16.1.9. Documentation of Statistical Methods

The original verified electronically signed version of the document included in this appendix is available upon request.

Statistical Analysis Plan, Version 2.0, 01 December 2023

Aimmune Therapeutics, A Nestle Health Science Company
Protocol: ARC008
Version: Version 2.0

Sponsor Name:	**Aimmune Therapeutics, A Nestle Health Science Company**
Protocol Number and Title:	**ARC008** **A Multicenter, Open-Label, Longer-Term Study of AR101 Characterized Oral Desensitization Immunotherapy in Subjects Who Participated in a Prior AR101 Study**
Protocol Version and Date:	Protocol Amendment 6.0 (Global) 22 December 2020
Author:	PPD Precision for Medicine PPD
SAP Version:	Version 2.0
SAP Version Date:	01Dec2023

Notice of Confidential and Proprietary Information:

Aimmune Therapeutics, A Nestle Health Science Company
Protocol: ARC008
Version: Version 2.0

Version:	**2.0**	**Version Date:**	**01Dec2023**
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I confirm that I have reviewed this document and agree with the content.

Precision for Medicine

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ACT	Asthma Control Test
AE	Adverse Event
AEI	Adverse Event of Interest
AR101	Characterized Peanut Allergen, the Investigational Product for Study ARC008
ATC	Anatomical Therapeutic Chemical
BIW	Twice Weekly
BP	Blood Pressure
BMI	Body Mass Index
C-ACT	Childhood Asthma Control Test
CI	Confidence Interval
CODIT™	Characterized Oral Desensitization Immunotherapy
CoFAR	Consortium of Food Allergy Research
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBPCFC	Double-Blind Placebo-Controlled Food Challenge
EAACI	European Academy of Allergy and Clinical Immunology
EASI	Eczema Area and Severity Index
EDC	Electronic Data Capture
EoE	Eosinophilic Esophagitis
FAIM	Food Allergy Independent Measure
FAQL-PB	Food Allergy Quality of Life – Parental Burden
FAQLQ	Food Allergy Quality of Life Questionnaires
GI	Gastrointestinal
ICF	Informed Consent Form

Abbreviation	Description
ICH	International Conference on Harmonisation
IgE	Immunoglobulin E
IgG4	Immunoglobulin G Subclass 4
IP	Investigational Product
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NHLBI	National Heart, Lung, and Blood Institute
OLFC	Open-Label Food Challenge
PEESS	Pediatric Eosinophilic Esophagitis Symptom Scores
PEF	Peak Expiratory Flow
PRN	As Needed
ps	Peanut-Specific
PT	Preferred Term
QD	Once Daily
QOD	Every Other Day
QoL	Quality of Life
QOW	Every Other Week
QW	Once Weekly
RWPC	Real World Peanut Challenge
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SPT	Skin Prick Test
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TLF	Table, Listing and Figure
TNSS	Total Nasal Symptom Score

Abbreviation	Description
TRACK	Test for Respiratory and Asthma Control in Kids
ULOQ	Upper Limit of Quantification
US	United States
WHO-DDE	World Health Organization Drug Dictionary Enhanced
WHODrug	World Health Organization International Drug Classification Dictionary

1. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the summary tables, data listings, and figures that will be produced and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions to be drawn with respect to the study objectives.

The ARC008 study took place during the global Coronavirus Disease 2019 (COVID-19) pandemic. The total duration of the study and duration of study treatment for individual subjects was extended as needed to allow subjects to complete study treatment following delays due to pandemic restrictions. Visits continued to occur remotely and so exposure data and specific safety data, including but not limited to adverse events (AEs) and concomitant medications, continued to be collected during this time. More details on how the study was to be conducted during the pandemic are given in Appendix 12 of the protocol.

1.1. DOCUMENT HISTORY

SAP Final Version 1 was approved prior to database lock (Oct2023). Updates for Version 2 of the SAP are being made post-database lock and are restricted to Appendix A to incorporate modifications to the adjudicated data as determined by the Nestle Health Science study team.

1.2. RESPONSIBILITIES

The SAP was prepared by Precision for Medicine ("Precision"). Precision will perform the final statistical analyses and be responsible for the production and quality control of all tables, listings, and figures.

1.3. TIMING OF ANALYSES

Interim Analysis No interim analysis of efficacy is planned for this study.

Final Analysis The final analysis of safety and efficacy is planned after all subjects complete Study Exit/Early Discontinuation Visit assessments. The final analysis will include data collected through to the time of database lock.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of the study is to describe safety and tolerability during longer-term administration of AR101 and follow-up observation after the last dose of AR101.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are to:

- Assess the level of desensitization achievable through extended maintenance dosing of AR101
- Characterize the interaction of AR101 and asthma control or nasal allergy symptoms in subjects with a history of asthma and/or allergic rhinitis
- Evaluate subjects' quality of life (QoL) and treatment satisfaction during AR101 treatment on daily and non-daily treatment regimens
- Evaluate parent/caregiver QoL during the child's treatment with AR101

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives of the study are:

- To evaluate effects on immunologic parameters after longer-term administration of AR101 and follow-up observation after the last dose of AR101
- To evaluate changes in control of pre-existing asthma or atopic dermatitis in subjects from prior study ARC005

2.4. BRIEF DESCRIPTION OF STUDY DESIGN

ARC008 is a phase 3, international, open-label, longer-term study of an AR101 Characterized Oral Desensitization Immunotherapy (CODIT™) regimen in children and adults with peanut allergy. Subjects entering ARC008 will originate from an Aimmune AR101 clinical study or any future clinical study that identifies ARC008 as a potential poststudy option in the parent study protocol. The potential number of subjects who may be enrolled in this study is approximately 950 subjects. The total duration of the study is approximately 10 years.

The study schematic is provided in Figure 1 and the treatment pathways and study visits and periods are briefly described in the sections that follow.

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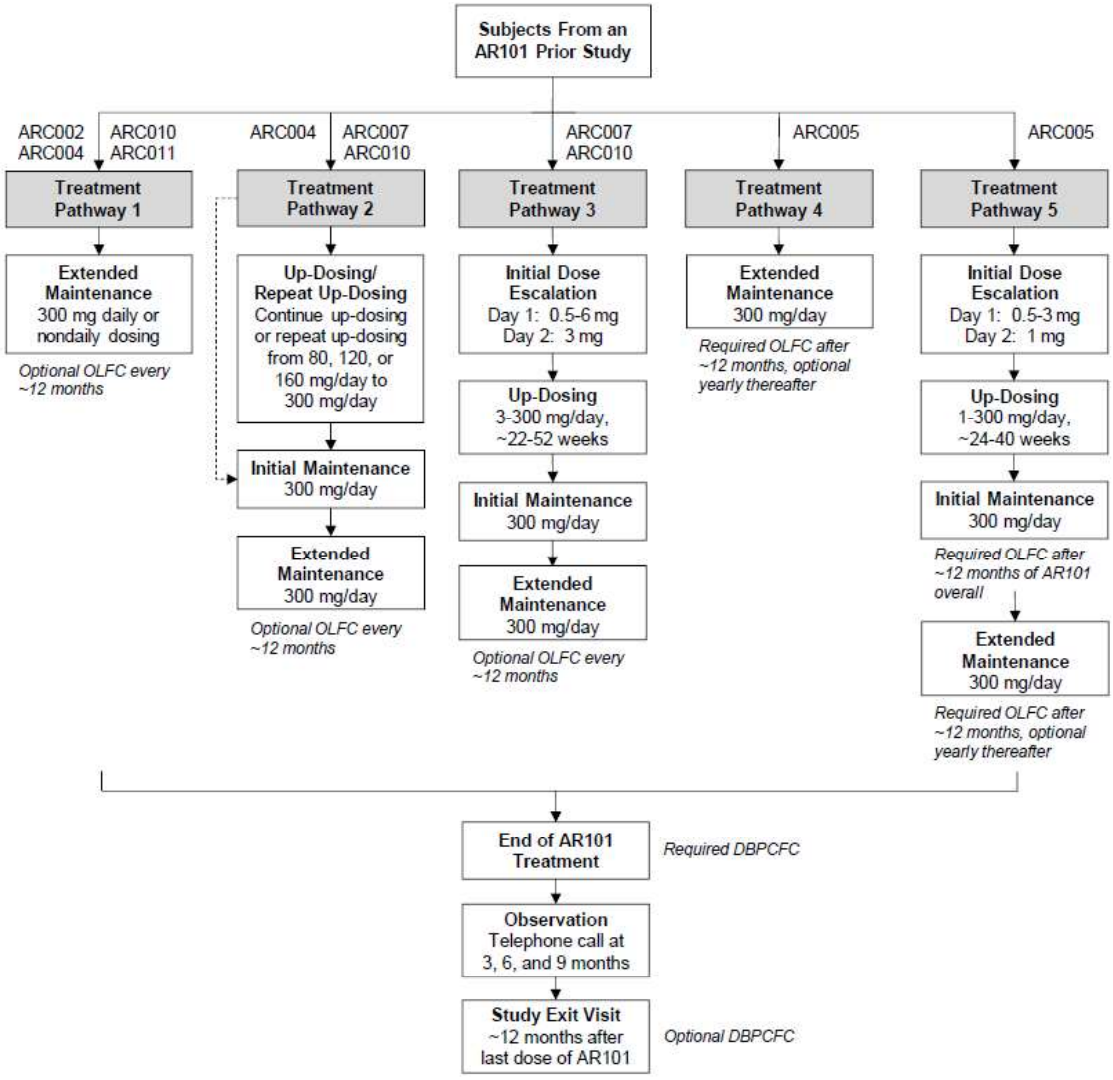
Figure 1: Study Schematic



DBPCFC, double-blind, placebo-controlled food challenge; OLFC, open-label food challenge.

For subjects in Treatment Pathway 1, 2, or 4, initiation of AR101 in ARC008 occurs on the same day as or within 3 days after the Exit/Early Discontinuation visit in the parent study, unless specified otherwise in the parent study protocol. For subjects in Treatment Pathway 3 or 5, initiation of AR101 in ARC008 occurs on the same day as or within 10 days after the Screening/Baseline visit.

Treatment Pathway 2 only: Subjects who enter Treatment Pathway 2 in ARC008 soon after completing the ARC004 Early Discontinuation visit will enter the Repeat Up-Dosing Period after the Screening/Baseline visit. Subjects who complete the Repeat Up-Dosing Period or who tolerate AR101 300 mg/day for 2 weeks in ARC004 will proceed to the Initial Maintenance Period after the ARC008 Screening/Baseline visit. Subjects who complete both the Repeat Up-Dosing and Initial Maintenance Periods or receive AR101 300 mg/day for at least 24 weeks in ARC004 will proceed to the Extended Maintenance Period after the ARC008 Screening/Baseline visit.

2.4.1. Treatment Pathways

Because the dosing regimens and procedures in the parent studies are not uniform, subjects will receive AR101 in 1 of 5 treatment pathways in ARC008:

- Treatment Pathway 1 is for subjects who received and tolerated AR101 in a daily or non-daily regimen in the parent study (except study ARC005). These subjects will undergo a Screening/Baseline visit, and eligible subjects will enter the Extended Maintenance Period. Subjects entering ARC008 on a dose > 300 mg once daily (QD) will switch to 300 mg QD on the first day of the Extended Maintenance Period. Subjects from parent study ARC004 on non-daily regimens who did not tolerate 600 mg peanut protein (1043 mg peanut protein cumulative dose) at the ARC004 Exit double-blind, placebo-controlled food challenge (DBPCFC) will switch to 300 mg QD on the first day of the Extended Maintenance Period. Subjects receiving non-daily AR101 regimens in parent study ARC004 who tolerated 600 mg peanut protein (1043 mg peanut protein cumulative dose) at the ARC004 Exit DBPCFC will continue the non-daily AR101 regimen in the Extended Maintenance Period.

- Treatment Pathway 2 is for the following subjects:

    - Subjects who did not complete their AR101 dosing regimen (eg, up-dosing, maintenance) in an eligible parent study (except study ARC005).

    - Subjects from parent study ARC004, or any future clinical study identifying ARC008 as a follow-on study, who received a non-daily AR101 dosing regimen and who did not tolerate this regimen.

    - Subjects from ARC004 who missed or withheld their non-daily AR101 dose for > 3 days, and subjects who received a non-daily AR101 dosing regimen and tolerated less than the 300 mg single dose of peanut protein (443 mg cumulative) at the ARC004 Exit DBPCFC, if continued treatment with AR101 was determined to be safe per investigator judgment and after discussion with the medical monitor.

  Subjects who did not complete their AR101 dosing regimen in an eligible parent study will have a Screening/Baseline visit and continue the regimen in ARC008, proceeding through the applicable study periods until the End of Treatment visit. Subjects who enter ARC008 soon after completing the ARC004 Early Discontinuation visit will have a Screening/Baseline visit, and eligible subjects will start the Repeat Up-Dosing Period at a dose of 80, 120, or 160 mg QD (a decrease in AR101 dose of approximately 50% to 75%) at the discretion of the investigator. These subjects will then proceed sequentially through the Initial Maintenance Period and Extended Maintenance Period. Subjects who complete the Repeat Up-

Dosing Period or who tolerate AR101 300 mg QD for 2 weeks in ARC004 will have a Screening/Baseline visit in ARC008 and then proceed to the Initial Maintenance Period. Subjects who complete both the Repeat Up-Dosing and Initial Maintenance Periods or receive AR101 300 mg QD for at least 24 weeks in ARC004 will have a Screening/Baseline visit in ARC008 and then proceed to the Extended Maintenance Period. In addition, ARC004 subjects who tolerated the non-daily regimen in ARC004 but who subsequently do not tolerate the non-daily regimen after entering ARC008 Treatment Pathway 1 may switch to Treatment Pathway 2 and start the Repeat Up-Dosing Period at investigator discretion.

- Treatment Pathway 3 is for subjects who received placebo in the parent study (except study ARC005). These subjects will undergo a Screening/Baseline visit, and eligible subjects will start the Initial Escalation Period with a dose of 0.5 mg. Subjects will then proceed sequentially through the Up-Dosing Period, Initial Maintenance Period, and Extended Maintenance Period.

- Treatment Pathway 4 is for subjects who received AR101 and tolerated the 300 mg/day dose for at least 2 consecutive weeks before the exit DBPCFC in parent study ARC005. These subjects will have a Screening/Baseline visit, and eligible subjects will start the Extended Maintenance Period.

- Treatment Pathway 5 is for subjects who received placebo in parent study ARC005. These subjects will have a Screening/Baseline visit, and eligible subjects will start the Initial Escalation Period at a dose of 0.5 mg. Subjects will then proceed sequentially through the Up-Dosing Period, Initial Maintenance Period, and Extended Maintenance Period.

2.4.2. Study Visits and Periods

2.4.2.1. Screening/Baseline Visit (All Treatment Pathways)

Subjects treated with placebo in their parent study will have a Screening/Baseline visit followed by initiation of AR101 treatment in ARC008, which should occur on the same day as or within 10 days after the Screening/Baseline visit.

Subjects treated with AR101 in their parent study will have a Screening/Baseline visit followed by initiation of AR101 treatment in ARC008, which will occur on the same day as or within 3 days after the Exit visit or Early Discontinuation visit of the subject's parent study, unless specified otherwise in the parent study protocol.

2.4.2.2. Initial Escalation Period (Treatment Pathways 3 and 5)

All Initial Escalation Period doses will be administered by study site personnel under direct observation in the clinic.

Treatment Pathway 3

Eligible subjects will initiate AR101 at a dose of 0.5 mg of AR101 and then increase the dose incrementally at 20- to 30-minute intervals over the course of a single day to a maximum dose of 6 mg.

Subjects who do not tolerate ≥ 3 mg dose on Day 1 will discontinue dosing and complete the End of Treatment visit.

Subjects who tolerate ≥ 3 mg dose on Day 1 will undergo confirmatory dosing of a single 3 mg dose on the following day, Day 2. Subjects who tolerate this confirmatory dose will enter the Up-Dosing Period. Subjects who do not tolerate this confirmatory dose will discontinue dosing and complete the End of Treatment visit.

Treatment Pathway 5

Eligible subjects will begin initial dose escalation on Day 1 with a stepwise dose escalation of AR101 (up to 4 single doses of 0.5, 1, 1.5, and 3 mg) administered at 20- to 30-minute intervals as tolerated. Subjects who tolerate the 3 mg dose on Day 1 will return on Day 2 for a single 1 mg dose. Subjects who tolerate the 1 mg dose with no more than mild allergy symptoms that are not dose-limiting will begin the Up-Dosing Period. Subjects who do not tolerate any dose on Day 1 or Day 2 will discontinue dosing and complete the End of Treatment visit.

2.4.2.3. Up-Dosing Period (Treatment Pathways 2, 3, and 5)

The Up-Dosing Period is designed to allow stepwise increases in AR101 dose over 2-week intervals to build up tolerance to the allergen while minimizing AEs. The first dose at each new dose level will be administered in the clinic. Subsequent doses will be dispensed to the subject or parent/caregiver and administered at home.

To escalate to the next dose, a subject must be tolerating the current dose. Some subjects may require de-escalation, and once the lower dose is tolerated they may again attempt increasing the dose.

Treatment Pathway 2

Subjects who did not complete their AR101 up-dosing regimen in an eligible parent study will have a Screening/Baseline visit and continue up-dosing in ARC008, proceeding through the applicable study periods until the End of Treatment visit.

Subjects who enter ARC008 soon after completing the ARC004 Early Discontinuation visit will have a Screening/Baseline visit in ARC008 and then enter a Repeat Up-Dosing Period, starting with a daily dose of AR101 at 80, 120, or 160 mg/day at the discretion of the investigator. The dose will be increased every 2 weeks until the maximum daily dose

of 300 mg is reached. Subjects who tolerate the 300 mg/day dose for 2 weeks will receive 300 mg QD for 24 weeks in the Initial Maintenance Period. ARC004 subjects who tolerated the non-daily regimen in ARC004 but who subsequently do not tolerate the non-daily regimen after entering ARC008 Treatment Pathway 1 may switch to Treatment Pathway 2 and start the Repeat Up-Dosing Period at investigator discretion.

Treatment Pathway 3

Subjects in Treatment Pathway 3 will receive AR101 starting at a dose of 3 mg QD and escalate every 2 weeks to a maximum of 300 mg QD, according to the Up-Dosing Schedule. Those subjects who reach the target dose of 300 mg QD of AR101 will take this dose for 2 additional weeks as part of the Up-Dosing Period. Subjects who do not tolerate the 300 mg QD dose of AR101 for 2 weeks within 52 weeks (ie, must reach 300 mg dose by 50 weeks) after starting the Up-Dosing Period will discontinue dosing and complete the End of Treatment visit. Once a subject tolerates the 300 mg dose for 2 weeks in the Up-Dosing Period, the subject will then enter the Initial Maintenance Period and receive the 300 mg dose for 24 weeks.

Treatment Pathway 5

Subjects will receive AR101 starting at the 1 mg/day dose and dose escalation will occur every 2 weeks until the maximum daily dose of 300 mg is reached. Subjects who tolerate the 300 mg/day dose for 2 weeks within 40 weeks after start of up-dosing will begin the Initial Maintenance Period. Subjects who do not tolerate the 300 mg/day dose for 2 weeks within 40 weeks after start of up-dosing will discontinue dosing and complete the End of Treatment visit.

2.4.2.4. Initial Maintenance Period (Pathways 2, 3, and 5)

Subjects in Treatment Pathways 2, 3, and 5 who reach the target dose of 300 mg daily of AR101 and tolerate the dose for 2 additional weeks will return for an in-clinic visit to mark the End of Up-Dosing in this study. The following day, subjects will enter the Initial Maintenance Period and continue dosing with AR101 at 300 mg QD. Dosing on study visit days will take place in the clinic under direct observation.

Subjects in Treatment Pathway 2 who completed the Up-Dosing/Repeat Up-Dosing Period or who tolerated AR101 300 mg QD for 2 weeks in ARC004 will enter the Initial Maintenance Period after the ARC008 Screening/Baseline visit. Subjects who did not complete their AR101 maintenance regimen in an eligible parent study (except study ARC005) will have a Screening/Baseline visit and begin the Initial Maintenance Period in ARC008.

Subjects in Treatment Pathways 2 and 3 will return for in-clinic visits at approximately Weeks 8 and 16 of the Initial Maintenance Period before returning at Week 24 to complete this Period and enter Extended Maintenance.

Subjects in Treatment Pathway 5 will continue initial maintenance (with clinic visits every 4 weeks) for an overall total of approximately 12 months of treatment (including initial dose escalation, up-dosing, and maintenance treatment). The duration of initial maintenance treatment may vary from a minimum of 12 weeks to a maximum of 24 weeks depending on the duration of up-dosing (24-40 weeks). Subjects in Treatment Pathway 5 will have an open-label food challenge (OLFC) at the end of initial maintenance (ie, after an overall total of approximately 12 months of treatment).

2.4.2.5. Extended Maintenance Period (All Treatment Pathways)

The last treatment period for all treatment pathways is the Extended Maintenance Period. Subjects who completed initial maintenance in the parent AR101 study (Treatment Pathways 1 and 4) will enter the Extended Maintenance Period after the Screening/Baseline visit, and the other subjects (Treatment Pathways 2, 3, and 5) will enter this period after completing the Initial Maintenance Period in this study, after completing both the Repeat Up-Dosing and Initial Maintenance Periods in their parent study, or after receiving AR101 300 mg QD for at least 24 weeks in their parent study.

During the Extended Maintenance Period, subjects will continue their current dosing regimen (300 mg QD, every other day [QOD], twice weekly [BIW], once weekly [QW], or every other week [QOW]), and study visits will occur approximately every 3 months. Subjects in Treatment Pathways 1, 2, and 3 who enter this period will have the option to participate in an OLFC to assess level of desensitization to peanut protein after 12 months in the Extended Maintenance Period and yearly thereafter. For subjects in Treatment Pathways 4 and 5, the OLFC after the first 12 months of extended maintenance treatment is required and then optional yearly thereafter.

2.4.2.6. End of Treatment Visit (All Treatment Pathways)

After protocol amendment 6.0 is approved at the study site:

- Subjects in the United States (US) from prior studies ARC007 and ARC011 who have access to commercially available product will have the End of Treatment visit at their next scheduled study site (not remote) visit.

- Subjects in the US from prior studies ARC002 or ARC004 who have access to commercially available product may have the End of Treatment visit at their next scheduled study site (not remote) visit if so directed by the study sponsor when necessary for operational considerations.

- Subjects from prior study ARC005 will return to the study site for the End of Treatment visit when they complete at least approximately 3 years total of AR101 treatment including study ARC005 and AR101 is commercially available in their country, or discontinue early.

- All other subjects will return to the study site for the End of Treatment visit when they complete at least approximately 5 years total of AR101 treatment including all prior studies and AR101 is commercially available in their country, or discontinue early.

A DBPCFC will be performed at the End of Treatment visit; subjects who discontinue AR101 treatment early for safety reasons will not have the DBPCFC. All subjects will have telephone follow-up at least 14 days after the last dose of AR101 or last food challenge, whichever is last.

2.4.2.7. Follow-Up Observation Period (All Treatment Pathways)

The End of Treatment visit will be followed by a 12-month observation period. During observation, management of peanut allergy will be guided by the subject's physician. Observation assessments will be conducted by telephone at 3, 6, and 9 months to enquire about the following:

- Current treatment plan (eg, commercially available product, complete peanut avoidance, use of food equivalents for peanut oral immunotherapy, other investigational immunotherapy, other)

- Events of systemic allergic reactions, eosinophilic esophagitis (EoE), accidental/non-accidental exposures to food allergens and their outcomes, use of epinephrine, hospitalizations (all causes), emergency department visits (all causes), and serious adverse events (SAEs)

2.4.2.8. Study Exit Visit (All Treatment Pathways)

The Study Exit visit will be conducted approximately 12 months after the last dose of AR101. An optional DBPCFC may be performed.

2.5. DETERMINATION OF SAMPLE SIZE

The potential number of subjects who may be enrolled in this study is approximately 950. The sample size will be determined by the number of eligible subjects from each of the prior AR101 studies who participate in this study.

2.6. TREATMENT ASSIGNMENT

ARC008 is an open-label study. Subjects will receive AR101 in 1 of 5 treatment pathways in ARC008 as described in Section 2.4.

2.7. ADMINISTRATION OF STUDY TREATMENT

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 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 capsules will be provided in prepackaged dosing kits. 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 a 7-day overage to accommodate potential visit scheduling issues.

For Initial and Extended Maintenance Period dosing, a 300 mg AR101 dose will be provided in sealed, foil-laminate (1 sachet/day). Sachets will be provided in kits containing 35 individual doses.

All doses scheduled to be administered on clinic visit days will be taken at the clinic. Subjects should withhold their daily home AR101 dose on in-clinic dosing days. At each clinic visit in the Up-Dosing, Initial Maintenance, and Extended Maintenance Periods, the subject or parent/caregiver will receive a kit of capsules or sachets to be taken at home according to the current dose level. For Treatment Pathways 4 and 5 only, the parent/caregiver will be instructed to record the capsules/sachets taken at home in a diary log.

3. ENDPOINTS

3.1. SAFETY ENDPOINTS

The primary safety endpoints are as follows:

- Frequency of AEs
- Frequency of premature discontinuation of AR101 dosing due to AEs
- Frequency of premature discontinuation of dosing due to chronic/recurrent gastrointestinal (GI) AEs
- Frequency of AEs that lead to a change in treatment regimen
- Frequency of AEs that lead to early withdrawal
- Frequency of anaphylaxis
- Frequency of use of epinephrine as a rescue medication
- Frequency of accidental/non-accidental ingestion of peanut and other allergenic foods
- Frequency of AEs following accidental/non-accidental exposure to peanut and other allergenic foods
- Frequency of EoE

The secondary safety endpoints are as follows:

- Change in peak expiratory flow (PEF)
- Change in Childhood Asthma Control Test (C-ACT) and Asthma Control Test (ACT) score
- Change in Total Nasal Symptom Score (TNSS)

3.2. EFFICACY ENDPOINTS

The secondary efficacy endpoints are as follows:

- Proportion of subjects tolerating each challenge dose in the OLFC and the DBPCFC

- The maximum tolerated challenge dose at each food challenge
- Change in tolerated dose of peanut protein
- Maximum severity of symptoms in each food challenge
- Frequency of use of epinephrine as a rescue medication during the food challenges
- Changes in food allergy QoL scores as measured by Food Allergy Quality of Life Questionnaires (FAQLQ), and the Food Allergy Independent Measure (FAIM) questionnaire
- Change in Food Allergy Quality of Life – Parental Burden (FAQL-PB) questionnaire score

3.3. EXPLORATORY ENDPOINTS

The exploratory endpoints are as follows:

- Change in peanut-specific (ps) and peanut component-specific serum immunoglobulin G subclass 4 (IgG4)
- Change in total, peanut-specific, and peanut component-specific serum immunoglobulin E (IgE)
- Change in peanut skin prick test (SPT) mean wheal diameter
- Change in Test for Respiratory and Asthma Control in Kids (TRACK) and Eczema Area and Severity Index (EASI) scores

4. ANALYSIS POPULATION

The following analysis population will be defined for this study:

Safety Population: The Safety Population will consist of all subjects who receive AR101 during ARC008. The Safety Population will be used for all analyses.

5. PROTOCOL DEVIATIONS

Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. All protocol deviations will be reported on a specific case report form (CRF) as follows:

- Inclusion Criteria
- Exclusion Criteria
- Received Incorrect Study Treatment
- Informed Consent Form (ICF)
- SAE Not Reported
- Visit Out Of Window
- Missed Study Visit
- Procedure Not Per Protocol
- Prohibited Concomitant Medication
- Lab Sample Missed
- Study Drug Compliance
- Other, Specify

These protocol deviations will be reviewed prior to database lock and their categorization as major or minor will be determined prior to database lock. All protocol deviations, both major and non-major, will be listed and included in the study report.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. STATISTICAL NOTATION AND METHODOLOGY

Unless otherwise stated, the term “descriptive statistics” refers to the number of subjects (n), mean, median, standard deviation, minimum, and maximum for continuous variables and frequencies and percentages for categorical variables.

Unless specified otherwise, the denominator for percentages for categorical data will be based on the number of subjects or observations with non-missing data appropriate for summary purposes. The denominator for percentages for incidence data (such as AEs) will be based on the number of subjects in the analysis population “at risk”. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of subjects in each category, as appropriate.

Minimum and maximum values will be presented at the precision of the original value, means and medians will be rounded to 1 decimal place greater than the precision of the original value, standard deviations and standard errors will be rounded to 2 decimal places greater than the precision of the original value. Percentages will be rounded to 1 decimal place. Percentages that round down to 0 or up to 100% will be displayed as “<0.1%” and “>99.9%”, respectively. Other statistics (e.g., confidence intervals [CIs]) will be presented using the same general rules outlined above or assessed for the most appropriate presentation based on the underlying data.

Unless otherwise noted, values reported as greater than or less than some quantifiable limit (e.g., “< 1.0”) will be summarized with the sign suppressed in summary tables and figures, using the numeric value reported. Data will display on subject listings to include the sign.

In general, summary tables will be presented by combining subjects from each of the treatment pathways into a single treatment group (AR101).

All relevant data collected in the database and any derived data will be included in data listings and unless otherwise noted sorted by treatment pathway, subject ID, test/measurement, and visit and time point as appropriate.

All statistical methods will be based on the International Conference on Harmonisation (ICH)-E9 Guidance for Industry "Statistical Principles for Clinical Trials".

A review of the database will be conducted before database lock. Any decision to amend the planned statistical analysis will be documented in an amendment to the SAP prior to database lock and details will be included in the clinical study report (CSR).

If the assumptions underlying the formal statistical methods proposed are not met during the analysis of the final data, an alternative, more appropriate, statistical method will be

used and any changes documented in the statistical methods section of the CSR, including the rationale for use.

Additional exploratory analyses of the data will be conducted as deemed appropriate. These analyses will be fully documented and clearly identified as post-hoc and exploratory.

6.2. STRATA AND COVARIATES

There are no planned applications of covariate adjustments or stratification; all statistical results are descriptive in nature.

6.3. SUBGROUP ANALYSES

The overall summary of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) (Section 9.1) and the summary of rescue medications (Section 9.12) will be repeated for the following subgroups:

- Treatment Pathways 1-3
- Treatment Pathways 4-5
- Daily dosing regimen
- Non-daily dosing regimen

Daily and non-daily dosing regimen subgroups are based on the initial regimen assigned in ARC008.

The overall summary of treatment-emergent AEs of interest (AEIs) and treatment-emergent serious AEIs will also be summarized separately for Treatment Pathways 1-3 and 4-5.

Immunoglobulin values will also be summarized separately for Treatment Pathways 1-3, 4, and 5.

6.4. MULTIPLE COMPARISONS AND MULTIPLICITY

No adjustments will be made for multiple comparisons. Results are descriptive in nature and there will be no formal comparisons made.

6.5. SIGNIFICANCE LEVEL

No formal statistical analysis will be performed. This study is exploratory in nature; descriptive statistics will be tabulated and reviewed to evaluate all study endpoints.

7. DATA HANDLING METHODS

7.1. VISIT WINDOWS

All data other than those described below will be listed, summarized, and analyzed according to the nominal visit time points or study period.

7.1.1. Subjects Tolerating Each Challenge Dose and the Maximum Tolerated Dose at Each OLFC

In the summary and listings of subjects tolerating each OLFC dose and the maximum tolerated dose (MTD) at each food challenge (Section 10.1), visits will be reassigned to a study visit based on the actual days relative to the start of Extended Maintenance using the visit windows identified in Table 1 below. As described in Section 2.4, subjects in Treatment Pathway 5 will have an OLFC at the End of Initial Maintenance (ie, after an overall total of approximately 12 months of treatment). Subjects in Treatment Pathways 1, 2, and 3 will have the option to participate in an OLFC after 12 months in the Extended Maintenance Period and yearly thereafter. For subjects in Treatment Pathways 4 and 5, the OLFC after the first 12 months of extended maintenance treatment is required and then optional yearly thereafter. Visit windows are therefore defined to capture all possible OLFCs for each treatment pathway.

For Treatment Pathways 1 and 4, the start of Extended Maintenance is defined as the date and time of first in-clinic or at home dose of treatment in ARC008. For Treatment Pathways 2, 3, and 5, the start of an Extended Maintenance is defined as the first visit labeled as an Extended Maintenance visit.

Table 1 Visit Windows for Analysis of Subjects Tolerating Each Challenge Dose and the MTD at Each Food Challenge

Treatment Pathway	Visit	Months Since Start of Extended Maintenance	
		Target Month	Window Interval
5	End of Initial Maintenance	0	< 6
1-4	Extended Maintenance: Month 12	12	< 18
5	Extended Maintenance: Month 12	12	[6 , 18)
All (1-5)	Extended Maintenance: Month 24	24	[18, 30)
All (1-5)	Extended Maintenance: Month 36	36	[30, 42)
All (1-5)	Extended Maintenance: Month 48	48	[42, 54)
All (1-5)	Extended Maintenance: Month 60	60	≥ 54

If more than one value is mapped to the same visit, the value collected closest to the target month will be considered for summarization. If two values collected on different days are mapped to the same scheduled visit and are equidistant from the target month, the earlier of the values will be considered.

7.1.2. Peanut-Specific and Peanut Component-Specific IgE and IgG4

In the summaries of peanut-specific and peanut component-specific IgE and IgG4 (Section 11.1), End of Up-Dosing, End of Initial Maintenance, and Extended Maintenance visits will be reassigned to a study visit based on the actual days relative to the start of Extended Maintenance using the visit windows identified in Table 2 below. According to schedules of events in the appendices of the protocol, subjects in Treatment Pathways 2 and 3 will have scheduled immunology blood sample collection at End of Up-Dosing and subjects in Treatment Pathways 2, 3, and 5 will have a scheduled collection at the End of Initial Maintenance. Subjects from all treatment pathways will also have scheduled blood sample collection after the first 12 months of extended maintenance treatment and yearly thereafter as well as at End of Treatment and Study Exit. Visit windows are therefore defined to capture all scheduled blood sample collection for each treatment pathway. Nominal visits will be used in the summary of End of Treatment and Study Exit visits.

For Treatment Pathways 1 and 4, the start of Extended Maintenance is defined as the date and time of first in-clinic or at home dose of treatment in ARC008. For Treatment Pathways 2, 3, and 5, the start of an Extended Maintenance is defined as the first visit labeled as an Extended Maintenance visit.

Table 2 Visit Windows for Analysis of Immunoglobulin Results

Treatment Pathway	Visit	Months Since Start of Extended Maintenance	
		Target Month	Window Interval
2, 3	End of Up-Dosing	-6	< 0
2, 3	End of Initial Maintenance	0	[0, 6)
5	End of Initial Maintenance	0	< 6
1, 4	Extended Maintenance: Month 12	12	[0, 18)
2, 3, 5	Extended Maintenance: Month 12	12	[6 , 18)
All (1-5)	Extended Maintenance: Month 24	24	[18, 30)
All (1-5)	Extended Maintenance: Month 36	36	[30, 42)
All (1-5)	Extended Maintenance: Month 48	48	[42, 54)
All (1-5)	Extended Maintenance: Month 60	60	≥ 54

If more than one value is mapped to the same visit, the value collected closest to the target month will be considered for summarization. If two values collected on different days are mapped to the same scheduled visit and are equidistant from the target month, the earlier of the values will be considered. Nominal visits will be presented in the data listings of peanut-specific and peanut component-specific IgE and IgG4 results.

7.1.3. Skin Prick Test

In the summaries of skin prick test results (Section 11.2), End of Up-Dosing, End of Initial Maintenance, and Extended Maintenance visits will be reassigned to a study visit based on the actual days relative to the start of Extended Maintenance using the visit windows identified in Table 3 below. According to schedules of events in the appendices of the protocol, subjects in Treatment Pathways 2 and 3 will have scheduled skin prick tests at End of Up-Dosing and subjects in Treatment Pathway 5 will have a scheduled test at the End of Initial Maintenance. Subjects from all treatment pathways will also have scheduled skin prick tests after the first 12 months of extended maintenance treatment and yearly thereafter as well as at End of Treatment and Study Exit. Visit windows are therefore defined to capture all scheduled skin prick tests for each treatment pathway. Nominal visits will be used in the summary of End of Treatment and Study Exit visits.

For Treatment Pathways 1 and 4, the start of Extended Maintenance is defined as the date and time of first in-clinic or at home dose of treatment in ARC008. For Treatment Pathways 2, 3, and 5, the start of an Extended Maintenance is defined as the first visit labeled as an Extended Maintenance visit.

Table 3 Visit Windows for Skin Prick Test Results

Treatment Pathway	Visit	Months Since Start of Extended Maintenance	
		Target Month	Window Interval
2, 3	End of Up-Dosing	-6	< 0
5	End of Initial Maintenance	0	< 6
1-4	Extended Maintenance: Month 12	12	[0, 18)
5	Extended Maintenance: Month 12	12	[6 , 18)
All (1-5)	Extended Maintenance: Month 24	24	[18, 30)
All (1-5)	Extended Maintenance: Month 36	36	[30, 42)
All (1-5)	Extended Maintenance: Month 48	48	[42, 54)
All (1-5)	Extended Maintenance: Month 60	60	≥ 54

If more than one value is mapped to the same visit, the value collected closest to the target month will be considered for summarization. If two values collected on different days are mapped to the same scheduled visit and are equidistant from the target month, the earlier of the values will be considered. Nominal visits will be presented in the data listings of skin prick test results.

7.2. DATA PRESENTATION

Individual subject data listings will be provided to support summary tables and serve as a data source. Unless otherwise noted, all electronic data capture (EDC) data collected in the clinical database for all enrolled subjects will be included in the data listings, including the derived study period flags and captured nominal visit labels. If a listing includes screen failures, they will be listed as such and sorted after all enrolled subjects.

Visits labelled as unscheduled will also be listed.

7.3. MAXIMUM TOLERATED CHALLENGE DOSE AT EACH FOOD CHALLENGE

The MTD for a food challenge is defined as the maximum single dose of peanut protein resulting in no more than mild symptoms and assessed by the investigator to have been tolerated (i.e., the subject did not experience any dose-limiting symptoms). Any symptom requiring treatment is inherently dose-limiting; thus, a dose during a food challenge cannot be considered “tolerated” if treatment was deemed necessary by the investigator.

7.4. DATA DERIVATIONS AND DEFINITIONS

The following definitions and derivations will be used throughout this study:

- Study Day is calculated as (assessment date – date of first dose of AR101 in ARC008 + 1) for assessments and visits performed on or after the date of first dose of AR101 in ARC008, and (assessment date – date of first dose of AR101 in ARC008) for assessments and visits prior to the date of first dose of AR101 in ARC008. There will therefore be no Study Day 0.

- Baseline is defined as the last non-missing value prior to the first dose of AR101 in ARC008.

- Change from baseline is calculated as observed value after the first dose of AR101 in ARC008 – baseline value.

- A duration expressed in months will be calculated by dividing the duration in days by (365.25 / 12).

- A duration expressed in years will be calculated by dividing the duration in days by 365.25.

The study periods are defined in Table 4 (used to create the study period flags) with the first and last dose dates for each study period being identified as follows:

Table 4 Study Period Definitions

Study Period	Treatment Pathways	First Dose Date	Last Dose Date
Initial Escalation	3 and 5	Date and time of first in-clinic dose at Initial Escalation Day 1	Date of latest in-clinic dose at Initial Escalation Day 1 or Day 2. Set the time to be 23:59 and 59 seconds on each of these respective days.
Up-Dosing	2	For subjects that do not undergo Repeat Up-Dosing: the date and time of first in-clinic or at home dose of treatment in ARC008 if prior to date of first Initial Maintenance Visit. For subjects that undergo Repeat Up-Dosing: the date repeat up-dosing (Treatment Pathway 2) was started.	Date of first in-clinic dose of 300 mg during the Up-Dosing period. For subjects who do not reach the 300 mg dose: the latest of the last in-clinic dose during the Up-Dosing period or the date of last dose at home. Set the time to be 23:59 and 59 seconds on the respective day.
	3 and 5	The day following the date of last in-clinic dose at Initial Escalation Day 2	Date of first in-clinic dose of 300 mg during the Up-Dosing period. For subjects who do not reach the 300 mg dose: the latest of the last in-clinic dose during the Up-Dosing period or the date of last dose at home. Set the time to be 23:59 and 59 seconds on the respective day.
Initial and Extended Maintenance	1 and 4	Date and time of first in-clinic or at home dose of treatment in ARC008	Date of last dose of study product
	2, 3, and 5	The day following the date of first in-clinic dose of 300 mg during the Up-Dosing period. For subjects who did not enter the Up-Dosing period: the date of first Initial Maintenance Visit.	Date of last dose of study product
Follow-Up Observation	All (1-5)	The day following the date of last dose of study product	Date of Study Exit visit. For subjects without a date of Study Exit visit: the date of study completion.
Overall	All (1-5)	Date and time of first in-clinic or at home dose of treatment in ARC008	Date of Study Exit visit. For subjects without a date of Study Exit visit: the date of study completion.

- The active treatment period is defined as the time period beginning with the date and time of the first dose of study product and ending with the date and time of the last dose of study product.

- Duration of active treatment period (days) for AR101 is calculated as the date of last dose minus the date of first dose of AR101 plus 1.

7.5. MISSING DATA

All AEs, unless occurring during an OLFC, real world peanut challenge (RWPC), or DBPCFC, with partial/missing dates and times will be considered TEAEs unless a partial date clearly indicates that it occurred prior to first dose of AR101 in ARC008 or more than 30 days after the last dose of treatment. All therapies with partial or missing dates and times recorded on the Concomitant Medication or Non-Drug Therapy CRF pages will be considered concomitant unless a partial stop date and time clearly indicates it was stopped prior to the first dose of AR101 including parent studies. Start and stop dates will be imputed, to determine TEAEs and concomitant medications, as described below. No imputation will be done for a completely missing stop date or for subjects who did not receive study treatment.

Start dates with a missing day but which have month and year populated will be imputed such that:

- For TEAEs, if the provided month and year match the month and year for that subject's date of first dose of AR101 in ARC008, then the Day 1 date will be used
- For concomitant medications, if the provided month and year match the month and year for that subject's date of first dose of AR101 including parent studies, then the date of first dose of AR101 including parent studies will be used
- In all other cases the 1st of the month will be used with the provided month and year

Start dates with a missing day and month but which have year populated will be imputed such that:

- For TEAEs, if the provided year matches the year for that subject's date of first dose of AR101 in ARC008, then the date of first dose of AR101 in ARC008 will be used
- For concomitant medications, if the provided year matches the year for that subject's date of first dose of AR101 including parent studies, then the date of first dose of AR101 in including parent studies will be used
- In all other cases the 1st of January will be used with the provided year

For TEAEs, start dates that are completely missing will be imputed as the date of first dose of AR101 in ARC008 (Day 1). For concomitant medications, start dates that are completely missing will be imputed as the date of first dose of AR101 including parent studies.

Stop dates will be imputed as follows:

- Missing day with a provided year and month will use the last day of the month

- Missing day and month with provided year will use December 31

If the imputed stop date is greater than the last study date for the subject, then the imputed date will be replaced with the last known subject date.

The reported date of the most recent reaction to peanut on the peanut allergy history CRF page and date of diagnosis of peanut allergy will be imputed when the month or day is missing as follows:

- Missing day is set to 1 if the same year and month as the informed consent date. Otherwise it is set to 15.

- Missing month and day are set to Jan 1 if the same year as the informed consent date. Otherwise it is set to July 1.

Where the severity score of a symptom is missing during a food challenge (OLFC or DBPCFC), the severity score will be imputed as severe.

Where the severity score of an AE is missing, the severity score will be imputed as severe.

Where the relatedness of an AE is missing, the relatedness will be imputed as related to study product.

No imputations will be made for other missing data, unless specified otherwise.

7.6. POOLING

Data pooling will not be performed.

7.7. DATA ADJUDICATION

As the study ended much earlier than originally anticipated some of the locked or frozen data had to be adjudicated by the Nestle Health Science study team. All outcomes of this adjudication are documented in the Site Closure Plan, Adjudication Charter and in Appendix A.

Additional data issues and analysis issues identified during the analysis and how they were handled are captured in separate tracking documents.

8. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS

8.1. SUBJECT DISPOSITION AND WITHDRAWALS

Subject disposition and completion status will be summarized for all screened subjects. The number and percentage of subjects who were screened, were screen failures, were included in each analysis population, were in each treatment pathway, were assigned to daily/non-daily dosing regimens, entered each study period, completed all dosing as defined in the protocol, completed the study per protocol, and completed the safety follow-up per protocol will also be summarized.

Reason for early treatment discontinuation, early study discontinuation, and premature discontinuation from follow-up, including due to COVID-19 related reasons, will be summarized as well as whether subjects required follow-up due to chronic/recurrent GI symptoms.

The dates of last study visit, last contact, and study completion/early discontinuation will be listed as well as reason for early treatment discontinuation, reason for early study discontinuation, and reason for premature discontinuation from follow-up. Follow-up status for subjects who required follow-up due to recurrent GI symptoms will also be included in the subject data listings.

Inclusion and exclusion eligibility will be listed separately.

8.2. PROTOCOL DEVIATIONS

Major protocol deviations (identified by sponsor review before database lock) will be summarized for the Safety Population. All protocol deviations, as defined in Section 5, will be listed by treatment pathway and subject ID.

8.3. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Summary statistics for demographic and baseline characteristics will be provided for the Safety Population by treatment pathway.

Demographic data will include age, age category (1-3 years, 4-17 years, 18 years and older), race, country, ethnicity, sex, body weight, height and body mass index (BMI) where BMI is calculated as [weight (kg)]/[height (cm)/100]^2. Baseline characteristics include total IgE, ps-IgE, ps-IgG$_4$, and ps-IgE/IgG$_4$ ratio. Peanut-specific IgE and IgG4 components (Ara h 1, Ara h 2, Ara h 3, Ara h 8, Ara h 9) and the corresponding IgE/IgG4 ratio of each component will also be summarized where available. Baseline SPT mean wheal diameter and asthma history will also be summarized.

Age will be calculated relative to date of informed consent, as follows:

- If the month and day portion of the informed consent date is prior to the month and day portion of the birthdate, age will be calculated as the year of informed consent minus the year of birth, minus one;

- If the month and day portion of the informed consent date is on or after the month and day portion of the birthdate, age will be calculated as the year of informed consent minus the year of birth.

Demographic and baseline characteristic information will be listed by treatment pathway and subject ID for all enrolled subjects. Available demographic data for screening failure subjects will also be listed.

8.4. NON-PEANUT ALLERGY HISTORY

The presence of non-peanut food allergy history and causative allergen types will be summarized for the Safety Population, including the summarization of subjects who have one, two, three, or more than three types of other causative allergens. Additionally, non-food allergy history and causative allergen types will be summarized for the Safety Population, including the summarization of subjects who have one, two, three, or more than three types of other allergies and other causative allergens. This summary will include non-peanut allergy history from subjects' parent studies (ARC001, ARC003, ARC004, ARC005, ARC007, ARC010, and ARC011). ARC002 non-peanut food and non-food allergy histories were not collected separately and will not be summarized or listed.

All non-peanut food allergy history and non-food allergy history including history collected for parent studies other than ARC002 will be listed by treatment pathway and subject ID.

8.5. NON-ALLERGY MEDICAL HISTORY

Subjects who experience non-allergy medical history events will be summarized for the Safety Population; these data will be presented by system organ class (SOC) and preferred term (PT). This summary will include medical history from subjects' parent studies. Non-allergy medical history for ARC008 will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 26.0. Non-allergy medical history for parent studies were coded using MedDRA version 18.1 for ARC003, MedDRA version 19.1 for ARC004, ARC007, ARC010, and ARC011, and MedDRA version 21.1 for ARC005. Medical history was not coded for ARC001 and ARC002 and will not be included in the summary of medical history. Medical history including history collected for all parent studies (ARC001, ARC002, ARC003, ARC004, ARC005, ARC007, ARC010, and ARC011) will be listed by treatment pathway and subject ID.

9. ANALYSIS OF SAFETY ENDPOINTS

Safety will be assessed based on extent of exposure, concomitant medications, physical examinations, vital signs, laboratory data and all the safety endpoints defined in Section 3.1.

Unless otherwise noted, safety data will be summarized descriptively, and the Safety Population will be used for all summaries of safety parameters. Safety listings will include all enrolled subjects, sorted by treatment pathway and subject ID.

9.1. ADVERSE EVENTS

TEAEs will be summarized excluding symptoms recorded during the food challenges.

AEs will be classified by severity using the Consortium of Food Allergy Research (CoFAR) grading system for allergic reactions, modified European Academy of Allergy and Clinical Immunology (EAACI) guidelines for anaphylactic reactions, and Common Terminology Criteria for Adverse Events (CTCAE) for all other AEs, all as per Section 8.2.2.1 of the protocol.

If symptoms are recorded as part of an anaphylactic reaction, only the single anaphylactic reaction event will be summarized and not the individual symptoms.

All reported AEs will be classified into SOC and PT using MedDRA version 26.0.

TEAEs are defined as those AEs with onset after the first dose of AR101 in ARC008 and no more than 30 days after the last dose of study drug. Non-TEAEs will be listed by treatment pathway and subject ID; these events will not be summarized. TEAEs will be summarized for the Safety Population by study period as follows:

- Initial Escalation
- Up-Dosing
- Initial and Extended Maintenance
- Overall (Initial Escalation, Up-Dosing, and Initial and Extended Maintenance)

Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class. Summaries displayed by preferred term only will be ordered by descending incidence of preferred term. Summaries of the following types will be presented:

- Overall summary of the number of unique TEAEs and TESAEs and subject incidence of TEAEs and TESAEs meeting various criteria;

- Overall summary of the number of unique TEAEs and TESAEs and subject incidence of TEAEs and TESAEs meeting various criteria by total exposure including parent studies;
- Subject incidence of TEAEs by MedDRA system organ class and preferred term;
- Subject incidence of TEAEs by severity grade, MedDRA system organ class, and preferred term;
- Subject incidence of grade ≥ 3 severity TEAEs by MedDRA system organ class and preferred term;
- Subject incidence of TESAEs by MedDRA system organ class and preferred term;
- Subject incidence of TEAEs leading to discontinuation of study product by MedDRA system organ class and preferred term;
- Subject incidence of TEAEs leading to discontinuation of study product by total AR101 exposure including parent studies, MedDRA system organ class, and preferred term;
- Subject incidence of treatment-related AEs by MedDRA system organ class, and preferred term;
- Subject incidence of grade ≥ 3 severity treatment-related AEs by MedDRA system organ class and preferred term;
- Subject incidence of treatment-related AEs leading to discontinuation of study product by MedDRA system organ class and preferred term;
- Subject incidence of TEAEs associated with epinephrine use by MedDRA system organ class and preferred term; and
- Subject incidence of TEAEs associated with accidental/non-accidental non-study product food allergen exposure by MedDRA system organ class and preferred term.

The overall summary of TEAEs and TESAEs will be repeated for the subgroups described in Section 6.3.

At each level of summarization (e.g., any AE, SOC, and PT), subjects experiencing more than one TEAE will be counted only once within each study period. In the summary of TEAEs by severity grade, subjects will be counted once at the highest severity reported at each level of summarization.

AE data will be presented in data listings by treatment pathway, subject ID, and event date. TEAEs for subjects who did not tolerate non-daily dosing in Treatment Pathway 1 and switched to Treatment Pathway 2 will be presented in the data listings. Non-TEAEs, TEAEs, TEAEs identified as the primary reason for early study product discontinuation, TEAEs identified as the primary reason for early study discontinuation, treatment-emergent GI AEs in subjects who discontinued treatment due to GI AEs and had follow-up due to recurrent GI symptoms, treatment-emergent allergic AEs excluding food allergens, and treatment-emergent allergic AEs caused by food allergens will also be presented in separate data listings.

A listing of deaths will also be presented.

9.2. ADVERSE EVENTS OF INTEREST

AEIs include anaphylaxis, GI AEs with prolonged dose interruption (> 7 consecutive days) or that result in early discontinuation, accidental and non-accidental food allergen exposure, severe AEs, and use of epinephrine. Allergic reactions during food challenges will not be considered related to study product or reported as AEIs.

A separate data listing and an overall summary of the number of unique treatment-emergent AEIs and treatment-emergent serious AEIs and subject incidence of treatment-emergent AEIs and treatment-emergent serious AEIs meeting various criteria will be presented for the following AEIs: GI AEs leading to disruption of dosing (with prolonged dose interruption > 7 consecutive days or leading to treatment discontinuation), AEs associated with epinephrine use (excluding use for food allergen exposure or food challenges) or anaphylactic reactions (excluding food challenges unless the reaction was serious), serious treatment-related AEs, treatment-related AEs leading to study product discontinuation, and treatment-related AEs that are severe, life-threatening, or fatal.

The overall summary of treatment-emergent AEIs and treatment-emergent serious AEIs will be repeated for the subgroups described in Section 6.3.

9.2.1. Anaphylaxis

Anaphylactic AEs will be considered AEIs. Anaphylaxis is defined by a number of signs and symptoms that occur alone or in combination within minutes up to a few hours after exposure to a provoking agent. The severity of the reaction will be assessed according to the EAACI system for grading the severity of anaphylactic reactions (Muraro, 2007).

All reported anaphylactic reaction episodes will be listed by treatment pathway and subject.

Each anaphylactic reaction will be identified by the following triggers:

- Study product/Investigational product (IP)

- Peanut or peanut-containing food
- Other food allergen
- Medication
- Insect sting
- Environmental allergen(s)
- Other
- Unknown

Treatment-emergent anaphylactic reactions include anaphylactic reactions that occur after first dose of AR101 in ARC008 through 30 days after last dose of study product, but excluding anaphylactic reactions that occur during or related to a food challenge. Treatment-emergent anaphylactic reactions will be summarized in the Safety Population separately for the following study periods:

- Initial Escalation
- Up-Dosing
- Initial and Extended Maintenance
- Overall (Initial Escalation, Up-Dosing, and Initial and Extended Maintenance)

Summaries of each study period will include:

- The number of anaphylactic reactions.
- The number of anaphylactic reactions by trigger, study product, peanut or peanut-containing food, other food allergen, medication, insect sting, environmental allergen, other and unknown.
- Incidence of subjects experiencing an anaphylactic reaction by number of episodes, subjects experiencing an anaphylactic reaction by severity using modified EAACI guidelines, subjects experiencing an anaphylactic reaction that was a SAE, subjects experiencing an anaphylactic reaction that required epinephrine use, the location of epinephrine episodes (home or study site), and the individual symptoms involved.

The above summary will be produced for all treatment-emergent anaphylactic reactions, all treatment-emergent anaphylactic reactions by total AR101 exposure including parent studies, and for treatment-related anaphylactic reactions. Anaphylactic reactions will also be listed by treatment pathway, subject ID, and episode date.

9.2.2. Gastrointestinal AEs Resulting in Prolonged Interruption of Dosing

GI AEs, typically chronic/recurrent GI AEs, that result in prolonged interruption of dosing will also be considered AEIs and will be assessed longitudinally. To delineate these AEIs, prolonged interruption of dosing is defined as withholding AR101 for > 7 days. This will include 3 categories of subjects:

- Any subject whose dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level
- Any subject who develops chronic/recurrent GI AEs at or before reaching the 20 mg dose level and resumes dosing after a 30-day dosing hiatus
- Any subject who experienced GI AEs and discontinues early from the study

Subjects who discontinue AR101 treatment early due to chronic/recurrent GI AEs will 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 substitute for in-clinic visit, at the investigator's discretion). If chronic/recurrent GI AEs persist beyond 6 months, subjects will continue to be followed with monthly clinic visits (telephone follow-up with an investigator may substitute for in-clinic visit, at the investigator's discretion) until the symptoms have resolved or are assessed to have stabilized with optimal medical management.

If chronic/recurrent GI AEs do not completely resolve within 6 weeks after discontinuation of AR101 dosing, the subject should be referred to a (pediatric) gastroenterologist. Subjects with EoE confirmed by biopsy will have safety follow-up monthly for at least 6 months or until resolution of symptoms and/or tissue eosinophilia, whichever is last.

9.2.3. Accidental and Non-accidental Food Allergen Exposures

An accidental food allergen exposure is any known or suspected exposure to a food to which the subject is allergic, including peanut, whether or not it results in an AE. A non-accidental food allergen exposure is an intentional exposure to a food to which the subject is allergic, including peanut, whether or not it results in an AE.

The non-serious AEI form will be completed for each of these events, in addition to events where consumption of peanut without a reaction occurs, unless the accidental/non-

accidental food ingestion safety event meets the definition of an SAE as defined in Section 8.1.3 of the protocol, in which case the SAE form will be completed.

If an accidental/non-accidental food allergen exposure does not result in an AE, no assessment of severity, seriousness, or relatedness is required. Treatment-emergent food allergy episodes include food allergy episodes that occur after first dose of AR101 in ARC008 through 30 days after last dose of study product, but excluding food allergy episodes that occur during or related to a food challenge.

These treatment-emergent food allergy episodes will be summarized by study period:

- Initial Escalation
- Up-dosing
- Initial and Extended Maintenance
- Overall (Initial Escalation, Up-Dosing, and Initial and Extended Maintenance)

For each period, the number of subjects experiencing any food allergy episode, the number of subjects experiencing a food allergy episode in response to peanut (or non-peanut), the number of subjects experiencing an accidental (or non-accidental) food allergy episode, the number of episodes of each (peanut-related, non-peanut related, accidental, and non-accidental) experienced per subject, and the total number of food allergy episodes (peanut-related, non-peanut related, accidental, and non-accidental) will be summarized. In addition, the number of episodes considered SAEs, those that required treatment, and those that required epinephrine use will also be summarized.

All reported food allergy episodes will be listed by treatment pathway and subject.

9.2.4. Adverse Events Associated with Use of Epinephrine

AEs may result in epinephrine use. Upon awareness of such an event, site staff will report it within 24 hours using the AEI form, independent of severity or relatedness, or whether it was administered at the study site or at home. If the epinephrine was used for an allergic reaction that meets criteria for anaphylaxis, an accidental/non-accidental food allergen exposure, a severe AE, or an SAE, the use need not be reported separately. The intent of this AEI is to record events that do not fall into one of the other categories.

9.3. LABORATORY DATA

Blood samples will be collected at the visits identified in the schedules of events in the appendices of the protocol after the predose vital signs and PEF and before administration of AR101.

All sexually active females of childbearing potential will undergo a serum pregnancy test at Screening and urine pregnancy testing at the visits indicated in the schedules of events in the appendices of the protocol.

Laboratory data (hematology, blood sample collection, and pregnancy test results) and abnormal laboratory values will be listed by treatment pathway, subject ID, and visit.

9.4. VITAL SIGNS

Vital signs (blood pressure [BP], pulse rate, and body temperature) will be measured at the visits indicated in the schedules of events in the appendices of the protocol. For Treatment Pathways 4 and 5, vital signs also include respiratory rate and oxygen saturation level. Measurement of BP and pulse rate should be preceded by at least 5 minutes of rest for the subject.

Vital signs (temperature, heart rate, respiratory rate, systolic/diastolic blood pressure, and oxygen saturation) will be listed by treatment pathway, subject ID, and visit.

9.5. PHYSICAL EXAMINATION

Complete and abbreviated (symptom-directed) physical examinations will be conducted at the visits indicated in the schedules of events in the appendices of the protocol. Height and weight will be recorded as part of a complete physical exam. Physical examination results will be listed by treatment pathway, subject ID, and visit. BMI will be included in the listing and calculated as [weight (kg)]/[height (cm)/100]^2.

9.6. PEDIATRIC EOSINOPHILIC ESOPHAGITIS SYMPTOM SCORES

Subjects with GI AEIs will be asked to complete the Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS) v2.0 questionnaire (Franciosi, 2011) while they are symptomatic, at the End of Treatment visit, and then monthly for 6 months thereafter. Parents/caregivers will also complete the PEESS v2.0 as appropriate. Subjects who discontinue AR101 treatment early due to chronic/recurrent GI AEs will return to the clinic for evaluation monthly for at least 6 months. If the subject is asymptomatic, telephone follow-up with an investigator may substitute for in-clinic visit, at the investigator's discretion. If chronic/recurrent GI AEs persist beyond 6 months, subjects will continue to be followed up with monthly clinic visits (telephone follow-up with an investigator may substitute for in-clinic visit, at the investigator's discretion) until the symptoms are resolved or stable with optimal medical management or the investigator considers them irreversible, in which case the sponsor must be notified.

The PEESS questionnaire is composed of 20 items investigating the frequency and severity of EoE symptoms in the last month. The total score consists of all 20 items. The frequency of symptoms is assessed by items 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 20, where each item is scored as: 0=Never, 1=Almost never, 2=Sometimes, 3=Often, 4=Almost always. The

severity of symptoms is assessed by items 2, 4, 6, 8, 10, 12, 14, 16, and 18, where each item is scored as: 0=Not bad at all, 1=A little bad, 2=Kind of bad, 3=Bad, 4=Very bad. Each item score is transformed to 0-100 as follows: 0=0, 1=25, 2=50, 3=75, 4=100.

The total, frequency total, and severity total scores are computed as the sum of the items divided by the number of items answered. If more than 50% of the items for the calculation of a score are missing, the score will not be calculated.

All PEESS data (collected from subjects and parents/caregivers) will be listed, including the frequency total, severity total, and total scores.

9.7. PEAK EXPIRATORY FLOW

The PEF should be measured at approximately the same time of day at each visit (eg, morning, afternoon, evening). The PEF will be measured in triplicate using a hand-held device at the visits indicated in the schedules of events in the appendices of the protocol. The subject will be asked to stand and forcefully blow into the device 3 times.

PEF results will be listed by treatment pathway, subject ID, and visit.

9.8. ASTHMA CONTROL TEST AND THE CHILDHOOD ASTHMA CONTROL TEST QUESTIONNAIRE

The ACT or C-ACT will be administered only to subjects with known asthma at the visits indicated in the schedules of events in the appendices of the protocol during each visit and prior to the measurement of lung function.

The ACT (Schatz, 2006) is a self-administered 5-item questionnaire for subjects 12 years of age or older. It assesses the level of asthma control during the prior 4 weeks. Specifically, the test asks about shortness of breath, general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and the overall self-assessment of asthma control. Each question is scored with a 5-point scale, with lower numbers equating to worse control. The scores for each question are totaled, and a composite score of more than 19 indicates well-controlled asthma. Missing data will not be imputed. If any of the 5 questions have a missing response, the total ACT score will not be calculated. Subjects who have turned 12 since entry into the ARC008 study will be asked to complete the ACT.

The C-ACT (Liu, 2007) is a 7-item questionnaire for subjects aged 4 to 11 years. It assesses the control of asthma during the prior 4 weeks. The child completes the first part, which has 4 questions and with a choice of 4 responses to each question. The child should read and respond to each question. If the child needs assistance with reading or understanding the question, the parent/caregiver may help; however, only the child should pick a response to the question. The parent/caregiver completes the second part, which has 3 questions with a choice of 6 responses ranging from 0 (worse asthma) to 5 (controlled asthma) for each question. The sum of all the responses to the questions provides a score

that ranges from 0 (very poor control) to 27 (well-controlled asthma) with a score of more than 19 indicating asthma that is well controlled.

Listing of the results from each questionnaire, including the total score will be provided, sorted by treatment pathway, subject ID, and visit.

9.9. ASTHMA EVALUATION

Asthma evaluation will be performed for subjects with asthma in Treatment Pathways 4 and 5 at visits according to the schedules of events in the appendices of the protocol. The evaluation of asthma severity will be assessed based on National Heart, Lung, and Blood Institute (NHLBI) classification (adapted from NHLBI, 2007).

Listing of the asthma evaluation results will be provided sorted by treatment pathway, subject ID, and visit.

9.10. TOTAL NASAL SYMPTOM SCORE

The TNSS (short form) will be administered only to subjects with known allergic rhinitis at the visits indicated in the schedules of events in the appendices of the protocol.

It consists of 3 questions that address nasal obstruction, rhinorrhea, and nasal itch/sneezing. Each question has a choice of 4 responses that range from 0 (no symptoms) to 3 (severe symptoms). The subject is asked to recall symptoms over the last week to allow calculation of the symptom score.

TNSS results will be listed by treatment pathway, subject ID, and visit.

9.11. STUDY TREATMENT EXPOSURE

The calculation of exposure will be based on in clinic dosing data and at home dosing as captured on the Study Product Exposure CRF page.

First and last dose dates for each study period are identified as described in Section 7.5.

The total amount of study product consumed will be calculated as the sum of in-clinic doses plus the estimated number of doses taken at home. At-home doses will be estimated by combining the doses across each dosing interval entered on the Study Product Exposure CRF page and taking into account the dosing frequency and any missed and partial doses as captured on the Subject Dosing Diary CRF.

The following calculations of study drug exposure will be made and summarized:

- Duration of Exposure (in days and in years): calculated as the date of last dose of study drug minus the date of the first dose of AR101 plus one during the study

period, except for the Initial Escalation period, where the duration of exposure will only be 1 or 2 days depending on whether drug was taken on Initial Escalation Day 1 and Initial Escalation Day 2. Duration of exposure will be summarized using descriptive statistics for continuous data as well as categorically by 28-day increments for the first year and by year for the overall treatment periods: ≤ 28 days, 29 to 56 days, 57 to 84 days, …, 1 to < 2 years, 2 to < 3 years, 3 to < 4 years, 4 to < 5 years, and ≥ 5 years.

- Total dose consumed (mg): calculated as the cumulative sum of all doses taken during the study period.

- Average dose per day (mg): calculated as the total dose consumed divided by the number of days during the study period.

- Maximum dose achieved (mg/day): summarized using descriptive statistics for continuous data as well as categorically using all possible dose levels: 0.5, 1, 1.5, 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, or 300 mg/day.

- Number of unsuccessful dose increases: calculated as the number of single doses given at the study site at a higher dose level followed by an immediate return to the previous dose level or a lower dose level.

- Number of dose reductions: calculated as the number of any decrease in dose level given at the study site that does not qualify as an unsuccessful dose increase.

Study treatment exposure parameters will be summarized by the following study periods:

- Initial Escalation

- Up-Dosing

- Initial and Extended Maintenance

- Overall (ARC008 Only: Initial Escalation, Up-Dosing, and Initial and Extended Maintenance)

Duration of exposure will also be summarized including parent studies (Overall [Including Parent Studies]).

All ARC008 exposure data from the Dose Administration, Study Product Exposure, Missed and Partial Doses Log, and Subject Dosing Diary CRFs will be included in the subject listings.

9.12. PRIOR, CONCOMITANT, AND RESCUE MEDICATIONS

All medications recorded on the Concomitant Medications CRF page for ARC008 will be coded using the World Health Organization international drug classification dictionary (WHODrug) Global C3 March 2023 version. Medications for all parent studies were coded using WHODrug 01 Mar 2013 for ARC002, WHODrug June 2015 for ARC003, and World Health Organization Drug Dictionary Enhanced (WHO-DDE) September 2016 for ARC004, ARC005, ARC007, ARC010, and ARC011. Medications were not coded for ARC001 and will not be included in medication summaries but will be included in the data listing of prior and concomitant medications. Medications will be listed and summarized by Anatomical Therapeutic Chemical (ATC) level 4 and preferred name. If ATC drug class level 4 is not available, then ATC drug class level 3 will be utilized. If ATC drug class levels 4 and 3 are not available, then ATC drug class level 2 will be utilized. If ATC drug class levels 4, 3, and 2 are not available, then ATC drug class level 1 will be utilized.

Prior medications are defined as those which are only taken prior to the date of the first dose of AR101 including parent studies (i.e., medication end date is prior to the date of first dose of study drug).

Concomitant medications are medications taken at any time during the active treatment period. Any medications recorded for which dosing began after the last dose of study treatment will also be classified as concomitant medications. As needed (PRN) medications, which may or may not be taken for long periods of time, but which are prescribed to the subject for a period that overlaps with the active treatment period, will be considered concomitant medications. If it cannot be determined whether a medication was received prior to the start of study drug dosing due to partial or missing medication start and/or end dates, it will be considered a concomitant medication.

Rescue medications are any medication used to treat individual acute allergic reactions during ARC008 should be according to recognized standards of care for allergy practice. In general, this could include either an antihistamine or epinephrine, along with intravenous fluids, a beta-adrenergic agonist (eg, albuterol), oxygen, or steroids, as indicated.

Prior medications, concomitant medications, and rescue medications will be summarized separately by ATC Class and generic drug name. Summaries of prior and concomitant medications will include medications from parent studies (ARC002, ARC003, ARC004, ARC005, ARC007, ARC010, and ARC011). Subjects will be counted no more than one time per generic drug name and no more than one time per ATC Level 4.

Rescue medications will be summarized by ATC Class and generic drug for the following study periods:

- Initial Escalation

- Up-Dosing
- Initial and Extended Maintenance (excluding rescue medications taken as a result of an OLFC)
- OLFCs (Total AR101 Exposure < 1 year; 1 to < 2 years; 2 to < 3 years; 3 to < 4 years; 4 to < 5 years; ≥ 5 years)
- DBPCFCs (Total AR101 Exposure < 1 year; 1 to < 2 years; 2 to < 3 years; 3 to < 4 years; 4 to < 5 years; ≥ 5 years)
- Overall, including all rescue medications reported on the CRF

The summary of rescue medications will be repeated for the subgroups described in Section 6.3.

Prior medications and concomitant medications (including medications from parent studies [ARC001, ARC002, ARC003, ARC004, ARC005, ARC007, ARC010, and ARC011]), prior and on-study rescue medications, prior and on-study epinephrine, and concomitant non-drug therapies will be listed by subject.

10. ANALYSIS OF EFFICACY ENDPOINTS

Unless otherwise noted, efficacy data will be summarized descriptively, and the Safety Population will be used for all summaries of efficacy parameters. Efficacy listings will include all enrolled subjects, sorted by treatment pathway.

10.1. SUBJECTS TOLERATING EACH CHALLENGE DOSE AND THE MTD AT EACH FOOD CHALLENGE

Open-Label Food Challenge

Subjects in Treatment Pathway 5 will have an OLFC at the end of initial maintenance (ie, after an overall total of approximately 12 months of treatment, including initial escalation, up-dosing, and maintenance). The OLFC is adapted for young children based on accepted food challenge procedures. During the OLFC at the end of initial maintenance, single doses of peanut protein (3, 10, 30, 100, 300, 600, 1000, and 2000 mg) will be conditionally tested using a food challenge mixture administered sequentially at 20- to 30-minute intervals.

Subjects in Treatment Pathways 4 and 5 will have an OLFC after completing 12 months of Extended Maintenance treatment and may participate in an optional OLFC yearly thereafter and at the End of Treatment visit. Subjects in Treatment Pathways 1, 2, and 3 may participate in an optional yearly OLFC during the Extended Maintenance Period (ie, after completing 12 months of Extended Maintenance treatment and yearly thereafter) and the End of Treatment visit OLFC to assess the level of desensitization to peanut protein. Each OLFC during the Extended Maintenance Period will be conducted over a single day and in keeping with accepted food challenge procedures, will conditionally test 4 unblinded single doses sequentially at 20- to 30-minute intervals: 300 mg, 600 mg, 1000 mg, and 2000 mg of peanut protein using a defatted peanut flour.

OLFC data and derived desensitization response at each OLFC will be listed by treatment pathway and subject ID.

Double-Blind, Placebo-Controlled Food Challenge

A DBPCFC will be performed at the End of Treatment visit; subjects who discontinue AR101 treatment early for safety reasons will not have the DBPCFC. An optional DBPCFC will be performed after approximately 1 year of follow-up observation.

Each DBPCFC will be conducted over 2 days and consistent with accepted food challenge procedures. Single doses of peanut protein and placebo will be conditionally tested at the DBPCFC (3, 10, 30, 100, 300, 600, 1000, and 2000 mg) using a food challenge mixture administered sequentially at 20- to 30-minute intervals up to a single highest challenge dose of 2000 mg (4043 mg cumulative).

DBPCFC data and derived desensitization response at each DBPCFC will be listed by treatment pathway and subject ID.

For each OLFC and DBPCFC at End of Treatment, the proportion of subjects who tolerate each challenge dose (3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, 1000 mg, and 2000 mg) of peanut protein with no more than mild allergy symptoms will be assessed using the Safety Population. Desensitization response rates and associated 95% CIs will be presented using exact Clopper Pearson CIs. The number and percentage of subjects at each dose level for MTD will also be summarized. Summaries for the OLFCs will be presented at each time point (End of Initial Maintenance, Extended Maintenance every year) and by years of total AR101 exposure (including parent studies) and overall. A summary of the DBPCFC at End of Treatment will be presented for each treatment pathway by years of total AR101 exposure and overall.

10.2. MAXIMUM SEVERITY OF SYMPTOMS IN EACH FOOD CHALLENGE

The maximum severity of allergy symptoms after consuming peanut protein during each food challenge (OLFC or DBPCFC) will be included in the subject listings.

Symptom severity is determined according to the CoFAR scale at 5 levels: 1-Mild, 2-Moderate, 3-Severe, 4-Life-threatening, and 5-Fatal. Analysis is done on 4 levels: 0-None, 1-Mild, 2-Moderate, 3-Severe or higher (severe, life-threatening, fatal). Subjects who experience no symptoms will be assigned a severity of 0-None. Symptom severity data are collected at each challenge dose of peanut protein during the OLFC and DBPCFC (for dose levels 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, 1000 mg, and 2000 mg); the maximum severity of symptoms observed at any of these dose levels will be listed for each subject.

10.3. FOOD ALLERGY QUALITY OF LIFE SCORES (FAQLQ, FAQL-PB, FAIM)

The questionnaires will be administered to subjects at the visits indicated in the schedules of events in the appendices of the protocol. The questionnaires should be completed before in-clinic dosing. The questionnaires may be completed during the observation period after completion of peanut protein administration as part of the OLFC.

Subjects may also be asked to complete health-related QoL questionnaires during the 1-year follow-up observation period.

FAQLQ

The FAQLQ are questionnaires that measure health-related QoL in patients with food allergy. The following versions of the FAQLQ forms have been developed.

- Children 8 to 12 years of age (FAQLQ-CF) (Flokstra-de Blok, 2009)
- Adolescents 13 to 17 years of age (FAQLQ-TF) (Flokstra-de Blok, 2008)
- Adults 18 years of age and older (FAQLQ-AF) (van der Velde, 2009)
- Parents/caregivers of allergic children (FAQLQ-PF) (DunnGalvin, 2008)
- Parents/caregivers of allergic teenagers (FAQLQ-PFT)

Each subject or parent/caregiver should complete the same version of the form completed in the parent study, regardless of current age.

For subjects aged ≤ 12 years, the parent/caregiver will complete the FAQLQ-PF. For subjects completing the FAQLQ-CF, subjects and parents/caregiver should be instructed to have the child provide his/her own responses. The parent/caregiver can help read the question or explain the meaning of the question, but the response should be selected only by the child.

The questionnaires include 4 domains common to each (allergy avoidance, dietary restrictions, emotional impact and risk of accidental exposure), and the adult form also includes a food allergy related health domain. The number of items ranges from 23 to 29. Each item is scored on a 7-point scale from 0 (no impact) to 6 (extreme impact).

The total score is the arithmetic average of all non-missing items. Domain scores are calculated similarly. If less than 80% of the items are complete, then the total score will not be calculated. Similarly, if less than 80% of the items within a domain are complete, then the domain score will not be calculated.

FAQLQ questionnaire scores will be listed by treatment pathway and subject ID.

FAQL-PB

The FAQL-PB is a 17-item self-administered questionnaire that measures QoL in caregivers for children with food allergy (Cohen, 2004). Each of the 17 questions is a 7-point Likert item, and the index is scored as a summated rating scale, with a higher FAQL-PB score indicating a worse QoL. Two domain scores will be calculated (life limitations and emotional stress).

The total score is the arithmetic average of all non-missing items. Domain scores are calculated similarly. If less than 80% of the items are complete, then the total score will not be calculated. Similarly, if less than 80% of the items within a domain are complete, then the domain score will not be calculated.

A listing of the raw scores as recorded in the CRF will be provided, sorted by treatment pathway and subject ID.

FAIM

The FAIM questionnaires were developed to measure construct validity of the FAQLQ. The FAIM questionnaires consist of 4 to 8 questions and measure the subject's perception of disease severity and their expectation of allergen exposure outcome. The FAIM may be used within a study to check the construct validity of the FAQLQ and explore changes in subject and parent/caregiver expectation of outcome (van der Velde, 2010). Each question is scored on a 7-point scale from 0 (low likelihood of a bad outcome) to 6 (extremely likely to have a bad outcome).

FAIM questionnaire scores will be listed by treatment pathway and subject ID.

11. ANALYSIS OF EXPLORATORY ENDPOINTS

11.1. PEANUT-SPECIFIC AND PEANUT COMPONENT-SPECIFIC IGE AND IGG4

Blood samples to measure ps-IgE, ps-IgG_4 levels, and total IgE levels will be collected at the timepoints as indicated in the schedules of events in the appendices of the protocol.

Ps-IgE/IgG_4 ratio will be calculated, listed by subject, and summarized by visit and treatment group (AR101). Results outside the limits of quantification will be displayed as less than the lower limit of quantification (LLOQ), or greater than the upper limit of quantification (ULOQ), as appropriate. These values will be summarized as either the LLOQ or the ULOQ. If the ps-IgE or ps-IgG_4 is outside of the limits of quantification, the ps-IgE/IgG_4 ratio will be calculated using the LLOQ or ULOQ as appropriate.

Summary statistics, including geometric means and geometric standard deviations, will be presented by time point and years of total AR101 exposure including parent studies and overall separately for Treatment Pathways 1-3, 4, and 5.

Summaries of change from baseline to Study Exit visit for total IgE, ps-IgE, ps-IgG_4, ps-IgE/IgG_4 ratio, peanut-specific IgE and IgG4 components (Ara h 1, Ara h 2, Ara h 3, Ara h 8, Ara h 9) and the corresponding IgE/IgG4 ratio of each component will be presented using change calculated on the $\log_{10}$ scale.

11.2. SKIN PRICK TEST

SPTs will be conducted at the visits indicated in the schedules of events in the appendices of the protocol. Results from the SPT will be listed by treatment pathway, subject ID, and visit, including test date and time, and measurements (in mm) of the following: peanut wheal (long axis), peanut wheal (short axis), saline wheal (long axis), saline wheal (short axis), histamine wheal (long axis), and histamine wheal (short axis).

A derived mean wheal diameter score will be calculated as the average of the long and short axis from the peanut wheal minus the average of the long and short axis from the saline wheal. Summary statistics for the derived SPT mean wheal diameter will be presented at each visit, for change from baseline to End of Treatment, and for change from baseline to Study Exit visit by years of total AR101 exposure including parent studies and overall.

11.3. TEST FOR RESPIRATORY AND ASTHMA CONTROL IN KIDS (TRACK) AND ECZEMA AREA AND SEVERITY INDEX (EASI)

TRACK and EASI scores are measured as indicated in the schedules of events in the appendices of the protocol.

TRACK

In Treatment Pathways 4 and 5, asthma control in subjects aged 1 to < 5 years with pre-existing asthma will be assessed using TRACK scores and by the incidence of asthma rescue medication use. Subjects who turn age 5 years during the study or who are aged ≥ 5 years at enrollment in Treatment Pathways 4 and 5 will be administered the C-ACT questionnaire instead of the TRACK questionnaire.

The TRACK questionnaire will be administered at the visits indicated in the schedules of events in the appendices of the protocol. The parent/caregiver is to complete the TRACK, a 5-item standardized questionnaire used to evaluate respiratory and asthma control in children aged < 5 years with symptoms consistent with asthma (Zeiger, 2011). Each item is scored on a 5-point scale from 0 (4 or more times a week) to 20 (not at all). Higher scores indicate better respiratory and asthma control.

EASI

For subjects with pre-existing eczema or atopic dermatitis in Treatment Pathways 4 and 5, the severity of clinical signs of eczema or atopic dermatitis will be assessed using the EASI scoring system. Higher scores indicate greater severity of eczema or atopic dermatitis.

A listing of the results from the TRACK and EASI questionnaires will be provided, sorted by treatment pathway, subject ID, and visit.

12. INTERIM ANALYSIS

There is no interim analysis of efficacy planned for this study.

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

The raw values for the following endpoints will be included in data listings, but the change values will not be listed or summarized:

- Secondary safety endpoints
    - Change in PEF
    - Change in C-ACT and ACT score
    - Change in TNSS
- Secondary efficacy endpoints:
    - Change in tolerated dose of peanut protein
    - Changes in food allergy QoL scores as measured by FAQLQ and the FAIM questionnaire
    - Change in FAQL-PB questionnaire score
- Exploratory endpoint:
    - Change in TRACK and EASI scores

Real world peanut challenge results will be presented in data listings and used to identify TEAEs. An analysis of these data was described in a previous version of the protocol (Protocol amendment 3 / Appendix 8).

14. REFERENCE LIST

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Zeiger RS, Mellon M, Chipps B, Murphy KR, Schatz M, Kosinski M, et al. Test for Respiratory and Asthma Control in Kids (TRACK): clinically meaningful changes in score. J Allergy Clin Immunol. 2011;128(5):983-8.

15. PROGRAMMING CONSIDERATIONS

All tables, data listings and figures (TLFs) will be generated using SAS® for Windows, Release 9.4 or higher (SAS® Institute Inc., Cary, NC, USA).

Report summaries will be generated using validated Base SAS® software, version 9.4 or higher, on a server-based platform. Additional validated software may be used to generate analyses, as needed.

Data will be analyzed by Precision for Medicine personnel. Statistical analyses will be reported with tables, listings and figures, presented in both rich text and pdf format, and using recommended ICH numbering. Output specifications for all tables, figures and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the *Electronic Common Technical Document Specification* (2008).

16. QUALITY CONTROL

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member who is also an appropriately qualified statistician before finalization.

The content of the source data will be reviewed on an ongoing basis by statistical programmers and statisticians. Data will be checked for missing values, invalid records, and extreme outliers through defensive programming applications, analysis-based edit checks, and other programmatic testing procedures. All findings will be forwarded to data management for appropriate action and resolution.

17. STUDY SCHEDULE

Refer to the protocol for the full study schedule of events (Appendices 1-6).

18. INDEX OF TABLES, LISTINGS AND FIGURES

An index of the planned statistical outputs will be provided in the shell TLF document.