxide

Fractional exhaled nitric oxide is a non-invasive marker that has been shown to correlate with allergic airway inflammation and IgE sensitization. The measurement of FeNO has shown predictive value on the outcome of peanut oral food challenge (Preece, 2014). Although no manufacturer has validated the FeNO device for children under 7 years old, due to inadequate exhalation force, there are no contraindications with the use of FeNO for 6-year-old children. Also, specific guidance and reference ranges are available for collection in children as young as 6 years of age (Brody, 2013) (Menou, 2017). As FeNO is an exploratory biomarker, it will be collected for children 6 years old unless the investigator declines to collect. Fractional exhaled nitric oxide will be performed prior to spirometry. During the COVID-19 pandemic, measurements of FeNO no longer need to be completed (at the discretion of the investigator).

9.2.2.3. Peanut Skin Prick Test

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

The titrated SPT is the skin testing for atopic response at different concentrations of peanut extract with saline as negative control and histamine as positive controls. The test will be performed at time points shown in Table 3 and Table 4. Testing of peanut extract will be conducted at the following dilutions: Neat, 1:20, 1:200, 1:2000, 1:20,000. The longest diameter and longest orthogonal diameter will be collected.

Mean wheal size induced by peanut extract, histamine, and saline at each concentration will be calculated by adding the longest diameter to the longest orthogonal diameter and dividing by 2. Normalized SPT will be calculated by subtracting mean saline wheal size from mean peanut wheal size.

9.2.2.4. Eczema Area and Severity Index

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (Hanifin, 2001). The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) 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%). The EASI will be collected for subjects with AD at screening and at subsequent time points according to Table 3 and Table 4.

9.2.2.5. 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), at time points according to Table 3 and Table 4. The ACQ-5 is for subjects aged 11 years or more and the ACQ-interviewer administered (IA) is for subjects 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 the next age bracket.

9.2.2.6. Daily Allergy Symptom Diary

The daily allergy symptom diary is a questionnaire that was designed to capture the daily signs and symptoms of peanut OIT. The measure was developed with input from patients currently or recently treated with peanut OIT as well as clinicians with experience treating patients with peanut OIT. The daily allergy symptom diary has also been cognitively debriefed within the target population. 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, and health states. Compliance to e-diary will be tracked closely by sites and should be reviewed via IRT portal for follow-up. During clinic visit, sites should review entry and reconcile for missing data.

9.2.2.7. Food Allergy Quality of Life Questionnaire

The Food Allergy Quality of Life Questionnaire (FAQLQ) is a validated food allergy-specific health-related quality of life (HRQL) questionnaire, which measures the impact of social and dietary limitations and assesses the emotional impact of these restrictions on the lives of patients. Patients self-report the impact of food allergy on HRQL using different forms of FAQLQ depending on their age; the child form (FAQLQ-CF) is used by patients aged 8 to 12 years and the teenager form (FAQLQ-TF) is used for patients aged 13 to 17. The parent form (FAQLQ-PF) is a measure of children's HRQL that is reported by parent proxy from the child's perspective and can be used for patients of ages 0 to 12 years. The FAQLQ will be administered to subject and, when appropriate, parents at time points in accordance with Table 3 and Table 4. Subjects will continue using the FAQLQ version first administered at baseline regardless of moving to the next age bracket.

9.2.3. Safety Procedures

9.2.3.1. Vital Signs

Vital signs, including temperature, sitting blood pressure, pulse, and respiration rate will be collected pre-dose at time points according to Table 3 and Table 4. 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.

9.2.3.2. Physical Examination

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

9.2.3.3. 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. The same spirometer and standard spirometric techniques, including calibration, should be used to perform spirometry at different visits and, whenever possible, the same person should perform the measurements (Pellegrino, 2005). FeNO should be done prior to spirometry. If spirometry cannot be completed after enrollment, peak flow may be performed instead at the discretion of the investigator.

9.2.3.4. Laboratory Testing

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

Samples for laboratory testing will be collected at visits according to Table 3 and Table 4. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Total cholesterol*
Chloride	Blood urea nitrogen (BUN)	Triglycerides
Carbon dioxide	AST	Uric acid
Calcium	ALT	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.

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

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

9.2.3.5. Pediatric Eosinophilic Esophagitis Symptom Score Questionnaire

The Pediatric Eosinophilic Esophagitis 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. Nevertheless, the PEESS v2.0 has shown good content and construct validity (Franciosi, 2011) (Martin, 2015).

9.2.4. Pharmacokinetic and Anti-Drug Antibody Procedures

9.2.4.1. Drug Concentration Measurements and Samples

Samples for drug concentration will be collected at time points listed in Table 3 and Table 4.

Any unused samples may be used for exploratory biomarker research.

9.2.4.2. Anti-Drug Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Table 3 and Table 4.

9.2.5. Pharmacodynamic and Other Biomarker Procedures

Biomarker samples will be collected at time points according to Table 3 and Table 4. Biomarker measurements will be performed in serum or plasma to determine effects on biomarkers of relevant physiological and pathogenic processes.

The biomarkers studied will be ones believed to be relevant to the pathophysiology of peanut allergy, mechanism of action of dupilumab, and possible toxicities. Biomarkers studied may include but need not be limited to: Total IgE, Thymus and Activation-Regulated Chemokine, specific IgE, IgG4, and IgG against peanut extract and main peanut allergen components (including but not limited to Ara h1, Ara h2, and Ara h3), blood stimulation in TruCulture (supernatant cytokine and chemokine profiling), basophil sensitivity to allergen stimulation and peanut-specific T-cell profiling.

Exploratory biomarker results not required for protocol-defined endpoint analyses will not be reported in the CSR.

9.2.6. Future Biomedical Research (Optional)

Research samples (serum/plasma/peripheral blood mononuclear cells) will be banked for future biomedical research related to Type 2/Th2 inflammation, allergic diseases, IL-4/IL-13, dupilumab (including mechanism of action, efficacy, toxicity), and circulating factors that inhibit allergen-specific IgE from binding to allergen (eg, IgE blocking factor). Additional samples will be collected as detailed in the schedule of assessments for Future Biomedical Research. The research may also include, but is not limited to, the study of allergen epitope diversity recognized by allergen-specific antibodies (both IgE and IgG4), T-cell and B-cell receptor repertoire (requires DNA/RNA sequencing), and the effects of dupilumab treatment on non-peanut allergies. The list may be altered or expanded as it is recognized that more relevant or novel biomarkers may be discovered during the course of this study. Any unused samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for future biomedical research (described below). After 15 years, any residual samples will be destroyed. Results of these future biomedical research analyses will not be reported in the CSR.

9.2.6.1. Genomics Analysis (Optional)

Parents or legal guardians who agree to participate in the genomics sub-study will be required to indicate their consent to participate in the sub-study on the informed consent form (ICF) before collection of the samples. Subjects are not required to participate in the genomics sub-study in order to enroll in the primary study. Samples for DNA extraction is recommended to be collected on day 1/baseline (predose) but may be collected at any study visit.

DNA samples for the genomics analyses will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response, other clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of peanut allergy, as well as related diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate

genomic markers related to the study drug or other diseases. Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, and transcriptome sequencing may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analysis will not be reported in the CSR.

10. SAFETY DEFINITIONS, REPORTING, AND MONITORING

10.1. Obligations of Investigator

The investigator must promptly report to the Institutional Review Board (IRB) all unanticipated problems involving risks to subject. This includes death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB, regardless of assessed causality.

10.2. Obligations of Sponsor

During the course of the study, the sponsor will inform health authorities, IRBs, and the participating investigators of any suspected unexpected serious adverse reaction occurring in other study centers for dupilumab and AR101, and also other studies for dupilumab.

Any AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered as unexpected. Any worsening of or new onset of symptoms related to peanut allergy which occur during the screening/washout period prior to study drug administration will be considered expected.

In addition, the sponsor will report in an expedited manner all SAEs that are expected and at least reasonably related to the study drug to the health authorities, according to local regulations.

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

10.3. Definitions

10.3.1. Adverse Event

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

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

10.3.2. Serious Adverse Event

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

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

longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event or is prolonged due to the development of a new AE as determined by the investigator or treating physician.

- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events. See Section 10.4 for more information on recording and reporting SAEs.

10.3.3. Adverse Events of Special Interest

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

10.4. Recording and Reporting Adverse Events

10.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent/assent is signed until the end of 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. Refer to the study reference manual for the procedures to be followed.

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

10.4.2. Serious Adverse Events

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

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

In the event the investigator is informed of an SAE after the subject completes the study (ie, the follow-up period), the following will apply:

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

10.4.3. Other Events that Require Accelerated Reporting to Sponsor

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

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

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

Adverse events of special interest for dupilumab in this study include the following:

- Anaphylactic reactions
- Systemic or extensive 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

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

10.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a subject's withdrawal from the study must be reported to the sponsor's medical monitor within 30 days.

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

10.4.5. Abnormal Laboratory or Vital Signs Results

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:

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

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

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

Please refer to FDA Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials for reporting severity of laboratory abnormalities:

(https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf)

10.4.6. Follow-Up

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

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

10.5. Evaluation of Severity and Causality

10.5.1. Evaluation of Severity

The severity grading of allergic reactions will be according to the definitions developed the CoFAR group (Appendix 2) and the severity of anaphylactic reactions will be graded according to the EAACI system for grading the severity of anaphylactic reactions (Appendix 3).

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

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

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

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

Injection Site Reactions

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

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

10.5.2. Evaluation of Causality

Relationship of Adverse Events to Study Drug:

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

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

The possible answers are:

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

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

The investigator should justify the causality assessment of each SAE.

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

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

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to subject's disease state or clinical condition

- do not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- do not reappear or worsen when dosing with study drug is resumed
- are not a suspected response to the study drug based upon preclinical data or prior clinical data

Yes:

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

Relationship of Adverse Events to Background Treatment:

The relationship of AEs to background treatment, etc. will be assessed by the ("blinded") investigator and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the background treatment, etc.?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the background treatment, etc.

Related: There is a reasonable possibility that the event may have been caused by the background treatment, etc.

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

A list of factors to consider in assessing the relationship of AEs to background treatment, etc. is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the event may have been caused by the background treatment?

No:

- due to subject's disease state or clinical condition
- do not follow a reasonable temporal sequence following the background treatment
- do not reappear or worsen when background treatment is resumed

- are not a suspected response to the background treatment based upon preclinical data or prior clinical data

Yes:

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

10.6. Safety Monitoring

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

10.7. Investigator Alert Notification

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

11. STATISTICAL PLAN

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

Analysis variables are listed in Section 5.

Handling of missing data or delayed procedures due to COVID-19, and any additional analyses required to investigate the impact of COVID-19 to understand estimated treatment effect and safety, will be detailed in the SAP.

11.1. 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 plus AR101 arm and the placebo plus AR101 arm will be made.

Let p_D (and p_P) be the true proportion 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 plus AR101 and placebo plus AR101, respectively. The following hypothesis for the superiority testing will be tested at the 5% 2-sided significance level:

H_0: $p_D = p_P$, ie, the proportion of subjects who achieve a cumulative dose of 2044 mg peanut protein during a post up-dosing DBPCFC at visit 16 is the same between dupilumab plus AR101 arm and the placebo plus AR101 arm

against the alternative

H_a: $p_D \neq p_P$, ie, the proportion of subjects who achieve a cumulative dose of 2044 mg peanut protein during a post up-dosing DBPCFC at visit 16 are different between the dupilumab plus AR101 arm and the placebo plus AR101 arm

11.2. Justification of Sample Size

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 the 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 the 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) 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 the placebo plus AR101 treatment effect is 40% at the 2-sided Fisher exact test with 5% significance level.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

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

The modified full analysis set (mFAS) includes all FAS subjects who undergo the post up-dosing DBPCFC at week 28 (visit 16 with a window of -7/+30 days) or discontinue from study prior to week 28 (visit 16 with a window of -7/+30 days).

The mFAS will be used for primary analysis for all efficacy endpoints. Analysis of the FAS will also be done for supportive analyses.

11.3.2. Safety Analysis Set

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

11.3.3. Other Analysis Sets

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

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

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

11.4. Statistical Methods

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

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

All data will be summarized by treatment groups as outlined below:

- Double-blind treatment period with pre-dosing and up-dosing of AR101 (28 to 40 weeks): placebo plus AR101 vs dupilumab plus AR101.
- Double-blind maintenance phase (24 weeks): continuously on placebo + AR101, previously on dupilumab + AR101 and re-randomized to placebo + AR101, continuously on dupilumab + AR101.

11.4.1. Subject Disposition

The following will be provided:

- The total number of screened subjects: met the inclusion criteria regarding the target indication and signed the ICF
- The total number of randomized subjects: received a randomization number
- The total number of subjects in each analysis set (eg, mFAS, FAS defined in Section 11.3.1 for all efficacy analysis sets)
- The total number of subjects who discontinued the study, and the reasons for discontinuation
- A listing of subjects treated but not randomized, subjects randomized but not treated, and subjects randomized but not treated as randomized
- A listing of subjects prematurely discontinued from treatment, along with reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

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

11.4.3. Efficacy Analyses

The primary efficacy analyses for all the efficacy endpoints will be conducted using the mFAS population. As supportive evidence, the same analysis approach will be repeated with the FAS population.

11.4.3.1. Primary Efficacy Analysis

The primary endpoint will be analyzed using the Cochran-Mantel-Haenszel test adjusted by randomization stratification factors to assess the treatment difference in the proportion of responders (ie, 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 will be provided.

In addition, the primary efficacy endpoint will be performed on the FAS as a supportive analysis.

If a subject does not have available post up-dosing DBPCFC data at visit 16, the subject will be considered as a non-responder regardless of reasons for missing data.

Sensitivity analyses will include an analysis of the subset of subjects with available post up-dosing DBPCFC data from visit 16.

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

11.4.3.2. Secondary Efficacy Analysis

Continuous Endpoints at Visit 16

Change in the cumulative tolerated dose (log transformed) of peanut protein during a post up-dosing 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 as covariates. In addition, a non-parametric analysis using the Van Elteren test will be conducted to assess the sensitivity to the assumption about normality of response variable as required by ANCOVA.

If a subject does not have an available post up-dosing DBPCFC at visit 16, their baseline value will be used to impute the missing DBPCFC data at visit 16 (ie, baseline observation carried forward). Sensitivity analysis using complete cases will be conducted to assess the robustness of the result, with regard to handling of missing data. Other sensitivity analyses may be conducted and will be specified in the SAP.

Continuous secondary efficacy endpoints that are measured repeatedly over time during the 28 to 40 week double-blind treatment period (eg, EASI) will be analyzed using ANCOVA in a similar way to the endpoint of change in the cumulative tolerated dose of peanut protein. For these endpoints, missing data will be imputed by multiple imputations.

Endpoints at Visit 22 or 25

Secondary endpoints at visit 22 (the end of the maintenance period) or at visit 25 (the end of study) will be analyzed descriptively at given visits. These descriptive analyses may include statistical tests depending on the type of data in the same way as described above.

11.4.3.3. Multiplicity Considerations

The overall Type-1 error rate of 0.05 (2-sided) will be controlled for the primary endpoint and the first secondary endpoint (ie, change in the cumulative tolerated dose [log transformed] of peanut protein during a post up-dosing 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.

11.4.3.4. Timing of Analyses

A primary analysis may be performed when the last subject completes 28 to 40 weeks of the double-blind treatment period as specified in the protocol (visit 16 or earlier for those subjects who are withdrawn prematurely from the study). No changes in the conduct of the study will be made based on this primary analysis. The assessment of primary and secondary endpoints up to visit 16 as specified in Section 11.4.3.1 and Section 11.4.3.2 and performed during the analysis will be the final analysis of the primary endpoint and the secondary endpoints up to visit 16. Hence there will be no need for alpha adjustment due to the primary analysis. If a decision is made to perform the primary analysis, in order to maintain study integrity with respect to the maintenance phase and the post-treatment follow-up visits, and analyses, a dissemination plan will be written. This plan will clearly identify the team (including the statistician) that will perform the primary analysis and all related activities, restrict other clinical team members and other sponsor personnel from access to individual subject treatment allocation and site level analysis results, and ensure that the

dedicated team will not participate in the data review or data decisions for the following post-treatment analyses. However, the dedicated team can participate in the analysis following the final database lock. In addition, an end of maintenance phase analysis may be performed when the last subject completes the maintenance treatment period (week 52 to 64 visit or earlier for those who are withdrawn prematurely from the study). If a decision is made to perform the end of maintenance phase analysis, measures similar to those taken for the primary analysis will be used in order to maintain study integrity with respect to the post-treatment follow-up visits and analyses.

11.4.4. Safety Analysis

11.4.4.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent period is defined as the day from first dose of study drug to the end of the study. The treatment-emergent period includes the 28 to 40 week up-dosing treatment period, the 24-week maintenance treatment period, and the follow-up 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.

Analysis

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

Summaries of all TEAEs by treatment group will include:

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

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

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

11.4.4.2. Other Safety

Vital Signs

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

The number and percentage of subjects with a treatment-emergent potentially clinically significant value (PCSV) will be summarized for each vital sign variable. The criteria for treatment-emergent PCSV will be defined in the SAP.

Laboratory Tests

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

Number and percentage of subjects with a treatment-emergent PCSV at any post-randomization time point will be summarized for each clinical laboratory test. The criteria for treatment-emergent PCSVs will be defined in the SAP.

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

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

11.4.4.3. Treatment Exposure

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

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

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

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

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

11.4.4.4. Treatment Compliance

The compliance with study treatment will be calculated as follows:

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

The compliance with AR101 will be calculated as follows:

> Treatment Compliance of AR101 = (total actual peanut dose protein [mg] received during exposure period)/(total planned dose protein [mg] during exposure period) × 100%

The treatment compliance of study drug and AR101 will be presented by specific ranges for each treatment group. The ranges of interest will be specified in the SAP.

11.4.5. Analysis of Drug Concentration Data

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

11.4.6. Analysis of Immunogenicity Data

- Listings of pre-existing, treatment-emergent and persistent ADA responses, titers, and NAb positivity presented by subject, time point, and dose group will be provided. Incidence of treatment-emergent and treatment-boosted ADA will be assessed as absolute occurrence (N) and percent of subjects (%), grouped by study cohorts and ADA titer level as follows:
- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses less than 4-fold over baseline titer levels.
- Treatment-emergent - defined as any post-dose ADA-positive response when baseline results are negative or missing.
  - Treatment-emergent ADA response may be further characterized as persistent, transient, or indeterminate.
- Treatment-boosted – defined as any post-dose positive ADA response that is at least 4-fold over the baseline level when baseline is positive in the ADA assay.
- Titer category (Maximum ADA titer values)
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤10,000)
  - High (titer >10,000)
  - NAb status for samples that are positive in the ADA assay

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

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

11.4.7. Analysis of Pharmacodynamic Data

The exploratory biomarker data will be summarized by descriptive statistics.

11.5. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

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

General rules for handling missing data:

- Rules for handling missing data for assessment (other than efficacy)

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

Visit windows:

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

Unscheduled assessments:

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

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

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

12. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

12.1. Data Management

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

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

The CRF data for this study will be collected with an EDC tool.

12.2. Electronic Systems

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

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

13. STUDY MONITORING

13.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization monitor) will visit each site prior to enrollment of the first subject, and periodically during the study. Remote monitoring may be used if applicable.

13.2. Source Document Requirements

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

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

13.3. Case Report Form Requirements

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

14. AUDITS AND INSPECTIONS

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

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

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

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

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Good Clinical Practice Statement

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

15.2. Assent and Informed Consent

Pediatric Subjects

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

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

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

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

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

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

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

15.3. Subjects Confidentiality and Data Protection

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

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

15.4. Institutional Review Board

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

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

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

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

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

16. PROTOCOL AMENDMENTS

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

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

17.1. Premature Termination of the Study

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

17.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

18. STUDY DOCUMENTATION

18.1. Certification of Accuracy of Data

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

18.2. Retention of Records

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

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

19. DATA QUALITY ASSURANCE

Authority Inspections.

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

Data Management

The sponsor is responsible for the data management of this study including quality checking of the data (Section 12.1).

Study Monitoring

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

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

All subject data collected during the study will be recorded on paper or electronic CRF unless the data are transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for affirming that data entries in the CRF are accurate and correct by electronically

signing a declaration that accompanies each set of subject final CRF (Section 13.3 and Section 18.1).

Study Documentation

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

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

20. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

21. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

22. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

23. REFERENCES

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24. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A 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) and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

APPENDIX 1. PEANUT DBPCFC SCHEDULE OF DOSING PERFORMED AT SCREENING, VISITS 16, 22, AND 25

	Challenge Doses			
	Amount of Peanut Protein at Each Challenge Dose (mg)	**Amount of Peanut Flour with 50% Protein Content (mg)**	**Cumulative Amount of Peanut Protein (mg) at Screening**	**Cumulative Amount of Peanut Protein (mg) post-screening (V16, V22, and V25)**
Screening	1	2	1	1
Screening	3	6	4	4
Screening	10	20	14	14
Screening	30	60	44	44
Screening	100	200	144	144
Endpoint	300	600	-	444
Endpoint	600	1200	-	1044
Endpoint	1000	2000	-	2044

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

APPENDIX 2. ALLERGIC REACTION SEVERITY GRADING

The CoFAR grading system for allergic reactions

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

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

Mild Symptoms:

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

Moderate Symptoms:

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

Severe Symptoms:

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

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

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

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

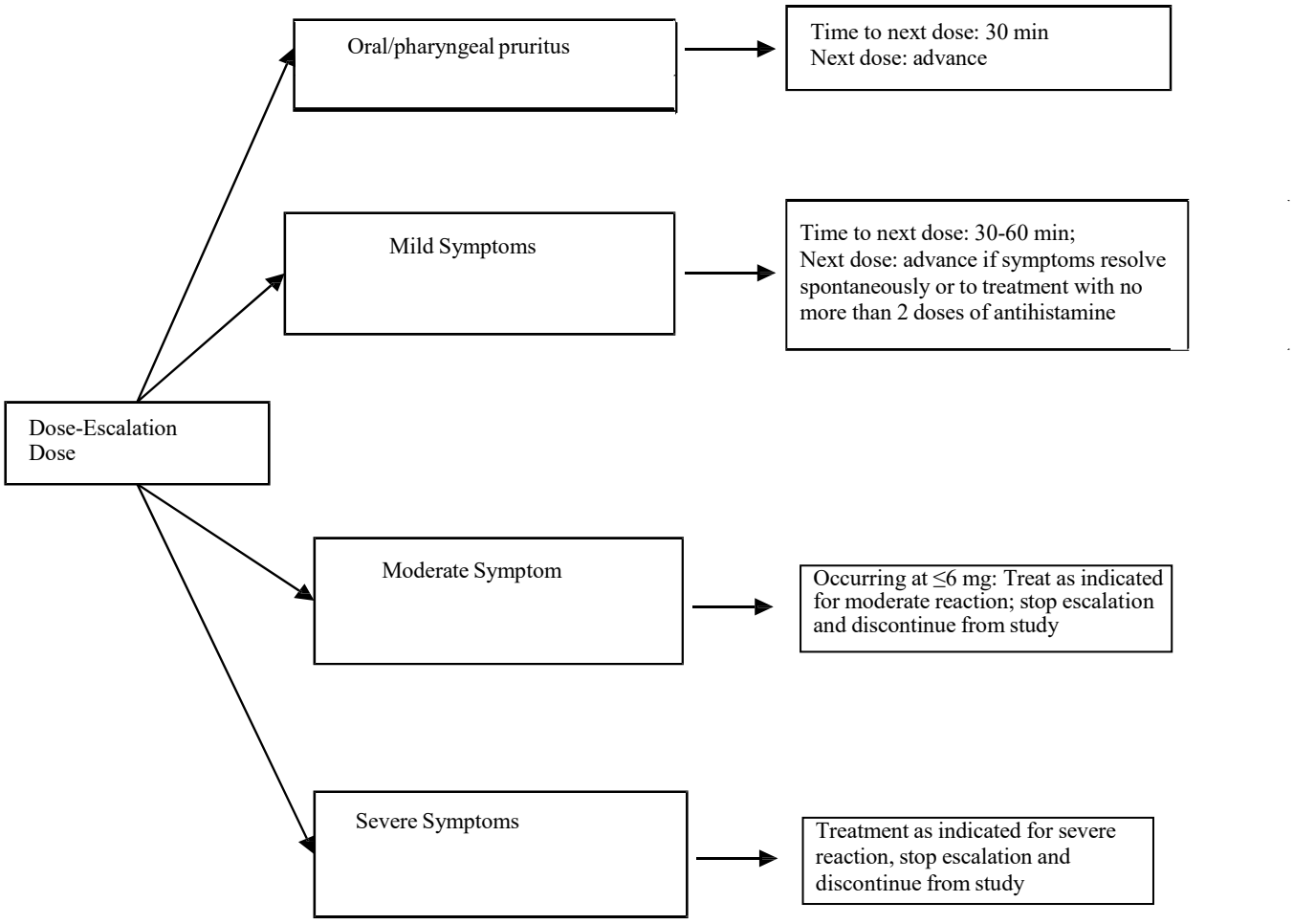
* Low systolic BP for children is defined as < 70 mmHg from 1 month to 1 year; less than (70 mmHg + [2 x age]) from 1 to 10 years; and < 90 mmHg from age 11 to 17 years.

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

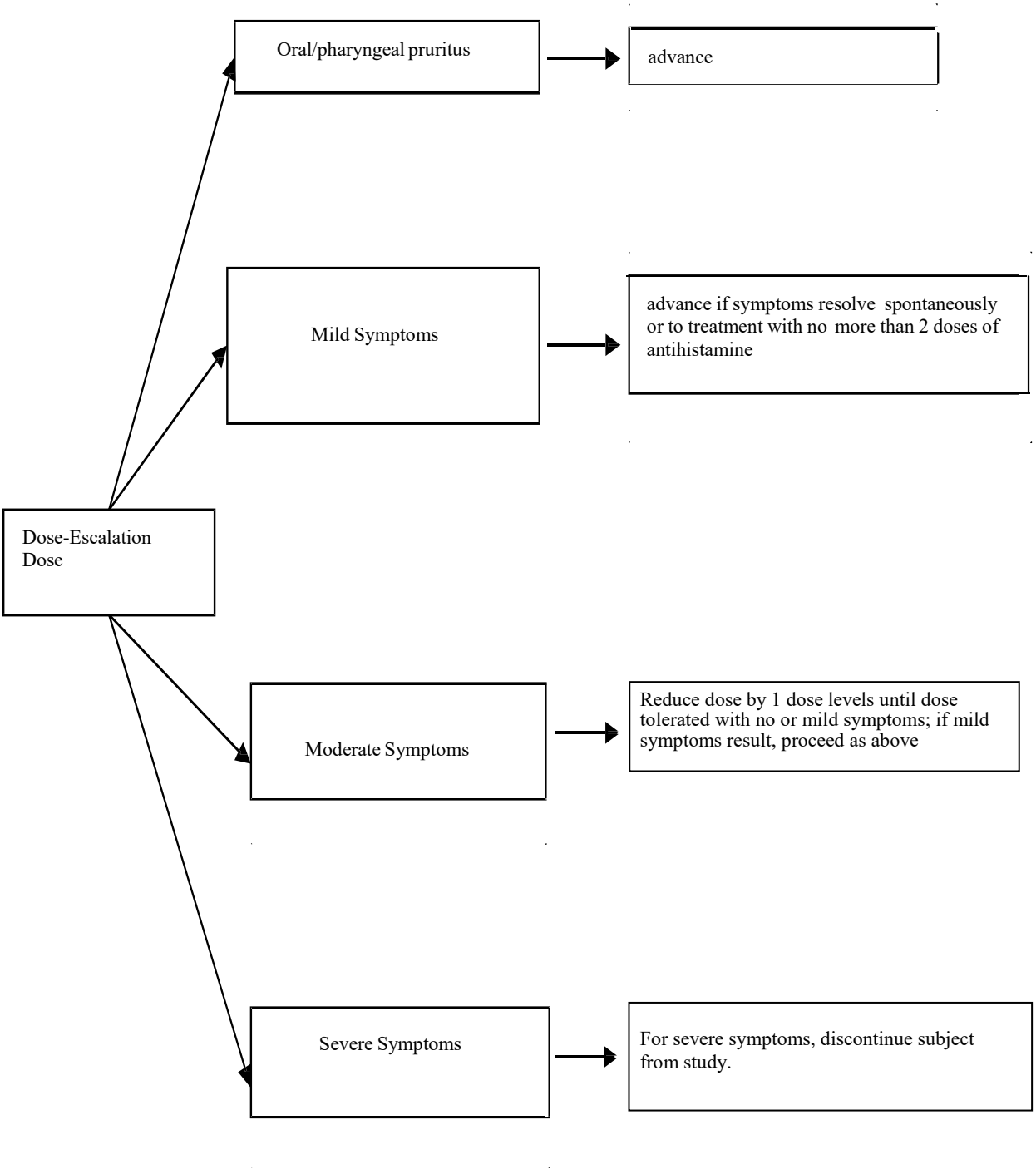
Criteria for Severity Grading (Muraro 2007)

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

APPENDIX 4. SCHEMATIC FOR AR101 INITIAL DOSE ESCALATION DAY PERFORMED IN-CLINIC AT WEEK 4



APPENDIX 5. SCHEMATIC FOR SUBSEQUENT AR101 DOSE ESCALATION DAYS PERFORMED IN-CLINIC AT WEEKS 6 THROUGH END OF UP-DOSING (WEEK 28 TO 40)



SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

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

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

Study Title: A 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)

Protocol Number: R668-ALG-16114

Protocol Version: R668-ALG-16114 Amendment 4

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor

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Sponsor's Responsible Regulatory Representative

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

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Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00116697 v1.0

ESig Approval	[redacted] 23-Jul-2020 00:35:37 GMT+0000
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