STATISTICAL ANALYSIS PLAN

ARC002
Oral Desensitization to Peanut in Peanut-Allergic Children and Adults Using Characterized Peanut Allergen (CPNA) Peanut Oral Immunotherapy (OIT)
Safety Follow-On Study

Version 1.0 – 02 Apr 2018
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Protocol Title:	Oral Desensitization to Peanut in Peanut-Allergic Children and Adults Using Characterized Peanut Allergen (CPNA) Peanut Oral Immunotherapy (OIT) Safety Follow-On Study
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STATISTICAL ANALYSIS PLAN APPROVAL

PROTOCOL ARC002

Version 1.0

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Description
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CoFAR	Consortium of Food Allergy Research
CTCAE	Common Terminology Criteria for Adverse Events
DBPCFC	Double-blind, placebo-controlled food challenge
DMC	Data monitoring committee
eCRF	Electronic case report form
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
LLOQ	Lower Limit of Quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
OFC	Open-Label Food Challenge
OIT	Oral Immunotherapy
PEFR	Peak Expiratory Flow Rate
PRACTALL	PRACTical issues in ALLergology Joint United States/European Union Initiative
PRN	pro re nata (when necessary)
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SPT	Skin Prick Test
TEAE	Treatment-Emergent Adverse Event
TLF	Table, listing, and figure
TSQM-9	Treatment Satisfaction Questionnaire for Medication
VAS	Visual Analogue Scale
WHO	World Health Organization
ULOQ	Upper Limit of Quantitation

1 INTRODUCTION

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

TKL Research prepared a preliminary SAP dated 04 Nov 2014 based on the final protocol (03 Jun 2014) and protocol amendment 1 (19 Mar 2015). The preliminary SAP provided guidance for data analysis and reporting of preliminary results from ARC002 for the ARC001/ARC002 Data Monitoring Committee (DMC), and it was also used for reporting preliminary results for regulatory purposes and for presentation at scientific meetings.

ARA finalized the SAP, and will perform the final analyses and be responsible for the production and quality control of the final analysis summary tables, figures, and listings.

2 STUDY OVERVIEW

ARC002 is a multicenter, open-label, follow-on study to gather additional information on the safety and tolerability of oral desensitization with AR101 in subjects who participated in ARC001:

- Group 1: Subjects who completed placebo treatment in ARC001 and consented to enroll in ARC002 will cross over to open-label AR101 treatment with an initial escalation phase, low-dose buildup phase, post low-dose double-blind, placebo-controlled food challenge (DBPCFC), and plateau phase.
- Group 2: Subjects who completed AR101 treatment in ARC001 and consented to enroll in ARC002 will enter the plateau phase and continue AR101 treatment.

For additional details on study design, treatment and procedures, refer to sections 3 and 6 of the protocol.

3 STUDY OBJECTIVES

3.1 Primary Objective

- The primary objective is to assess the safety and tolerability of AR101 when used in an oral immunotherapy (OIT) paradigm over an extended period (≥ 18 months) in peanut-allergic children and young adults who initiated OIT between the ages of 4 and 26 years, inclusive.

3.2 Secondary Objectives

- To confirm and extend prior observations from ARC001 on the efficacy of AR101 in OIT, as assessed through reduction in clinical reactivity to limited amounts of peanut allergen. Specifically, as follows:
  - To assess the efficacy of OIT in inducing desensitization of allergic responses to peanut in placebo-treated subjects from ARC001 (group 1) challenged with peanut flour in a DBPCFC after approximately 6 months of open-label treatment.
  - To assess the efficacy of OIT in sustaining and/or enhancing desensitization of allergic responses to peanut in AR101-treated subjects from ARC001 (group 2) and placebo-treated subjects from ARC001 (group 1) challenged with peanut flour in a DBPCFC after approximately 3 additional months of open-label treatment.
- To evaluate the immunologic effects of peanut OIT.
- To determine the time course of tolerated up-dosing.
- To evaluate safety based on physician global assessment of disease activity.

3.3 Exploratory Objective

The exploratory objective is to assess a higher degree of desensitization, based on an oral food challenge (OFC) up to a cumulative dose of 4043 mg of total peanut protein.

4 STUDY ENDPOINTS

4.1 Primary Endpoint

The primary endpoint is the incidence of treatment-related adverse events (AEs) and dosing symptoms (defined in Section 9.9.2.1) occurring with peanut OIT over a protracted treatment period of at least 18 months.

4.2 Secondary Endpoints

Secondary endpoints are as follows:

- Efficacy:
  - The proportion of subjects who tolerate at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms during DBPCFC
  - The proportion of subjects who tolerate at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms during DBPCFC
  - The proportion of subjects who tolerate 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms during DBPCFC (post plateau DBPCFC only)

  - Change from baseline (carried over from ARC001) in maximum dose of peanut protein tolerated with no or only mild symptoms during DBPCFC
  - Maximum dose of peanut protein tolerated with no or only mild symptoms during DBPCFC
  - Changes in peanut-specific immunoglobulin (Ig) E and IgG4 and changes in skin prick test (SPT) mean wheal diameters
  - The maximum severity of symptoms occurring at each challenge dose of peanut protein during DBPCFC
  - Physician global assessment: Disease activity as measured on a 100 mm visual analogue scale (VAS)
- Safety:
  - Frequency of allergic reaction (hypersensitivity) AEs overall and occurring during each treatment period, normalized for duration of treatment
  - Frequency of use of epinephrine as a rescue medication during OIT by treatment period
  - Frequency of accidental ingestions of peanut and other allergenic foods and severity of resultant reactions

4.3 Exploratory Endpoint

The exploratory endpoints are:

- The proportion of subjects who tolerate, with no more than mild symptoms, a study exit visit OFC to a cumulative dose of 4043 mg of peanut protein.
- Treatment Satisfaction Questionnaire for Medication (TSQM-9) Scale scores
- Parent/Patient Exit Survey Scores

5 SAMPLE SIZE CONSIDERATIONS

The sample size for this study was based on the number of eligible subjects from study ARC001 consenting to continue treatment in the ARC002 open-label extension study. As such, no formal power calculations were performed.

6 ANALYSIS POPULATIONS

- Enrolled population: all subjects with completed informed consent.
- Safety Population: all subjects who received any dose of AR101. The safety population will be the population for all analyses unless otherwise specified.
- Low-Dose Buildup DBPCFC Completer Population: all safety subjects who complete the DBPCFC in the low-dose buildup phase
- Plateau DBPCFC Completer Population: all safety subjects who complete the DBPCFC in the plateau phase
- OFC Completer Population (OFCCP): all safety subjects who complete the OFC.

7 DEFINITIONS, COMPUTATIONS, AND CONVENTIONS

7.1 Definitions and Computations

All summary tables will be presented by treatment group as the following:

- Group 1: Placebo-treated subjects in ARC001
- Group 2: AR101-treated subjects in ARC001
- ARC002 Total: Groups 1 and 2 combined

Statistics: Unless stated otherwise, descriptive statistics refers to the number of subjects (n), mean, median, SDs, 25th and 75th percentile, minimum, and maximum for continuous variables and frequencies and percentages for categorical variables.

Denominators for percentages: Unless specified otherwise, the denominator for percentages for categorical data will be based on the number of subjects or observations with nonmissing data appropriate for summary purposes. The denominator for percentages for incidence data (eg, AEs) will be based on the number of subjects at risk in the analysis population.

Rounding: Minimum and maximum values will be presented at the precision of the original value; means, medians, and 25th and 75th percentiles will be rounded to 1 decimal place greater than the precision of the original value; and SDs 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.

Strata and covariates: No stratification factors or covariates will be evaluated.

Subgroup analyses: No subgroup analyses are planned. Subgroup analyses may be performed later on an exploratory basis.

Pooling: No data pooling is planned.

Multiple comparisons and multiplicity: No adjustments will be made for multiple comparisons.

Significance level: No formal statistical testing is planned. Unless stated otherwise, all statistical tests will be 2-sided, with a significance level of 0.05 and should be considered informational. CIs will be calculated at the 95% level, reflecting a type I error rate of 0.05.

Where applicable, p-values will be presented to 4 decimal places. P-values less than 0.0001 will be presented as < 0.0001 and p-values greater than 0.9999 will be displayed as > 0.9999.

Baseline and Changes from baseline: Baseline is defined as the last value before the first dose of AR101 in ARC002. This could include the value obtained at the ARC001 exit visit.

For efficacy endpoints (eg, MTD at DBPCFC, peanut-specific IgE, peanut-specific IgG4, SPT), the AR101 baseline value is defined as the baseline value for group 1 subjects. AR101 baseline is not defined for group 2, as these subjects received AR101 in ARC001.

Change from baseline is calculated as observed value after the first dose – baseline value. The end of low-dose buildup phase value is defined for efficacy endpoints as the last assessment at or before the end of the low-dose buildup phase. Change from the end of low-dose buildup phase value is calculated as observed post low-dose buildup phase value – end of low-dose buildup phase value.

First dose and calculation of Study Day: First dose is defined as the first dose of AR101 in ARC002. Study day is calculated as (assessment date – first dose date + 1) for assessments and visits performed on or after the first dose date, and (assessment date – first dose date) for assessments and visits before the first dose date.

7.2 Programming Conventions

All tables, data listings, figures (TLFs) will be generated using SAS for Windows, Release 9.4 or higher (SAS Institute Inc., Cary, NC, United States [US]). Computer-generated table, listing, and figure output will adhere to specifications as follows.

General Considerations:

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in rich text format.
- Numbering of TLFs will follow International Council for Harmonisation (ICH) E3 guidance.

Individual subject data listings will be provided to support summary tables and serve as a data source. Unless otherwise noted, all data collected during the study for all subjects will be included in data listings. Listings will be sorted by treatment group, subject identifier, and visit date or time point (where applicable).

Unscheduled visits will be listed but not included in by-visit summaries. Results from unscheduled visits may be used as baseline values and for other derivations not tied to visit names (for example, unscheduled visits are included in the determination of worst postbaseline values for physical examination results).

Table, Listing, and Figure Format

At the top of each output, a number followed by the title will be presented. After the title line, optional subtitle or population information will be presented. Horizontal lines will appear before and after the column heading of the output. Footnotes will be located under the main body of text. All footnotes will be left-justified with single-line spacing immediately below the solid line underneath the data display.

The sponsor name, protocol number, status of the output (ie ,draft or final), SAS program name, and the date and time of creation will appear on the output.

The page number will appear as Page X of Y.

Outputs will be prepared in landscape layout unless otherwise specified.

All margins will be a minimum of 1 inch.

All TLFs will be produced using the Courier New font, size 8.

Table Conventions

In general, alphanumeric values will be presented as left-justified or appropriately indented. Wherever possible, data will be decimal aligned.

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n = 0

If the categories are not ordered (eg, medical history, reasons for discontinuation from the study), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.

Listing Conventions

Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day/time and/or period, as appropriate.

Missing data may be represented on subject listings as either a hyphen (-) with a corresponding footnote (- = unknown or not evaluated), or as N/A with the footnote N/A = not applicable, whichever is appropriate.

Dates should be printed in SAS DATE9.format (ddMMMyyyy: 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as N/A, unless otherwise specified.

All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (eg, 11:26:45 or 11:26). Time will only be reported if it was measured as part of the study.

Figure Conventions

Unless otherwise specified, study visits will be displayed on the X-axis and endpoint (eg, treatment mean change from baseline) values will be displayed on the Y-axis.

Legends will be used for all figures with more than 1 variable, group, or item displayed.

7.2.1 Rules for Missing Data

Imputation of missing dates will be undertaken for AEs, concomitant medications, allergy history dates and MTD, as specified below:

All AEs with partial or missing dates and times will be considered treatment-emergent adverse events (TEAEs) unless a partial date clearly indicates that it occurred before the first dose of study treatment or more than 30 days after last dose of treatment. All therapies with partial or missing dates and times recorded on the concomitant medication or non-drug therapy electronic case report form (eCRF) pages will be considered concomitant unless a partial stop date and time clearly indicates it was stopped before the first dose of study treatment. Start and stop dates will be imputed when partial dates are present as needed to determine treatment-emergent events and concomitant medications. No imputation will be done for a completely missing start or stop date or for subjects who did not receive study treatment.

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

- If the provided month and year match the month and year for that subject's first dose date, then the first dose date will be used
- In all other cases the first of the month will be used with the provided month and year

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

- If the provided year matches the year for that subject's first dose date, then the first dose date will be used
- In all other cases the first of January will be used with the provided year

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 (including follow-up call and / or visits).

For allergy history, the reported date of anaphylactic reactions 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 Jul 1

Subjects who do not undergo either end-of-phase DBPCFC for any reason will be categorized as 'desensitization nonresponders' and their maximum tolerated challenge dose will be imputed based on the treatment period:

- Post low-dose buildup phase DBPCFC (group 1 only): maximum tolerated challenge dose at the ARC001 exit DBPCFC.
- Post plateau phase DBPCFC:
  - Group 1: maximum tolerated challenge dose at the post low-dose buildup phase DBPCFC (ie, no change in maximum tolerated challenge dose from post low-dose buildup DBPCFC to post plateau phase DBPCFC).
  - Group 2: maximum tolerated challenge dose at the ARC001 exit DBPCFC (ie, no change in maximum tolerated challenge dose from ARC001 exit DBPCFC to post plateau phase DBPCFC).

7.2.2 Visit Windows

All information will be listed, summarized, and analyzed according to the time point or dose. Time points will be based on the nominal visit (eg, low-dose buildup phase week 6) for listings and summaries and the last assessment for each study phase (eg, the last available

assessment during the low-dose buildup phase) will be used for summaries, as applicable. No visit windowing will be performed.

8 TIMING OF ANALYSES

Analyses for DMC review were planned to occur approximately every 3 months to monitor safety. A preliminary analysis was performed when all subjects entered the extended maintenance phase.

The final analysis of safety and efficacy will be performed after all subjects complete exit/early termination visit assessments. Subjects will be offered the opportunity to continue dosing with AR101 in another Aimmune-sponsored study until AR101 becomes commercially available or development is discontinued in the US. The final analysis will include all ARC002 data collected at the time of database lock.

9 STATISTICAL METHODS

9.1 Patient Disposition

The number and percentage of subjects enrolled, included in each population defined in Section 6, completed and discontinued, and entered each treatment period will be summarized by treatment group and overall. Reasons for discontinuation from the study will be summarized by treatment group overall and for the low-dose, plateau, low-dose extended maintenance, high-dose, and high-dose extended maintenance phases. Subjects who complete a treatment period but discontinue before starting the next period will be considered discontinuations from the last treatment period with the reason "did not continue to next period".

Subject completion status, date of study completion/discontinuation, study treatment discontinuation, and reason for discontinuation collected in the eCRFs will be listed. Other information collected during screening will also be included in the data listings.

Inclusion and exclusion criteria for study eligibility and informed consent dates(s) will be listed separately.

9.2 Protocol Deviations

A protocol violation (ie, major protocol deviation) is a deviation from the protocol approved by the institutional review board that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations or policies; any action that is inconsistent with medical and ethical principles; and a serious or

continuing noncompliance with federal, state, local, or institutional human subject protection regulations, policies, or procedures.

A non-major protocol deviation is any change, divergence, or departure from the study design or procedures that does not have a major impact on the subject's rights, safety, or well-being or the completeness, accuracy, and reliability of the study data.

Protocol deviations will be reviewed and their categorization as major or minor will be determined before database lock. All major protocol deviations will be listed by subject.

9.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be listed for all enrolled subjects. Summary statistics for demographics and baseline characteristics will be provided for all subjects in the safety population. The tables will include age, race, ethnicity, sex, and baseline values for body weight, height, body mass index, peanut-specific IgE, peanut-specific IgG4, results from SPT, and maximum tolerated dose (MTD) of peanut protein.

Age in years, at informed consent for ARC002, will be calculated as the number of elapsed months between the date of birth and the informed consent date and this will be calculated programmatically in SAS as follows:

AGE=FLOOR((INTCK('month',DOB,ICDT)-(day(ICDT)<day(DOB)))/12)

where DOB = date of birth and ICDT = date of informed consent

Subject visits and phone calls will be listed.

9.4 Disease Characteristics and Previous Therapies

Medical history will be listed by subject and body system.

Allergy history will be listed by subject. The months since the most recent anaphylactic reaction to peanut, and months since the most recent anaphylactic reaction to peanut that was treated with a therapy will be calculated as the difference between the reported date of the reaction and the informed consent date, in months, using the SAS formula:

INTCK('month', date of reaction, informed consent date, 'C')

The duration of peanut allergy (in months), total number of anaphylactic reactions to peanut (if experienced), months since the most recent anaphylactic reaction to peanut, and months since the most recent anaphylactic reaction to peanut that was treated with a therapy will be summarized continuously by treatment group and overall. Descriptive history corresponding to peanut allergy (whether the subject has experienced anaphylactic reactions to peanuts during his lifetime, the therapies administered for the most recent anaphylactic reaction to

peanut, and the symptoms experienced during the most recent peanut exposure) will be summarized categorically by treatment group and overall.

All nonpeanut allergy history will be listed by subject. The presence of nonpeanut allergy history and causative allergens will also be summarized by treatment group and overall.

9.5 Extent of Exposure and Compliance of Study Drug

The overall treatment duration is defined as the date and time of the first dose of AR101 in ARC002 to the date and time of the last dose of AR101 in ARC002 or 24 hours after the last dose of the DBPCFC or OFC, whichever is later. The duration of treatment in weeks will be calculated as the duration of treatment in days divided by 7. The overall duration of treatment in weeks will be summarized continuously by treatment. The overall treatment duration in days will be summarized in 28-day increments: ≤ 28 days, 29-56 days, … 337-364 days, and > 364 days.

The duration of each treatment period will be calculated as (date of last study treatment administration within the period – date of first study treatment within the period + 1), where treatment periods are defined in Table 1 of section 9.6 . These treatment periods are the following and will include the food challenge periods in their calculations:

1. Low-dose **initial escalation phase,**
2. Low-dose **buildup phase,**
3. Low-dose **buildup phase** DBPCFC**,**
4. Plateau phase**,**
5. Plateau phase DBPCFC,
6. Low-dose **extended maintenance phase,**
7. High-dose **buildup phase,**
8. High-dose **extended maintenance phase**,
9. Exit OFC
10. Post-treatment

The maximum dose of AR101 achieved will be listed and summarized continuously overall. Maximum dose achieved will also be summarized categorically displaying the number and percentage of subjects by treatment group overall. The last dose achieved, defined as the last assigned dose taken before end of study, will be listed and summarized similarly.

A dose escalation will be defined as a subject consuming an increased dose from the previous dose. An unsuccessful dose escalation will be defined as a subject consuming an increased dose, followed by a dose reduction. A dose reduction will be defined as any decrease in dose level that does not qualify as an unsuccessful dose escalation. The numbers of dose escalations, unsuccessful dose escalations, and dose reductions will be listed and summarized by treatment group overall.

In-clinic dosing, including visit, date and time, dose level, whether it was a dose reduction (and reason), and whether the dose was tolerated will be listed by subject.

To evaluate at-home dosing compliance, the number of days with planned at-home dosing will be summarized by treatment group and overall. The percentage of days of planned at-home dosing on which any: at-home dose (ie, full or partial) was consumed, a full dose was consumed, a partial dose was consumed, a dose was missed, or days with dosing symptoms, will all be summarized similarly.

At-home dosing data will be listed. Daily diary records, including date and time, whether a full or partial dose was consumed (or the dose was missed), and reason for partial or missed dose will be displayed as well as the presence of any dose-related symptoms, symptoms, onset times, resolution times, and medications used to treat symptoms.

The number of days of planned at-home dosing, calculated as the number of days on study minus the number of days of in-clinic dosing, will be listed by subject. For each subject, the number and percent of days for each type of dose (full dose, partial dose, and missed dose) will be listed. The percent of days will be calculated as the number of days for that type of dose divided by the number of days of planned at-home dosing. The number and percentage of days with dose-related symptoms, as recorded in the daily diary, will also be listed for each subject.

9.6 Treatment Phases

Summaries will be provided by treatment period as appropriate (Table 1).

Table 1: Treatment Periods

Treatment Period	Start as Defined	End as Defined [1]	Duration
Low-dose Phase (group 1 only)			
Low-dose **initial escalation phase**	First in-clinic dose of AR101	24 h after last initial escalation dose or first at-home dose [2]	days 1 to 3
Low-dose **buildup phase**	24 h after last initial escalation dose or first in-home dose [2]	First dose of plateau phase	20-36 weeks
Post low-dose **buildup phase DBPCFC**	First DBPCFC dose	24 h after last dose of DBPCFC or start of dose in next period [2]	24 h
Plateau Phase	Group 1: 24 h after last dose of DBPCFC or start of dose in plateau phase [2] Group 2: first dose of AR101	Start of post plateau phase DBPCFC	12-24 weeks
Post plateau phase DBPCFC	First DBPCFC dose	24 h after last dose of DBPCFC or start of dose in next period [2]	24 h
Low-dose **extended maintenance phase** (if not high-dose buildup)	24 h after last dose of post plateau phase DBPCFC or start of dose in maintenance phase [2]	Last dose of AR101 before exit OFC or 24 h after last dose [2]	

Treatment Period	Start as Defined	End as Defined [1]	Duration
High-dose buildup phase (optional)			
High-dose **buildup phase**	24 h after last initial escalation dose or first at-home dose [2]	24 h after last dose of AR101 or first dose of high-dose extended maintenance [2, 3]	
High-dose **extended maintenance phase** (optional)	First dose of high-dose extended maintenance	24 h after last dose of AR101 before exit OFC or 24 h after last dose [2, 4]	
Exit OFC (optional)	First OFC dose after low-dose or high-dose extended maintenance phase	24 h after last dose of OFC	
Post-treatment	24 h after optional exit OFC or 24 h after last dose of AR101		

[1] If subject discontinues during a treatment period, the end date will be 24 h after the last dose of study treatment.

[2] Whichever is earlier of the 2 times.

[3] If the dose at the extended maintenance phase week 0/initiation visit is higher than the last dose from the high-dose buildup phase, the high-dose buildup phase is expanded to include the higher dose.

[4] If the dose at the extended maintenance phase week 0/initiation visit is higher than the last dose from the high-dose buildup phase, the high-dose buildup phase is expanded to include the higher dose and the high-dose extended maintenance start revised.

DBPCFC, double-blind placebo-controlled food challenge; h, hour; OFC, oral food challenge.

The DBPCFC is given in 2 parts on the same day, consecutive days, or occasionally nonconsecutive days. For challenges performed on nonconsecutive days, the period of time more than 24 hours after the first part and before the second part begins will be attributed to the low-dose buildup phase at-home/in-clinic continuation period or the plateau phase, depending on the period of the DBPCFC.

9.7 Concomitant Medications

All medications recorded on the concomitant medications eCRF will be coded using the World Health Organization (WHO) drug dictionary, Mar 1, 2013 version. Medications will be listed and summarized by ATC Level 1, and preferred name.

Prior medications are defined as medications which are only taken prior to the beginning of the treatment period.

Concomitant medications are medications taken at any time during the treatment period. Medications taken any time after the last dose are considered concomitant as well. As needed medications (PRN), which may or may not be taken for long periods of time, but are prescribed for a period that overlaps with the treatment period, will be considered concomitant medications.

Rescue medications are any medication used to treat individual allergic reactions during peanut OIT. Concomitant medications that are considered rescue medications are indicated by the investigator on the concomitant medications eCRF.

Concomitant medications will be summarized by treatment group. Subjects will be counted no more than 1 time per preferred name and no more than 1 time per ATC level 1 in the summary.

A similar summary will be presented for rescue medications. Concomitant non-drug therapies will be listed by subject.

9.8 Efficacy Analyses

9.8.1 Analyses of the Secondary Efficacy Endpoints

9.8.1.1 Desensitization Response

DBPCFCs will be performed post low-dose buildup phase and post plateau phase. The number and percentage of desensitization responders at challenge dose levels of 300, 600, and 1000 mg of peanut protein will be reported by treatment group separately for each DBPCFC. The desensitization response rate and its 95% CI will be calculated for each treatment group with Wilson (score) confidence limits for the binomial proportion. This analysis will be performed using all subjects in the safety population; subjects who did not complete the DBPCFC for any reason are considered nonresponders. The analysis will also be repeated to only include subjects who completed each DBPCFC (see the two DBPCFC populations defined in section 6).

The number and percentage of desensitization responders at challenge dose levels of 300, 600, 1000, and 2000 mg of peanut protein during the exit OFC will be summarized similarly with 95% Wilson (score) confidence limits. This desensitization response analysis will be performed only in subjects who completed the optional exit OFC (see the matching population defined in section 6).

Classification of Responder Status

Desensitization response will be evaluated for group 1 subjects at the post low-dose buildup phase DBPCFC and for all subjects at the post plateau phase DBPCFC. Response will be assessed at 300 mg (443 mg cumulative), 600 (1043 mg cumulative), and 1000 mg (2043 mg cumulative) of peanut protein. The 1000 mg level only applies to the post plateau phase DBPCFC.

Responders and nonresponders for the post low-dose buildup phase DBPCFC and post plateau phase DBPCFC are defined as follows:

- Desensitization responder at 300, 600, or 1000 mg: a subject who tolerates at least 300, 600, or 1000 mg dose of peanut protein, respectively, at an end-of-phase DBPCFC with no more than mild symptoms.
- Desensitization nonresponder at 300, 600, or 1000 mg: a dose-escalation failure or a subject who experienced dose-limiting symptoms (moderate or worse) or had dose-limiting symptoms at or before the 300, 600, or 1000 mg dose of peanut protein, respectively, at an end-of-phase DBPCFC.

As a general rule, subjects who do not undergo the end-of-phase DBPCFC for any reason will be categorized as desensitization nonresponders. Their maximum tolerated challenge dose will be imputed based on the treatment period: *see section 7.2.1 "Rules for Missing Data" for details*.

The desensitization responder analysis for the post low-dose buildup phase DBPCFC and post plateau phase DBPCFC will be repeated to only include subjects who undergo the DBPCFC (see the two DBPCFC populations defined in section 6). Subjects who do not have evaluable DBPCFC results will be excluded.

Responders and nonresponders for the exit OFC are defined similarly but only include subjects who undergo the exit OFC:

- Desensitization responder at 300, 600, 1000, or 2000 mg: a subject who tolerates at least 300, 600, 1000, or 2000 mg dose of peanut protein, respectively, at the exit OFC with no more than mild symptoms.
- Desensitization nonresponder at 300, 600, 1000, or 2000 mg: a subject who experienced dose-limiting symptoms (moderate or worse) at or before the 300, 600, 1000, or 2000 mg dose of peanut protein, respectively, at the exit OFC.

Subjects who do not participate in the optional exit OFC will not be included in the desensitization response analysis (see the matching population defined in section 6).

9.8.1.2 Maximum Tolerated Challenge Dose During Food Challenges

The maximum tolerated challenge is carried out on the food challenge completers only - see the matching populations as defined in section 6. The maximum tolerated challenge dose during the DBPCFC or the exit OFC 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 (ie, subject did not experience any dose-limiting symptoms). If a subject is administered nonstandard doses at a food challenge, the highest standard dose (whether administered or not) less than the highest tolerated nonstandard dose will be considered the maximum tolerated challenge dose.

The food challenges are based on a modified Practical Allergy (PRACTALL) guidelines dosing regimen. Except the 600 and 2000 mg doses, the modified PRACTALL doses are approximately on a logarithmic scale.

The number and percentage of subjects will be presented for each maximum tolerated challenge dose level by treatment group for each DBPCFC by type of challenge (peanut or placebo).

For the peanut challenge, summary statistics will be computed in logarithmic scale for the maximum tolerated challenge dose at the AR101 baseline DBPCFC, post low-dose buildup phase DBPCFC and post plateau phase DBPCFC; the change in maximum tolerated challenge dose from AR101 baseline (group 1 only) and the change in maximum tolerated challenge dose from post low-dose buildup phase (groups 1 and 2) at each subsequent DBPCFC. The 95% CI (on the ratios) will also be computed in the original scale and analysis of the changes will be performed using the Wilcoxon signed rank test. Results in the $\log_{10}$ scale will be transformed back to the original scale for summary statistics. The change in the $\log_{10}$ scale is a ratio (x-fold increase) in the original scale. The changes in the maximum tolerated doses are expressed as an x-fold ratio increase in the original untransformed values.

9.8.1.3 Maximum Severity of Symptoms During Food Challenges

Symptom severity data were collected during each challenge dose of peanut protein during food challenges. Symptom severity will be recorded at 5 levels: 0-none, 1-mild, 2-moderate, 3-severe, 4-life threatening.

The maximum severity of symptoms observed in the food challenge at each DBPCFC dose level (see Section 6.4 in the protocol for the different doses for each food challenge) will be used for each subject in the analysis. If a subject experienced multiple reactions at a challenge dose level, the most severe level will be used for the score. Categorical and continuous descriptive statistics for the maximum severity of symptom score will be summarized by treatment group for each food challenge. The analysis will be performed on patients who completed the appropriate food challenge only (see the matching population defined in section 6).

9.8.1.4 Peanut-Specific IgE and IgG4

Blood samples to measure peanut-specific IgE and IgG4 and total IgE were collected during the study. Peanut-specific IgE/IgG4 ratio will be calculated, listed by subject, and summarized by treatment period/visit and treatment group. Results from early termination visits will be combined into each applicable treatment period and summarized with end of treatment period results. 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 peanut-specific IgE or IgG4 is outside of the limits of quantification, the peanut-specific IgE/IgG4 ratio will be calculated using the LLOQ or ULOQ as appropriate.

Absolute values will be summarized using descriptive statistics, using the geometric mean and SD in lieu of arithmetic mean and SD. The 95% CI based on geometric calculations will also be provided. Relative changes from AR101 baseline will be calculated for group 1 subjects as the ratio of postbaseline values to baseline values. Relative changes from the end of the low-dose buildup phase will be calculated for both group 1 and group 2 subjects similarly. The relative changes will be summarized using descriptive statistics of: geometric mean, SD, and 95% CIs based on geometric calculations. Analysis of the relative changes will be performed using change on the logarithmic scale using the Wilcoxon signed rank test.

9.8.1.5 Skin Prick Test

The SPT is performed at the end of each treatment period (low-dose, plateau, high-dose, extended low/high-dose maintenance); early termination visit; at weeks 0, 12, 24, and then at alternative 3-month visits in the extended low/high-dose maintenance period; and at the study exit visit. Results from early termination visits will be combined into the applicable treatment period and summarized with end of treatment period results. The SPT results for measurement (mm) of peanut wheal, peanut erythema/flare, saline wheal, saline-glycerin erythema/flare, histamine wheal, and histamine erythema/flare will be listed.

Absolute values will be summarized using descriptive statistics. Changes from AR101 baseline and changes from the end of low-dose buildup phase value will also be summarized. The 95% CI for the absolute values and changes will be provided. Analysis of the changes will be performed using the Wilcoxon signed rank test. All SPT results will be included in data listings.

9.8.1.6 Physician Global Assessment

Overall disease activity will be assessed by investigators using a 100 mm VAS. This evaluation will be performed at the end of each treatment period, at early termination visits, and at the study exit visit. Results collected at early termination visits will be added to the appropriate treatment period for summary depending on when the early termination visit occurs.

Absolute values will be summarized using descriptive statistics. Changes from AR101 baseline and changes from the end of low-dose buildup phase value will also be summarized. The 95% CI for the absolute values and changes will be provided. Analysis of the changes will be performed using the Wilcoxon signed rank test.

9.8.2 Exploratory Endpoint Analysis

9.8.2.1 Maximum Tolerated Challenge Dose During OFC Exit Challenge

The exit OFC only includes the peanut challenge. The number and percentage of subjects will be presented for each maximum tolerated challenge dose level by treatment group. Summary statistics for the maximum tolerated challenge dose at the exit OFC will be tabulated similarly to DBPCFCs but will not include change in the maximum tolerated challenge dose.

9.8.2.2 Treatment Satisfaction Questionnaire for Medication (TSQM) Scale Scores

As per the Schedule of Assessments, the TSQM-9 (9 item) questionnaire will be administered at study exit (or early termination).

The TSQM-9 is a widely used instrument to assess treatment satisfaction with medication in studies where patient reported side effects have a potential to interfere with the objectives of the study. The instrument consists of 9 questions that comprise 3 scales.

Responses to the 9 individual items will be presented using descriptive statistics. The scale scores (effectiveness, convenience, and global satisfaction) will be calculated and summarized using descriptive statistics.

The Effectiveness scale includes items 1-3, the Convenience scale includes items 4-6, and the Global Satisfaction scale includes items 7-9. Each scale will be scored as: 100*[(sum of non-missing responses) minus the number of non-missing responses] divided by the maximum possible score of the sum of non-missing responses. If more than one item within the scale has a missing result then the scale score will not be calculated.

P-values will not be provided as this is an exploratory endpoint.

9.8.2.3 Parent/Patient Exit Survey Scores

As per the Schedule of Assessments, the Parent and Patient exit surveys will be administered at study exit (or early termination).

The survey includes questions on study drug palatability, frequency of taking study drug as instructed, impact on attending clinic visits, interest in continuing to take study drug, if the subject would recommend the study drug to others, and burden of treatment. Responses to each item will be summarized with descriptive statistics and type of instrument administered (parent or subject ages 12 and older).

P-values will not be provided as this is an exploratory endpoint. Note for children less than 12, only 1 item is required in this survey from the patient.

9.9 Safety Analyses

Safety will be assessed by extent of exposure, concomitant medications, physical examinations, and all the safety endpoints defined in Section 4.2.

Safety data will be summarized descriptively and the Safety population will be used for all summaries of safety parameters, unless otherwise noted. Safety listings will include all subjects sorted by treatment group, unless otherwise noted.

9.9.1 Primary Endpoint Analysis (Treatment Related AEs and Symptoms)

The primary endpoint is the incidence of treatment-related AEs and dosing symptoms over a treatment period of 18 months. The primary endpoint is all treatment-related AEs inclusive

of dosing symptoms as assessed by the investigator. Dosing symptoms are recorded on in-clinic dosing symptom and daily dosing diary eCRFs and assessed by the investigator to determine if they are 1 or more AEs, and are recorded on the AE eCRF with the severity and relationship to AR101.

The number and percentage of subjects with at least 1 treatment-related AE will be summarized overall and by treatment period using the safety population for each treatment group and overall. In addition, the number of treatment-related AEs in each period and exposure-adjusted incidence rate will be presented (separate tables). The exposure-adjusted is defined as total number of treatment-related AEs divided by total number of subject-years at risk. Total number of subject-years at risk for each period is the sum of duration in days across all subjects within each period.

Supportive analyses for the primary endpoint will include summaries of treatment-related AEs by system organ class and preferred term and dosing symptoms observed in-clinic and entered on the daily dosing diary.

9.9.2 Adverse Events, Use of Rescue Medications, Food Allergies and Symptoms

This section will describe safety analyses related to adverse events, hypersensitivity reactions, AEs of interest, food allergies, symptoms (food challenge, clinic and at home) as well as the need for epinephrine rescue medications.

9.9.2.1 Adverse Events

Safety events arising under certain defined conditions (eg, accidental food exposures, dosing symptoms) are recorded on specific eCRFs and evaluated by the investigator to determine if they meet the criteria for reporting as an AE per protocol Section 7.

TEAEs are defined as any event starting during or after the treatment period. Any event occurring on the same day as a food challenge or in-clinic escalation dosing will be considered to be associated with those events (and hence summarized in the appropriate food challenge summaries), and flagged as such in the listings.

Events will be further classified by onset using treatment periods (Section 9.6). AE related to study treatment are defined as those classified as possibly, probably, or definitely related to study treatment. If relationship is missing, the event will be conservatively summarized as related to study treatment. All reported AEs will be classified into SOC and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 or later. A summary of SOC, preferred term, and verbatim term will be provided. The summaries will be presented in order of descending frequency of SOC and preferred term (overall and by treatment period). In addition to the number and percent of subjects with AEs, the number of events and exposure-adjusted incidence rate will be calculated. Exposure incidence rates are defined as the total number of events divided by the total number of subject-years at risk. The total number of subject-years at risk is defined as total number of days for all subjects in the treatment period divided by 365.25. Summaries of AEs by treatment period, SOC, and preferred term will be provided for TEAEs, treatment-emergent

SAEs, and TEAEs related to study treatment. Subjects will be counted at most once per treatment period overall, SOC, and preferred term for these summaries. The number of subjects at risk for each treatment period (ie, the number of subjects on study at the beginning of each treatment period) will be used as the denominator. Note TEAE's that are ongoing will be counted in the treatment period they originated in; so as not to over count, they will not also be counted in the treatment periods that follow.

AE severity is classified as NCI-CTCAE v 4.0. If severity is missing, a separate category of missing severity will be included in the summary table, and no imputation of severity will be performed.

A summary of TEAEs by treatment period, SOC, PT and maximum severity will also be provided. Subjects will be counted at most once per treatment period overall, at most once per SOC, and at most once per PT at the maximum severity. The number of events and exposure-adjusted incidence will be calculated for each level of severity including missing severity.

9.9.2.2 Food Allergy Episodes

The occurrence of a safety event associated with accidental food ingestion will be reported as a food allergy episode per protocol Section 7.2. Any such event that meets the definition of an SAE will also be reported as an AE.

Food allergy episodes will be summarized as overall and by treatment period (Section 9.6). 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 nonpeanut), the number of episodes of each (peanut-related and nonpeanut-related) per subject, and the total number of food allergy episodes (peanut- and nonpeanut-related) will be summarized. The number of episodes with treatment administered or considered SAEs will also be summarized. The total number of episodes and exposure-adjusted incidence rate will also be calculated.

All reported food allergy episodes will be listed by subject. Episodes of allergic reaction associated with foods other than peanut will be flagged.

9.9.2.3 Hypersensitivity AEs

Hypersensitivity AEs (preferred term hypersensitivity) will have secondary coding performed to assign the events to more specific SOC and preferred term. An additional summary and listing of treatment-related hypersensitivity AEs will be provided by treatment group and treatment period using the more specific SOC and preferred term. The total number of events and exposure-adjusted incidence rate will also be calculated.

9.9.2.4 Adverse Events of Interest

Listings will be provided for each adverse events of interest: anaphylaxis events; GI AEs leading to study drug discontinuation; accidental food allergen exposure; AEs featuring a severe symptom; and AEs associated with the use of epinephrine.

9.9.2.5 Use of Epinephrine as a Rescue Medication During Food Challenges

Epinephrine use as a rescue medication is collected on the concomitant medication eCRF. and is defined as any rescue medication with a preferred name of 'epinephrine when coded as described in the concomitant medication section above.

Listings of epinephrine use as a rescue medication will be provided along with information of the treatment period in which it was initiated.

The day of epinephrine use will be listed by use during treatment period time points (Table 1), as well as any use as an accidental exposure (defined as a recorded food allergy episode) occurring on or after the first dose of AR101 in this study. Use during DBPCFC will be further categorized into peanut or placebo challenges.

Any epinephrine rescue medication usage reported on the same date as a food challenge will be considered to be used during the food challenge. For example, if a subject is at a low-dose buildup phase visit but the dose stays the same or decreases, that day will be classified as low-dose at-home continuation. If both peanut and placebo DBPCFCs were on the same date (either at screening or study exit), then any epinephrine use on that date will be categorized as used for the peanut challenge.

9.9.2.6 Symptoms During Food Challenge

During each food challenge, the severity of prespecified dosing symptoms (hives, throat tightness, throat swelling, throat discomfort, hoarseness, laryngeal edema, skin flushing, pruritus, rhinorrhea, sneezing, nasal congestion, coughing, wheezing, dyspnea, abnormal pain, nausea, vomiting, other) will be graded by CoFAR (protocol Section 6.6.1 and Section 6.6.2). In addition, the presence of dose-limiting symptoms was recorded.

Symptoms will be summarized separately for each food challenge using the safety population. For DBPCFCs, symptoms will also be summarized separately for the type of challenge (peanut or placebo); the exit OFC is peanut only. Subjects will be counted at most once per symptom for each summary, at the most severe level recorded for that subject. The presence of any dose-limiting symptom and maximum dose severity of any symptom, and the total number of symptoms overall and by severity will also be summarized.

Symptoms at the post low-dose buildup phase DBPCFC, post plateau phase DBPCFC, and exit OFC will be listed by subject.

9.9.2.7 Symptoms During In-Clinic Dosing

For each in-clinic dose (low-dose initial escalation, low-dose buildup, plateau, low-dose extended maintenance, high-dose initial escalation, high-dose buildup, or high-dose extended maintenance), the severity of prespecified symptoms was rated as none, mild, moderate, severe, or life-threatening (protocol Sections 6.6.1 and 6.6.2). In addition, whether the dose was tolerated was recorded for each dose. Symptoms are assessed by the investigator to determine if they are AEs; the AEs and the severity and relationship to AR101 will be recorded on the AE eCRF (protocol Section 7.1).

Maximum severity by symptom, maximum overall severity, and presence of any dose-related symptoms will be summarized across all dose levels. Symptoms, maximum severity of any symptom, presence of dose-related symptoms, and whether the dose was tolerated will be summarized for each dose level. If a subject is administered the same dose at more than 1 in-clinic visit in the same treatment period (either the subject's dose remained the same as the previous visit or a subject had a dose reduction after a dose increase), the most severe symptoms and dose-limiting symptoms will be summarized for that dose level. The total number of events and exposure-adjusted incidence rate will also be calculated. This summary will be performed overall and by treatment period.

Symptoms will be listed by subject and dose level.

9.9.2.8 Symptoms During At-Home Dosing

The subject diaries will serve as source documentation for the collection of any dose-related symptoms occurring at home (low-dose buildup, plateau, low-dose extended maintenance, high-dose buildup, high-dose extended maintenance). Symptoms are assessed by the investigator to determine if they are AEs; the AEs and the severity and relationship to AR101 will be recorded on the AE eCRF (protocol Section 7.1).

The presence of any dose-related symptoms and the use of medication to treat any reported symptoms will be summarized across all dose levels. Individual symptoms will also be summarized. The total number of events and exposure-adjusted incidence rate will also be calculated. This summary will be performed overall and by treatment period.

Symptoms will be listed by subject and dose level.

9.9.3 Laboratory Assessments

Pregnancy test results will be listed by subject and visit.

Optional blood samples were collected for exploratory analysis by the Immune Tolerance Network. These analyses will be conducted separately and are outside the scope of this analysis plan. Sample collection dates and times will be listed by subject and time point.

9.9.4 Vital Signs

Vital signs (pulse rate, systolic/diastolic blood pressure, body temperature, height, weight, and body mass index) will be listed by subject and visit (vital signs from early termination visits will be combined with the end of phase visits). Observed values and change from baseline will be summarized by visit and treatment group.

9.9.5 Physical Examination

Physical examination results will be summarized by treatment group for the safety population. The number and percentage of subjects with abnormal results will be tabulated for each assessment. By subject listing will be provided.

9.9.6 Peak Expiratory Flow Rate

Peak expiratory flow rate (PEFR) assessments are performed in triplicate throughout the study, with the best (highest) value recorded on the eCRF and in the by-subject listing. Only the best values will be summarized.

PEFR absolute values and changes from baseline values will be summarized by visit (early termination visits will be combined with the end of phase visits) and treatment groups for the safety population. Baseline PEFR is defined as the best value at the last PEFR assessment before the first dose of AR101 in ARC002. By subject listing will be provided.

10 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

The analyses described in the protocol have been expanded within this document. Any deviations from the plans detailed in this SAP will be described and justified in the final clinical study report. The following endpoints representing adverse events of interest were not specified in the protocol:

- The maximum severity of symptoms occurring at each challenge dose of peanut protein during DBPCFC
- Use of epinephrine as a rescue medication during DBPCFC
- Frequency of allergic reaction (hypersensitivity) AEs normalized for duration of treatment
- Frequency of use of epinephrine as a rescue medication during OIT by treatment period
- Frequency of accidental ingestions of peanut and other allergenic foods and severity of resultant reactions

11 REFERENCES

Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology – European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol 2012; 130(6):1260-74.