CLINICAL STUDY PROTOCOL

ARC003
Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE)

Protocol Amendment 4.0 – 31 Jul 2017
Reference Numbers: NCT02635776, EudraCT 2015-004257-41

Aimmune Therapeutics, Inc.
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CLINICAL STUDY PROTOCOL

Protocol Title:	**P**EANUT **AL**LERGY ORAL **I**MMUNOTHERAPY **S**TUDY OF **AR**101 FOR **DE**SENSITIZATION IN CHILDREN AND ADULTS (PALISADE)	
Investigational Drug:	AR101, Characterized Peanut Allergen	
Protocol Number:	ARC003	
IND:	15463	
EudraCT:	2015-004257-41	
Sponsor:	Aimmune Therapeutics, Inc. 8000 Marina Blvd, Suite 200 Brisbane, CA 94005 USA	
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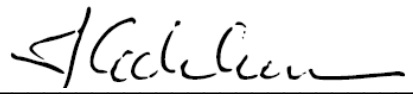
Sponsor Protocol Approval

Protocol ARC003	Version / Date: Protocol Amendment 4.0 / 31 July 2017
Sponsor: Aimmune Therapeutics, Inc.	
Short Title: PALISADE	

I have read protocol ARC003, Amendment 4.0 (Global), and I approve it. I agree to meet all obligations of the Sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other investigators of all relevant information that becomes available during the conduct of this study.

Daniel C. Adelman, MD
Chief Medical Officer (Print)



Chief Medical Officer (Signature) Date: 8/3/2017

Principal Investigator Protocol Approval

Protocol ARC003	Version / Date: Amendment 4.0 (Global) / 31 July 2017
IND: 15463 EudraCT: 2015-004257-41	Principal Investigator:
Short Title: PALISADE	

I have read protocol ARC003, Amendment 4.0 (Global), and I approve it. As the Principal Investigator, I agree to conduct this protocol according to Good Clinical Practice (GCP), as delineated in the United States Code of Federal Regulations (CFR) – 21 CFR Parts 50, 54, and 312 (Subpart D) and in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) "Guideline for Good Clinical Practice" E6(R1) 10 June 1996*, and according to the criteria specified in this protocol. Furthermore, I will conduct this protocol in keeping with local, state and federal requirements.*

_____ _____

Principal Investigator (Print) Date

_____ _____

Principal Investigator (Signature) Date

Synopsis

Protocol ARC003 Synopsis	
Title	**P**EANUT **AL**LERGY ORAL **I**MMUNOTHERAPY **S**TUDY OF **A**R101 FOR **D**ESENSITIZATION IN CHILDREN AND ADULTS (PALISADE)
Short Title	PALISADE
Clinical Phase	3
IND	15463
EudraCT	2015-004257-41
IND Sponsor	Aimmune Therapeutics, Inc. (formerly Allergen Research Corporation; ARC)
Number of Subjects	Approximately 500 peanut-allergic subjects will be randomized 3:1 to peanut oral immunotherapy (OIT) versus placebo. At least 80% of the subjects randomized will be children.
Objective	The primary objective is to demonstrate the efficacy of AR101, a pharmaceutical-grade peanut allergen formulation, through reduction in clinical reactivity to limited amounts of peanut allergen in peanut-allergic children (ages 4-17 years, inclusive). The secondary objectives are: • To demonstrate the safety of AR101 as measured by the incidence of adverse events, including serious adverse events in children (ages 4-17 years, inclusive). • To evaluate the immunological effects of peanut OIT therapy in children (ages 4-17 years, inclusive).
Study Design	This is an international, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of AR101 in a characterized desensitization OIT regimen in peanut-allergic individuals. The study will consist of a screening phase, that includes a Screening double-blind, placebo- controlled food challenge (DBPCFC), and a double-blind OIT treatment phase that includes an initial escalation period, an up-dosing period, and a maintenance period, followed by an Exit DBPCFC. An open-label safety follow-on study (ARC004) is planned after completion of ARC003. All eligible subjects will receive escalating doses of either AR101 or placebo. Eligible subjects who reach the targeted dose of 300 mg/d and maintain that dose for approximately 24 weeks will undergo an Exit DBPCFC. Subjects who do not reach 300 mg/d will be considered escalation failures and nonresponders for the primary analysis. A DBPCFC will be performed for those subjects achieving the target dose of 300 mg/d and continuing to receive that dose throughout the maintenance period (~24 weeks). Each subject will be unblinded when he/she completes the DBPCFC at the end of the ~24-week maintenance period, provided regulatory and IRB/EC approval for ARC004 have been received, the availability of IP for ARC004, and all major data queries for the subject have been resolved. If this is not the case, the subject shall remain on blinded treatment until these requirements are satisfied. The subject should continue his or her maintenance visits (completed as unscheduled visits), every 30 days and complete all protocol procedures at each visit until study completion and rollover to ARC004. All placebo subjects who complete ARC003 are eligible for rollover into the ARC004 protocol. Placebo subjects from ARC003 will, in ARC004, undergo an escalation schedule identical to that for active subjects in the ARC003 protocol. All subjects on active treatment in ARC003 who pass the DBPCFC at the 300 mg (443 mg cumulative) challenge dose level of peanut protein are eligible to proceed

Protocol ARC003 Synopsis	
Title	**P**EANUT **AL**LERGY ORAL **I**MMUNOTHERAPY **S**TUDY OF **AR**101 FOR **DE**SENSITIZATION IN CHILDREN AND ADULTS (PALISADE)
	to ARC004. Those who do not pass DBPCFC at the 300 mg (443 mg cumulative) challenge dose level will be considered endpoint failures and nonresponders for the primary analysis. They will not be eligible for rollover into the ARC004 protocol due to safety concerns. Those subjects who pass DBPCFC at the 300 mg (443 mg cumulative) challenge dose level, but fail at the 600 mg (1043 mg cumulative) or 1000 mg (2043 mg cumulative) challenge dose level, will also be considered endpoint failures and nonresponders for the primary analysis for North America or Europe, respectively; however, they will be eligible for rollover into the ARC004 protocol because tolerating a 300 mg (443 mg cumulative) dose of peanut protein is considered a clinically relevant level of desensitization in the event of accidental exposure. A Data Safety Monitoring Committee (DSMC) will be established to monitor the study for safety.
Study Duration	Approximately 12 months (44 to 68 weeks)
Primary Endpoint	**North America:** The primary clinical efficacy endpoint is the proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC **Europe:** The primary clinical efficacy endpoint is the proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC
Secondary Endpoints	<u>Key Secondary Endpoints, North America</u> • The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC • The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC • The maximum severity of symptoms in subjects aged 4 to 17 years occurring at any challenge dose of peanut protein during the Exit DBPCFC • The proportion of subjects aged 18 to 55 years who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC <u>Key Secondary Endpoints, Europe</u> • The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC • The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC • The maximum severity of symptoms in subjects aged 4 to 17 years occurring at any challenge dose of peanut protein during the Exit DBPCFC • The proportion of subjects aged 18 to 55 years who tolerate a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC

Protocol ARC003 Synopsis	
Title	**P**EANUT **A**LLERGY ORAL **I**MMUNOTHERAPY **S**TUDY OF **AR**101 FOR **D**ESENSITIZATION IN CHILDREN AND ADULTS (PALISADE)
	Other Secondary Endpoints, North America and Europe • Maximum dose achieved with no or mild symptoms at Exit DBPCFC in subjects aged 4 to 17 years • Change from baseline in maximum tolerated dose (MTD) of peanut protein at DBPCFC in subjects aged 4 to 17 years • Use of epinephrine as a rescue medication at Exit DBPCFC and comparison to its use at Screening DBPCFC in subjects aged 4 to 17 years • Changes in peanut-specific serum IgE and IgG4 levels in subjects aged 4 to 17 years • Changes in peanut skin prick test (SPT) mean wheal diameters in subjects aged 4 to 17 years • Quality of life assessment using the food allergy related quality of life questionnaire (FAQLQ), and the food allergy independent measure (FAIM) questionnaire in subjects aged 4 to 17 years
Secondary Safety Endpoints	Secondary Safety Endpoints, North America and Europe: • The safety of peanut OIT based on adverse events (AEs) including serious adverse events (SAEs) in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive • Use of epinephrine as a rescue medication during OIT (Initial Escalation, Up-dosing, and Maintenance Periods) in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive • Frequency of anaphylaxis during OIT (Initial Escalation, Up-dosing, and Maintenance Periods) in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive • Frequency of allergic reaction (hypersensitivity) AEs occurring during the Up-dosing versus the Maintenance Period, normalized for duration of treatment in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive • Frequency of accidental ingestions of peanut and other allergenic foods in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive • Severity of adverse events associated with accidental ingestions of peanut and other allergenic foods in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive • Frequency of premature discontinuation of dosing due to AEs; and frequency of premature discontinuation of dosing due to chronic/recurrent gastrointestinal (GI) AEs in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive • Assessment of asthma control using the Asthma Control Test questionnaire in in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
Exploratory Endpoints	Exploratory Endpoints, North America and Europe • The primary endpoints identified above will be repeated in the following 3 age groups: 4 to 11 years, 12 to 17 years, and 4 to 55 years, inclusive

Protocol ARC003 Synopsis	
Title	**PEANUT ALLERGY ORAL IMMUNOTHERAPY STUDY OF AR101 FOR DESENSITIZATION IN CHILDREN AND ADULTS (PALISADE)**
	• The first 3 key secondary endpoints and all other secondary endpoints identified above will be repeated in the following 4 age groups: 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive • Treatment satisfaction assessment using the Treatment Satisfaction Questionnaire for Medication (TSQM-9), an exit questionnaire, and palatability questions • (**North America sites only)** Optional mRNA expression patterns in saliva obtained longitudinally from peanut-allergic participants undergoing OIT in ARC003 **(Appendix 6)**
Study Product and Dispensing	AR101 or placebo. Doses characterized and normalized for total protein and specific peanut allergen ratios will ascend per the dosing regimen outlined below. Study product will be provided in pull-apart capsules formulated to contain 0.5, 1, 10, 20, and 100 mg of peanut protein. Matching placebo capsules identical to the active capsules will be used to maintain double-blinded conditions. For the Maintenance Period, 300 mg of peanut protein will be formulated in foil-laminate sachets. Matching placebo sachets will be used to maintain the double-blind. Study products will be shipped directly to the investigational site or the investigational site's pharmacy, depending on the investigational site's institutional requirements. Trained investigational site personnel will dispense the study product to the subject or the subject's parent or guardian in a manner consistent with the assigned dose level. Study product will be dispensed in double-blinded fashion according to subject randomization number, using an interactive voice/web response system.
Inclusion Criteria	• Age 4 through 55 years (inclusive) • Clinical history of allergy to peanuts or peanut-containing foods • Serum IgE to peanut of $\geq$ 0.35 kU_A/L [determined by UniCAP™ within the past 12 months] and/or a SPT to peanut $\geq$ 3 mm compared to control • Experience dose-limiting symptoms at or before the 100 mg challenge dose of peanut protein (measured as 200 mg of peanut flour) on Screening DBPCFC conducted in accordance with PRACTALL (Practical Issues in Allergology, Joint United States/European Union Initiative) guidelines • Written informed consent from adult subjects • Written informed consent from parent/guardian for minor subjects • Written assent from minor subjects as appropriate (eg, above the age of 7 years or the applicable age per local regulatory requirements) • Use of effective birth control by female subjects of child-bearing potential • Not be residing at the same address as another subject in this or any peanut OIT study
Exclusion Criteria	• History of cardiovascular disease, including uncontrolled or inadequately controlled hypertension (see also **Section 5.10** Prohibited Medications) • History of severe or life-threatening episode of anaphylaxis or anaphylactic shock within 60 days of Screening DBPCFC • History of chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that is, or is at significant risk of becoming, unstable or requiring a change in chronic therapeutic regimen • History of eosinophilic esophagitis (EoE), other eosinophilic gastrointestinal disease, chronic, recurrent, or severe gastroesophageal reflux disease (GERD),

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Title	**PEANUT ALLERGY ORAL IMMUNOTHERAPY STUDY OF AR101 FOR DESENSITIZATION IN CHILDREN AND ADULTS (PALISADE)**
	symptoms of dysphagia (eg, difficulty swallowing, food "getting stuck"), or recurrent gastrointestinal symptoms of undiagnosed etiology • Current participation in any other interventional study • Subject is in "build-up phase" of immunotherapy to another allergen (ie, has not reached maintenance dosing) • Severe asthma (2007 NHLBI Criteria Steps 5 or 6, see **Appendix 2)** • Mild or moderate asthma (2007 NHLBI Criteria Steps 1-4), if uncontrolled or difficult to control as defined by any of the following: o Forced expiratory volume in 1 second (FEV1) < 80% of predicted, or ratio of FEV1 to forced vital capacity (FEV1/FVC) < 75% of predicted, with or without controller medications (only for age 6 or greater and able to do spirometry) or o Inhaled corticosteroid (ICS) dosing of > 500 mcg daily fluticasone (or equivalent ICSs based on National Heart, Lung, and Blood Institute [NHLBI] dosing chart) or o One hospitalization in the past year prior to screening for asthma or o Emergency room (ER) visit for asthma within 6 months prior to screening • History of steroid medication use (via intravenous [IV], intramuscular [IM] or oral administration) in any of the following manners: o History of daily oral steroid dosing for > 1 month during the past year *or* o Burst oral (IM or IV) steroid course in the past 3 months prior to randomization *or* o > 2 burst oral (IM or IV) steroid courses in the past year ≥1 week in duration • Inability to discontinue antihistamines 5 half-lives before the initial day of escalation, skin prick testing, or DBPCFC • Lack of an available palatable vehicle food to which the subject is not allergic • Use of any therapeutic antibody (eg omalizumab, mepolizumab, reslizumab, etc.), any investigational peanut immunotherapy (eg oral, sublingual, epicutaneous), or any other immunomodulatory therapy excluding corticosteroids within the past 6 months (see also **Section 5.10** Prohibited Medications) • Use of beta-blockers (oral), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB) or calcium channel blockers (see also **Section 5.10** Prohibited Medications) • Pregnancy or lactation • Having the same place of residence as another subject in the study • Participation in another clinical trial within 30 days or 5 half-lives of the investigational product, whichever is longer, prior to randomization • Developing dose limiting symptoms in reaction to the placebo part of the Screening DBPCFC • History of a mast cell disorder, including mastocytosis, urticaria pigmentosa, and hereditary or idiopathic angioedema • Allergy to oat • Hypersensitivity to epinephrine and any of the excipients in the product

Protocol ARC003 Synopsis	
Title	**P**EANUT **A**LLERGY ORAL **I**MMUNOTHERAPY **S**TUDY OF **AR101** FOR **D**ESENSITIZATION IN CHILDREN AND ADULTS (PALISADE)
Treatment Description	Screening/baseline: All eligible subjects will undergo a DBPCFC at the end of the screening portion of the study. The Screening DBPCFC will be an abbreviated version of the DBPCFC described in the PRACTALL guidelines, progressing only up to a top challenge dose of 100 mg (144 mg cumulative) of peanut protein or placebo. Additionally, the DBPCFC will progress through the dose levels in an unaltered sequence, without repeating any dose. Those subjects who have dose-limiting symptoms (DLSs) at or before the 100 mg (144 mg cumulative) challenge dose of peanut protein (measured as 200 mg of peanut flour) will be randomized 3:1 to active treatment (AR101) or placebo. For each subject, a "blinded" Evaluating Physician is to be designated to assess the tolerability of the challenge doses presented in the DBPCFC. The Blinded Evaluating Physician (or Blinded Assessor) is not to be involved directly in the oversight of study product dosing (neither initial escalation, nor up-dosing, nor maintenance), nor the assessment or management of adverse events. To the extent practicable, the same Blinded Evaluating Physician who determines DLSs in the Screening DBPCFC should determine DLSs in the Exit DBPCFC. Initial Escalation (2 days): Eligible subjects will initiate OIT starting at a dose of 0.5 mg of peanut protein, 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 fail to tolerate at least a 3 mg dose will be considered escalation failures. Subjects who tolerate both the 3 mg and 6 mg doses of study product, or who tolerate the 3 mg, but not the 6 mg dose, will undergo confirmatory testing of the tolerability of a 3 mg dose the following day (refer to Initial Escalation Schedule at end of synopsis). Therapy details are found in **Section 3** and **Section 6** of the protocol. Up-dosing: Subjects will receive daily oral dosing of peanut or placebo OIT for about 5 months (20 weeks, if up-dosing proceeds without holding at, or reducing, a dose level; 40 weeks, maximum). All escalation doses (see escalation table below) will occur in a clinical research center (CRC) or other monitored setting (unless required by a specific institution, no distinction will be drawn between an investigational site, study center office, clinic, or CRC, provided the capability requirements for monitoring and emergency intervention are met by the facility). All up-dosing activities will be performed under direct observation. Therapy details are found in **Section 3** and **Section 6** of the protocol. Maintenance: Those subjects who reach the target maintenance dose of 300 mg/d of study product will enter an approximately 24-week Maintenance Period of continued dosing at 300 mg/d. Exit DBPCFC: Following completion of the ~24-week Maintenance Period, subjects will undergo an Exit DBPCFC (to a cumulative maximum of 2043 mg of peanut protein). Subjects who fail to tolerate the Exit DBPCFC at 300 mg (443 mg cumulative) of peanut protein will be discontinued from further study **(Section 3.3** for details).

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Title	**P**EANUT **AL**LERGY ORAL **I**MMUNOTHERAPY **S**TUDY OF **AR**101 FOR **DE**SENSITIZATION IN CHILDREN AND ADULTS (PALISADE)
Study Procedures	The following procedures will be performed according to the scheduled visits tabulated in **Appendix 1**: • Informed consent (and assent, as age appropriate) • Inclusion/exclusion criteria • Medical/allergy history • Concomitant medications • Physical examination, including height and weight • Vital signs (BP, PR, temperature) • Spirometry (FEV1) and/or Peak Expiratory Flow Rate (PEFR) • Pregnancy test • Diet history • Blood draw for peanut-specific IgE (including, at screening only, determination of Ara h 1, Ara h 2, Ara h 3, Ara h 8 and Ara h 9 IgE components) and IgG4 serum levels (immunoglobulin assays) • Complete blood cell count (CBC), obtained with the same venipuncture as the blood draw for the immunoglobulin assays • Additional blood samples for optional exploratory immune cell characterization by the Immune Tolerance Network (ITN). These can be obtained with the same venipuncture as the blood draw for the immunoglobulin assays (separate informed consent required). • Optional collection of saliva sample for exploratory biomarker development (separate informed consent required) • Optional post-DBPCFC blood draws for exploratory immune cell characterization by the ITN (separate informed consent required) • Skin prick test (SPT) • Clinical research center study product administration • Dispensing of study products for home dosing/Return of unused study products • Dose assessment to decide appropriateness of up-dosing or maintenance • Peak Expiratory Flow Rate (PEFR) prior to any DBPCFC • DBPCFC, performed in accordance with PRACTALL guidelines, but with the protocol-specified modifications • Quality of life assessment using the food allergy related quality of life questionnaire (FAQLQ), and the food allergy independent measure (FAIM) questionnaire • Monitoring for dosing compliance • Adverse event (AE) monitoring • Assessment of asthma control using the Asthma Control Test questionnaire in subjects with asthma • Assessment of treatment satisfaction using TSQM-9, exit questionnaires and palatability questions

Protocol ARC003 Synopsis		
Initial Escalation Period, Day-1, Dosing Schedule		
Day-1 Dose #	**Study Product Dose (mg peanut protein or placebo)**	**Cumulative Study Product Dose (mg peanut protein or placebo)**
1	0.5	0.5
2	1	1.5
3	1.5	3
4	3	6
5	6	12
Doses will be delivered at 20 to 30 minute intervals. Subjects who are unable to tolerate a dose of 3 mg at the end of Day -1 will be considered an initial day escalation failure. All subjects who tolerate a dose of at least 3 mg on Day -1 will return on Day -2 to receive a single confirmatory 3 mg dose under direct observation. Subjects with either no symptoms or mild, non-dose-limiting symptoms after receiving 3 mg on Day -2 are to start 2 weeks of daily dosing at 3 mg. Subjects who experience moderate or severe symptoms after receiving the 3 mg dose on Day -2 will be considered escalation failures. Future dose escalations will occur every 2 weeks with the initial dose increase administered in the clinical research center.		

Protocol ARC003 Synopsis			
Up-dosing Period Dosing Schedule			
Up-dosing Dose #	**Study Product Dose (mg peanut protein or placebo)**	**Interval (weeks)**	**% Increase**
1	3	2	
2	6	2	100%
3	12	2	100%
4	20	2	67%
5	40	2	100%
6	80	2	100%
7	120	2	50%
8	160	2	33%
9	200	2	25%
10	240	2	20%
11	300	24-Week Maintenance Period	25%
Capsules and sachets (introduced during the Maintenance Period) are opened, contents sprinkled over an age-appropriate food, and mixed thoroughly. 300 mg capsules will be used for at least the first 2 weeks of dosing during the 24-Week Maintenance Period.			

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Glossary of Abbreviations

Abbreviation	Definition
AC	Adjudication Committee
ACE	angiotensin-converting enzyme inhibitors
AE	adverse event
AESI	adverse event of special interest
Ag	Antigen
ANCOVA	analysis of covariance
ARB	angiotensin-receptor blockers
ARC	Allergen Research Corporation
BP	blood pressure
CBC	complete blood cell count
CFR	US Code of Federal Regulations
CI	confidence interval
CODIT	Characterized Oral Desensitization Immunotherapy
CoFAR	Consortium of Food Allergy Research
CPNA (AR101)	characterized peanut allergen
CRC	Clinical Research Center
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DBPCFCs	Double-Blind, Placebo-Controlled Food Challenges
DLS	dose-limiting symptom
DSMC	Data Safety Monitoring Committee
EAACI	European Academy of Allergy and Clinical Immunology
EC	Ethics Committee
EDC	electronic data capture
EGD	Esophagogastroduodenoscopy
ELISA	enzyme-linked immunosorbent assays
EoE	eosinophilic esophagitis
ER	emergency room
FAIM	Food Allergy Independent Measure
FAQLQ	food allergy related quality of life questionnaire
FDA	US Food and Drug Administration
FEV1	forced expiratory volume in 1 second
GCP / cGCP	Good Clinical Practice / Current Good Clinical Practice
GERD	gastroesophageal reflux disease
GI	Gastrointestinal
GLMM	generalized linear mixed model

Abbreviation	Definition
HIPAA	Health Insurance Portability and Accountability Act of 1996
HPLC	high-performance liquid chromatography
ICF	informed consent form
ICH	International Council for Harmonisation for Pharmaceuticals for Human Use
ICON	international consensus
ICS	inhaled corticosteroid(s)
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IM	Intramuscular
IND	Investigational New Drug Application
IP	investigational product
IRB	Institutional Review Board
ITN	Immune Tolerance Network
ITT	intent to treat
IV	Intravenous
kU_A/L	kilounits of antibody per liter
MedDRA	Medical Dictionary for Regulatory Activities
mg/d	milligrams per day
mITT	modified intent to treat
MMRM	mixed models repeated measures
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHLBI	National Heart, Lung, and Blood Institute
OFC	oral food challenge
OIT	oral immunotherapy
PCA	principal components analysis
PCR	polymerase chain reaction
PEESS	pediatric eosinophilic esophagitis symptom scores
PEFR	peak expiratory flow rate
PI	Principal Investigator
PP	per protocol
PR	pulse rate
PRACTALL	PRACTical issues in ALLergology Joint United States/European Union Initiative
REB	Research Ethics Board
RNA	ribonucleic acid

Abbreviation	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SLIT	sublingual immunotherapy
SPT	skin prick test
SUSAR	suspected unexpected serious adverse reaction
SVM	support vector machine
TEAE	treatment emergent adverse event
TSQM-9	Treatment Satisfaction Questionnaire for Medication
VAS	visual analogue scale
VITAL	Voluntary Incidental Trace Allergen Labeling
WHO	World Health Organization

1 BACKGROUND AND RATIONALE

1.1 Background

Peanut allergy is a common and serious condition that often affects children, and is commonly associated with severe reactions, including life-threatening anaphylaxis. Peanut and/or tree nut allergies account for the majority of fatal food-induced anaphylaxis (Sampson et al., 2005). Furthermore, published reports suggest that the prevalence of peanut allergy, like other food allergies, has been rising, and is now at high levels, affecting up to 10% of the population. (Branum & Lukacs, 2008; Sicherer et al., 2014). Peanut allergy, unlike many other types of food allergy, is usually life-long, with approximately 80% of patients remaining peanut-allergic in adulthood.

The current standard of care in management of food allergy is dietary avoidance of the allergenic food, and education of the patient/family in the acute management of an allergic reaction. Unfortunately, accidental ingestions remain common, with up to 50% of food-allergic patients having at least 1 allergic reaction over a 2-year period (Sicherer et al., 1998). Furthermore, strict adherence to an avoidance diet can be complicated due to difficulty in interpreting food labels (Joshi et al., 2002) and by the presence of undeclared or hidden allergens in commercially prepared foods (Altschul et al., 2001; Vierk et al., 2002). The burden of avoidance and constant fear of accidental exposure can negatively affect the health-related quality of life for both patients and their families (Primeau et al., 2000; Avery et al., 2003; Buchanan et al., 2007; Sicherer et al., 2010; Hofmann et al., 2009; Anagnostou et al., 2014).

Despite efforts at strict peanut avoidance, accidental exposure continues to be a major concern in peanut allergy because allergic responses can be triggered after ingestion of just milligram quantities of peanut protein. Accidental exposures may result from commercial food product mislabeling as well as inattention to, or mistrust of, food warning labels (Vierk et al., 2007). Foods prepared outside the home, including those encountered in schools, daycares, restaurants, or even the homes of friends and relatives present another ready source of accidental exposures. Oftentimes the origin of the accidental exposure remains unknown. The threat of accidental exposure and its consequences for patients with peanut allergy and their families continues to drive research in the field of food allergy.

While advances in understanding the causes of food allergy, strategies for food-allergy prevention, and the mechanisms underlying tolerance continue to be made, a cure for food allergy remains elusive. In the meantime, therapies with the potential to reduce the risk of severe allergic reaction in the event of an accidental exposure to an allergenic food continue to be developed. An approach that has shown consistently promising results is allergen-specific immunotherapy, a therapy that entails administration of increasing amounts of an allergen to individuals with IgE-mediated food allergy to raise the threshold and decrease the severity of allergic responses to the allergenic food. These allergen-based immunotherapies include sublingual, epicutaneous, and most advanced among these, oral immunotherapy (OIT).

Oral immunotherapy for peanut allergy has been widely studied in recent years and has demonstrated encouraging safety and efficacy results in early clinical trials. Additionally, beneficial immunologic changes have been shown to occur over time that would tend to indicate progression toward a clinical state of sustained desensitization with continued OIT

(Oppenheimer et al., 1992; Secrist et al., 1995; Nelson et al., 1997; Kapsenberg et al., 1999; Lehrer et al., 1999; Frew et al 2003; Bousquet et al., 2004; Wilson et al., 2005; Skripak et al., 2008; Jones et al., 2009; Narisety et al., 2009; Blumchen et al., 2010; Kim et al., 2011; Varshney et al., 2011).

The goal of Aimmune Therapeutics' characterized oral desensitization immunotherapy (CODIT™) program for peanut allergy is to induce a state of clinically meaningful desensitization to peanut protein, where clinically meaningful desensitization is defined as the absence of moderate or severe allergic reaction following ingestion of small, but potentially dangerous, amounts of peanut protein. In practical terms, this state of desensitization should be sufficient to protect a patient with peanut allergy in case of an accidental exposure to peanut while the patient is attempting to maintain a peanut- avoidant diet.

It is unfortunately inherent in the nature of accidental exposures that the level of exposure is typically unknown. Nevertheless, it is generally believed that most clinically relevant accidental exposures to peanut protein occur at low levels. In 1 well documented case of accidental peanut ingestion, the amount ingested was calculated to be approximately 45 mg (McKenna & Klontz, 1997). Moreover, work by French researchers that considered the peanut content of a variety of foods and the typical amounts of these foods consumed in a serving, showed that accidental exposures from peanut-contaminated or mislabeled foods are likely to occur at levels below 15 mg of peanut protein (Rimbaud et al., 2013). While across the peanut-allergic population the threshold levels at which allergic reactions are triggered varies widely, approximately 25% of peanut-allergic individuals would be expected to react to 15 mg of peanut protein and 5% to as little as 0.5-1.5 mg, based on a cross-study retrospective analysis performed by the Voluntary Incidental Trace Allergen Labeling (VITAL) 2.0 study group (Remington 2013; Allen et al., 2014). Moreover, fully half of the peanut allergic population would be expected to have an allergic reaction to no more than 100-150 mg of peanut protein. Accordingly, protection to the equivalent of 1 whole peanut kernel, containing approximately 250 to 300 mg of peanut protein, should afford a clinically meaningful level of protection against many accidental exposures to peanut.

In its Phase 2 study, ARC001, Aimmune Therapeutics showed that a clinically meaningful level of protection, defined as the ability to consume a maximum single dose of 300 mg and a cumulative dose of 443 mg in a double-blind, placebo-controlled food challenge (DBPCFC), an ethically acceptable model for accidental exposure, was achievable with daily dosing of AR101, a highly characterized, pharmaceutical grade formulation of defatted peanut flour, when administered in a controlled OIT regimen. As presented in greater detail below, 79% of subjects who embarked on the OIT regimen in ARC001 were able to achieve the target dose of 300 mg/d, after completing an up-dosing period that lasted, on average, approximately 20 weeks. Following just an additional 2 weeks of maintenance therapy at 300 mg/d, all subjects (ie, 23 of the 29 originally randomized to active treatment) were able to tolerate at least 443 mg cumulative of peanut protein with no more than mild symptoms in a DBPCFC.

It is, however, well known from clinical experience, and documented in clinical trials, that a peanut-allergic patient's threshold sensitivity to peanut can vary day to day by as much as two orders of magnitude (Glaumann et al., 2013). Also, accidental exposures of up to 1000 mg can occur from taking a single, inadvertent, bite of a peanut-dense food, such as a peanut candy or a

peanut butter sandwich. Hence, in the current Phase 3 study, Aimmune has chosen to test if a significantly greater proportion of subjects undergoing OIT to a maintenance dose of 300 mg/d of peanut protein as AR101, as compared to placebo, will be able to tolerate at least 1043 mg cumulative of peanut protein with no more than mild symptoms in a DBPCFC after completing approximately 12 months of treatment.

1.2 Peanut OIT

1.2.1 Published Literature on OIT Studies

A number of clinical trials of OIT for peanut allergy have been completed and their results published, including 4 open-label studies (Jones et al., 2009; Hofmann et al., 2009; Blumchen et al., 2010; Yu et al., 2012), a randomized, double-blind, placebo-controlled study (Varshney et al., 2011), and a randomized, contemporaneous natural history-controlled study (Anagnostou et al., 2014). All have shown peanut OIT to induce a clinically meaningful level of desensitization and to be overall safe and well-tolerated when performed in a supervised medical setting by trained personnel. All of the studies tested for desensitization by oral food challenge (OFC) after subjects had gone through a period of up-dosing with increasing amounts of peanut protein followed by a period of maintenance therapy. The two randomized controlled studies are discussed in greater detail below.

- **Varshney et al., 2011** used peanut flour as the desensitizing agent in the first multicenter, double-blinded, randomized, placebo-controlled study of OIT as a treatment for peanut allergy. The peanut flour used in their trial came from the same manufacturer that supplies the starting material for AR101 to Aimmune. They enrolled 28 subjects aged 1 to 16 years. After completing up-dosing to 4000 mg (a much higher level than is proposed in the AR101 trial) over a 44-week period, subjects were maintained at that dose for 1 month and then returned at week 48 for a DBPCFC. Three peanut OIT subjects withdrew early in the study because of allergic side effects. In the DBPCFC all remaining peanut OIT subjects (n = 16) ingested the maximum cumulative dose of 5000 mg of peanut protein (approximately 20 peanuts), whereas placebo patients (n = 9) could tolerate only a median cumulative dose of 280 mg (range, 0-1900 mg; $p < 0.001$). In contrast with the placebo group, the peanut OIT group showed reductions in skin prick test wheal size ($p < 0.001$) and increases in peanut-specific IgG4 ($p < 0.001$). Peanut OIT subjects had initial increases in peanut-specific IgE ($p < 0.01$), but this had returned to baseline by the time of oral food challenge.
- **Anagnostou et al., 2014 (STOP II trial)**: This single center randomized controlled crossover trial in 99 children aged between 7 and 16 years conducted in the UK used peanut flour as the desensitizing agent that, like the Varshney et al., 2011 study, came from the same manufacturer that supplies the starting material for AR101. The primary outcome was desensitization, defined as a negative peanut challenge to 1400 mg cumulative of peanut protein in a DBPCFC, after a total of 6 months of OIT and a maintenance dose of 800 mg/d of peanut protein. Daily dosing with 800 mg of peanut protein was tolerated by 84% of the children. Desensitization, was reported for 62% of the children in the active arm and 0% of children in the control arm. Also, quality-of-life scores improved (decreased) after OIT (median change –1·61; $p < 0.001$) relative to baseline in within-group comparisons. While this trial used a different dosage regimen

than is planned for use with AR101, it provides supportive evidence for the efficacy of a peanut flour-based product in OIT for desensitizing children with peanut allergy.

The results of these controlled studies are consistent with the results from open-label studies (Hofmann et al., 2009; Jones et al., 2009; Blumchen et al., 2010; Yu et al., 2012). Dosing symptoms typically associated with OIT across the various protocols have included rash, wheezing, rhinorrhea, sneezing, itching, abdominal pain, nausea, vomiting, and diarrhea. The vast majority of symptoms have been mild and consistent with stimulation of a transient, low-grade allergic reaction; and across the trials a trend for symptoms to diminish with increasing duration of treatment has been evident. Peanut OIT has consistently been assessed to be overall safe and well tolerated in the clinical trial setting, but the authors of even recent review articles on the subject conclude that additional work needs to be conducted before OIT for peanut allergy is ready for widespread adoption in clinical practice (eg, Campbell 2014; Trendelenburg et al., 2014; Nurmatov et al., 2014; Le & Burks, 2014).

The previously published clinical trial findings from peanut-allergic patients ranging in age from 1 to 65 years old, provided the basis for the Phase 2 trial, ARC001, conducted by Aimmune Therapeutics, to investigate the efficacy and safety of AR101 in desensitizing peanut-allergic subjects.

1.2.2 Clinical Trials Sponsored by Aimmune

1.2.2.1 Results of ARC001, A Phase 2 Study

Study design: ARC001 was a multicenter, randomized, double-blind placebo-controlled study of efficacy and safety of AR101 (characterized peanut allergen) OIT in peanut-allergic children and adults (4 to 21 years of age). ARC001 had a Data Safety Monitoring Committee (DSMC) to monitor the study for safety. The study consisted of a screening period, an initial escalation period, a double-blind OIT treatment (up-dosing and maintenance) period, followed by a double-blind, placebo controlled food challenge (DBPCFC).

Screening/baseline: All eligible subjects underwent a DBPCFC of up to 100 mg (143 mg cumulative) of peanut protein or placebo during the screening portion of the study. The Screening DBPCFC was an abbreviated version of the DBPCFC described in the PRACTALL guidelines using up to 100 mg (143 mg cumulative) of peanut protein or placebo. Additionally, the DBPCFC progressed through the dose levels in an unaltered sequence without repeating any dose. Those subjects who had dose-limiting symptoms at or before the 100 mg (143 mg cumulative) challenge dose of peanut protein (measured as 200 mg of peanut flour) were randomized 1:1 to AR101 or placebo.

Up-dosing OIT treatment: Subjects received daily oral dosing of AR101 or placebo OIT for about 6 to 9 months. All escalation doses occurred in a clinical research center or other monitored setting. All up-dosing was performed under direct observation.

Exit DBPCFC: After the subjects had been up-dosed to a 300 mg/d dose and had continued to receive that dose for 2 weeks, subjects underwent a DBPCFC of up to 600 mg (1043 mg cumulative) of peanut protein or placebo.

All placebo subjects who completed ARC001 were eligible for rollover into the ARC002 protocol. Placebo subjects in ARC002 underwent an escalation schedule identical to that for AR101 subjects in the ARC001 protocol. All subjects on AR101 who passed the DBPCFC by tolerating ≥ 443 mg cumulative of peanut protein with no more than mild symptoms were eligible to proceed to ARC002. Those who did not pass were considered endpoint failures.

Efficacy Results:

In ARC001, 56 subjects were randomized: 29 subjects to AR101 and 27 subjects to placebo. Consent for 1 subject was withdrawn after the subject was randomized, but before the first dose of study treatment was administered. The intent-to-treat (ITT) population, thus, comprised 55 subjects in total, 29 in the AR101 and 26 in the placebo arm. The 2 study groups were overall well matched for baseline characteristics including baseline sensitivity in the Screening DBPCFC. Six subjects in the AR101 arm withdrew from the study prior to the Exit DBPCFC.

For the primary efficacy analysis conducted in the ITT Population, AR101 was shown to be statistically significantly superior to placebo, with 23 of 29 (79%) AR101 desensitization responders as compared to 5 of 26 (19%) placebo desensitization responders, resulting in a treatment difference of 60% ($p < 0.0001$ by Fisher's exact test).

At the time of the Exit DBPCFC, 100% of the 23 AR101 subjects undergoing the DBPCFC (Completer Population) tolerated 300 mg as compared to, 5 of the 26 (19%) placebo study completers, resulting in a treatment difference of 81% ($p < 0.0001$ by Fisher's exact test).

It was also found at Exit DBPCFC that 18 of 29 (62%) AR101 subjects in the ITT Population tolerated 600 mg while none of placebo subjects tolerated 600 mg, resulting in a treatment difference of 62%. Post-hoc analysis by Fisher's exact test yielded statistical significance at the $p < 0.0001$ level. In the Completer Population, 18 of 23 (78%) AR101-treated subjects and no placebo subjects tolerated 600 mg at Exit DBPCFC.

For the key secondary endpoint of the maximum dose achieved with no or mild symptoms at the Exit DBPCFC, analyzed using a discrete hazard model, AR101 treatment was shown to increase the probability of tolerating higher maximum doses with no or mild symptoms as compared with placebo treatment. The adjusted probability of tolerating 300 mg was 0.82 for AR101 and 0.14 for placebo; the adjusted probability of tolerating 600 mg was 0.59 for AR101 and 0.01 for placebo. Overall, the treatment effect hazard ratio (95% CI) was determined to be 0.10 (0.04, 0.25) ($p < 0.0001$), indicating that the risk of failing the Exit DBPCFC in AR101 subjects was one-tenth the risk as compared to placebo subjects.

The percentage of subjects with a maximum symptom severity grade of moderate or severe/worse was lower in the AR101-treated group than in the placebo-treated group at every peanut protein level during the Exit DBPCFC. For AR101 subjects, no subject experienced a severe/worse symptom during Exit DBPCFC, and moderate symptoms were not encountered until a dose of 600 mg. In contrast, at the time of the Exit DBPCFC, at least 1 placebo subject experienced moderate or severe/worse symptoms at each evaluated dose.

For the key secondary endpoint of change from baseline in maximum tolerated dose of peanut protein at Exit DBPCFC analyzed in an analysis of covariance (ANCOVA) model, a treatment

difference of 0.912 $\log_{10}$ mg ($p < 0.0001$) was observed with a change from baseline in tolerated dose of 1.254 $\log_{10}$ mg for AR101 and 0.341 $\log_{10}$ mg for placebo. In terms of the ratio of maximum tolerated dose (MTD) of peanut protein at the Exit DBPCFC compared to Baseline, AR101 subjects were able to tolerate 17.94 times as much peanut protein at the Exit DBPCFC compared to Baseline, while placebo subjects were able to tolerate 2.19 times as much peanut protein at the Exit DBPCFC compared to Baseline.

For the secondary endpoints of changes in peanut-specific IgE and peanut-specific IgG4 levels and related measures, the relative treatment effect was calculated as a ratio of two ratios (study exit result : baseline result in the AR101 group / study exit result : baseline result in the Placebo group) The largest relative treatment effect, 4.756, was noted for peanut-specific IgG4, reflecting study exit values that were 5-times baseline in the AR101 group compared to levels that were nearly unchanged in the Placebo group. The 95% CI around this relative treatment effect (3.271, 6.915) excluded the null value of 1.

For the secondary endpoint of changes in skin prick test (SPT) results, the difference between treatments was calculated as the change from baseline to study exit in the AR101 group minus the change from baseline to study exit in the Placebo group. At exit visit, a notable difference in the change from baseline in maximum peanut SPT wheal diameter was observed between treatment groups, with a treatment difference of -5.2 mm. The 95% CI for this treatment difference (-9.2, -1.1) excluded the null value of 0.

Safety Results:

AR101 was generally well-tolerated. The overall incidence of treatment-emergent AEs (TEAEs) was 97% for the AR101 treatment group and 85% for the placebo group. One subject (3%) in the AR101 group experienced a treatment-emergent SAE of anaphylactic reaction related to treatment. And 1 subject (4%) in the placebo group experienced an SAE of anaphylaxis related to the peanut protein in the Exit DBPCFC, not study product. An additional subject experienced a non-treatment-emergent SAE of anaphylactic reaction following the Screening DBPCFC. Four (14%) AR101 subjects discontinued due to adverse events, with either hypersensitivity (n = 3) or vomiting (n = 1) being the most common adverse events leading to discontinuation. Two additional AR101 subjects discontinued due to treatment-related reasons that included GI AEs, but not exclusively. No placebo subjects discontinued due to adverse events. The most commonly occurring TEAE was hypersensitivity, which was reported in 71% of study subjects. The next most commonly reported TEAEs were pyrexia (16%), upper respiratory tract infection (13%), headache (11%), and vomiting (11%).

Treatment-emergent adverse events classified as an allergic reaction by the investigator occurred in 71% of subjects. For these treatment-emergent hypersensitivity events, MedDRA coding indicated that the most common preferred terms were vomiting (16%) and abdominal pain (15%). Treatment-emergent hypersensitivity adverse events were more common in AR101 subjects than in placebo subjects (90% vs. 50%, respectively), however these events tended to be mild or moderate in severity and did not typically lead to study withdrawal.

No treatment-specific differences in vital signs were observed. Most physical examination findings were normal at baseline and no treatment-specific differences in post-baseline abnormal findings were noted.

In summary, AR101 was safe, generally well-tolerated, and statistically superior to placebo for reducing clinical reactivity to peanut allergen in peanut-allergic children and adolescents to young adults. AR101 treatment significantly increased the probability of tolerating peanut allergen doses ≥ 300 mg and resulted in favorable changes in clinical markers of peanut allergen immunoreactivity, most notably peanut-specific IgG4 levels, as compared to placebo.

1.2.2.2 ARC003, A Phase 3 Study with AR101

Protocol ARC003 is designed to be a double-blinded, placebo-controlled study to confirm the efficacy and safety of AR101 as an oral immunotherapy for desensitizing children and adults with peanut allergy.

1.2.2.3 ARC004, A Phase 3 Follow-on Study with AR101

Protocol ARC004, an open-label follow-on study from ARC003, will be performed as a separate protocol. The study is intended to demonstrate the safety of daily dosing with AR101 for an extended period (months to years), with the following objectives:

- To expand, in unblinded fashion, the safety database for AR101;
- To confirm, unblinded, the efficacy of OIT with AR101 up-dosed to a maintenance dose of 300 mg/d of peanut protein in the former ARC003 placebo population;
- To provide an opportunity to the ARC003 trial participants to maintain the level of desensitization they may have achieved.

1.3 Rationale for Selection of Study Population

The study will enroll approximately 500 subjects from 4 to 55 years of age with a history of allergy to peanuts or peanut-containing foods. The sample size has been selected in consideration of the need to demonstrate robust efficacy and acquire a sufficiently large safety database to be representative of the peanut-allergic population balanced against the risks associated with repeated DBPCFC (**Section 9.4**).

All subjects enrolled must undergo a Screening DBPCFC to peanut that must be positive at or before the 100 mg (144 mg cumulative) dosing level of peanut protein (measured as 200 mg of peanut flour with approximately 50% protein content) in accordance with PRACTALL (Practical Issues in Allergology, Joint United States/European Union Initiative) consensus guidelines (Sampson et al., 2012), regardless of how they were initially diagnosed as peanut allergic. This should select for roughly the more sensitive half of the peanut-allergic population (Remington 2013; Allen et al., 2014), according to a logistical regression analysis performed by the VITAL 2.0 study group using food challenge data from multiple sources.

The current Phase 3 study will focus on the age group most at risk from accidental exposure, ie, ages 4 to 17 years, while allowing for older subjects who are motivated to seek desensitization to be included. It is intended that fully 80% of the study population (ie, 400 subjects) will be

pediatric, with at least 200 subjects randomized from the 4 to 11 years of age range and 150 subjects randomized from the 12 to 17 years of age range.

The lower age limit of 4 years was selected based on epidemiologic child-developmental considerations related to feeding behavior (Fallon et al., 1984; Cashdan 1994; Farrow & Blisset, 2012; American Academy of Pediatrics 2013), as well as practical clinical trial execution considerations and safety. Very young children, for example, have limited ability to reliably follow a study protocol.

As only about 20% of children with peanut allergy outgrow the condition, it is important to collect safety and efficacy data in adults. The upper age limit of 55 years was selected to reduce the chance of enrolling subjects with clinically significant heart disease (Mozaffarian et al., 2015) who could be at increased risk from the use of epinephrine if needed to treat anaphylaxis. This is particularly relevant in the clinical trial setting, where the risk of iatrogenic anaphylaxis is increased due to the requirement for repeated DBPCFC.

In the current study, subjects with severe or life-threatening episodes of anaphylaxis or anaphylactic shock will be excluded from enrolling if they have had such an episode in the 60 days prior to the Screening DBPCFC, but will not otherwise be prohibited from entering the study. This is because peanut-allergic subjects who have had prior life-threatening episodes on exposure to peanut can be considered at high risk for another such episode, and hence, are exactly the type of patients who could benefit from desensitization therapy.

1.4 Rationale for Selection of Study Drug Regimen (Dose and Duration)

For the Phase 3 study, ARC003, the dosing regimen to be used is predicated on the dosing regimen successfully used in the Phase 2 study, ARC001. The ARC001 dosing regimen, in turn was built on the work of the Consortium of Food Allergy Research (CoFAR) and its investigators. The basic structure of the dosing regimen consists of a single-day initial escalation at very low doses, followed by a buildup phase of dose escalations, with a single escalation occurring every 2 weeks, and then an extended maintenance phase at a fixed daily dose. This dosing regimen has been demonstrated to be well tolerated and efficacious in previous studies (Burks et al., 2012) and was shown to be similarly well tolerated and efficacious in the Phase 2 study, ARC001, conducted by Aimmune.

The total duration of treatment in the current Phase 3 study will be approximately 12 months (~6 months escalation and 6 months maintenance at 300 mg/d). Aimmune recognizes that any number of up-dosing regimens may be effective in escalating peanut-allergic patients to a daily maintenance dose of peanut protein, and the 1 chosen for the current Phase 3 study was selected empirically based on its success in Phase 2.

With respect to the duration of maintenance therapy prior to testing for clinical efficacy by DBPCFC in the current Phase 3 study, this too was selected empirically based on successful Phase 2 results. The clinical trials published to date for peanut OIT have had maintenance periods ranging from 1 to 7 months, and have demonstrated the ability to allow subjects to tolerate challenge doses ranging from 1.25 to 16.7 times their maintenance dose (Clark et al., 2009; Jones et al., 2009; Blumchen et al., 2010; Varshney et al., 2011; Anagnostou et al., 2014; Cronin, Wisniewski & Commins, 2014; Vickery et al., 2015). The data from Aimmune's Phase 2

studies indicate that a clinically meaningful level of desensitization is achieved after up-dosing and just 2 weeks of maintenance dosing at 300 mg (with > 95% passing DBPCFC at a cumulative challenge dose of 443 mg of peanut protein and the majority passing at a 1043 mg cumulative challenge) and that extending maintenance dosing from 2 to 14 weeks appears to be associated with only a modest improvement in the overall degree of desensitization. Accordingly, a blinded maintenance period of 6 months is considered sufficient to demonstrate efficacy and assess safety in the Phase 3 study. The ability to convey to patients that they are at a therapeutic level of desensitization in a reasonable timeframe is an important consideration. Thus, the duration of blinded placebo therapy is limited to 12 months in this study.

The data from Aimmune's Phase 2 trials, consistent with previously published studies, indicate that the use of a low dose maintenance phase can provide a clinically meaningful level of desensitization that is considerably higher than the daily maintenance dose. Three studies in particular (Jones et al., 2009; Cronin, Wisniewski, & Commins, 2014; Vickery et al., 2015) have specifically reported that daily dosing with 300 mg of peanut protein will allow quantities of peanut protein ranging from 2.1 to 5 grams to be tolerated in an oral food challenge.

1.5 Rationale for the Doses Used for the DBPCFC

The study DBPCFCs will be conducted in accordance with the recommended PRACTALL guidelines although the Screening DBPCFC will not exceed 100 mg (144 mg cumulative). This is to select subjects representative of approximately the more sensitive half of the peanut-allergic population **(Section 1.3)**. The Exit DBPCFC will not go above a 1000 mg (2043 mg cumulative) dose to help ensure subject safety. Additionally, the DBPCFCs will progress through the dose levels in an unaltered sequence without repeating any dose to provide standardization of the amounts of peanut protein subjects are exposed to when being tested in the clinical trial setting.

The Exit DBPCFC will assess protection against approximately 2-4 peanuts' worth of peanut protein at 600 mg (1043 mg cumulative) dose. To assess further desensitization, patients tolerating the 600 mg (1043 mg cumulative) incremental dose will also be challenged with 1000 mg (2043 mg cumulative), or approximately 4-8 peanut's worth of peanut protein. Additionally, since accidental exposures typically occur to limited amounts of allergen, the ability to tolerate 300 mg (443 mg cumulative) of peanut protein will be assessed as a key secondary endpoint. As discussed in **Section 1.1**, all of these challenge dose levels are believed to represent amounts of peanut protein in excess of what might typically be encountered in an accidental ingestion of peanut.

1.6 Known and Potential Risks and Benefits to Human Participants

1.6.1 Risks

Peanut is a commonly-consumed food and as such has a well understood safety profile. Except for allergic reactions in subjects with peanut allergy, it does not cause discernible side effects in humans.

As noted earlier (**Section 1.1**), there have been several oral immunotherapy studies performed in subjects with peanut allergy using procedures and dosing regimens similar to those used in our Phase 2 studies (ARC001 and ARC002) and proposed for the current Phase 3 study. In general, the safety profile from the completed Phase 2 study, ARC001, was similar to the safety profiles

reported from previous peanut OIT studies. At the start of the ARC001 study it was anticipated that approximately 80%, 15%, and < 1% of the subjects would have at least 1 mild, moderate, or severe symptom, respectively, at some point during the course of peanut immunotherapy. At the close of ARC001, the actual percentages of subjects treated with AR101 who had experienced a least 1 mild, moderate, or severe symptom, were 69%, 28%, and 0%, respectively. It is important to note that the vast majority of adverse events reported from our Phase 2 studies or in the literature have been allergy-related, predictable, and reversible. Specifically, the buildup and daily maintenance doses of peanut OIT may cause allergic symptoms including sneezing, rhinorrhea, urticaria, angioedema, flushing, flares of eczema, ocular, nasal, oral and/or throat pruritus, nausea, vomiting, abdominal discomfort, cough, wheezing, and/or shortness of breath, in addition to severe anaphylaxis. The likelihood of a subject experiencing any allergic symptoms is expected to be lessened by initiating dosing at extremely small amounts of AR101 and by buildup of dosing under observation in a clinical setting until the maintenance dose is achieved.

The major adverse event of concern from peanut OIT, other than anaphylaxis, that has been reported in the literature is eosinophilic esophagitis (EoE), reversible upon stopping dosing. In the ARC001 study, 6 (20%) of the AR101-treated subjects discontinued dosing prematurely for treatment-related reasons associated with GI AEs. One of these subjects subsequently underwent endoscopy and was found to have biopsy-proven EoE.

There is a strong association between IgE-mediated food allergy and EoE (Noel 2004; Spergel 2012; Greenhawt 2014). Consequently, patients with IgE-mediated food allergy who encounter the food to which they are allergic, such as must occur during OIT, are at increased risk for manifesting EoE. As of 2014, at least 20 cases of EoE emerging during the course of OIT for food allergy have been reported (Lucendo et al., 2014). At present, it remains unclear whether in such cases OIT induces EoE or causes pre-existing subclinical EoE to become symptomatic. When EoE occurs spontaneously, the current standard of care treatment generally entails removing known or suspected food allergens from the diet. When EoE occurs in the setting of OIT, treatment should similarly entail removal of the desensitizing (ie, allergenic) agent. As the diagnosis of EoE requires endoscopic biopsy, the true incidence of EoE related to OIT is difficult to know, because withdrawal of the offending allergen is typically associated with symptomatic recovery, which in turn tends to obviate the need to perform an invasive procedure. Given the association between IgE-mediated food allergy and EoE, a high index of suspicion for EoE or an EoE-like process should be maintained whenever chronic recurrent GI symptoms occur during OIT.

Oral food challenges are expected to induce an allergic response in food-allergic individuals. Allergic reactions can be severe, including life-threatening allergic reactions; however, the risk of an allergic reaction is reduced by initiating the challenge with a very small amount of the food, gradually increasing the dose, and stopping the challenge at the first definitive sign of a significant reaction. If subjects have an allergic reaction during the challenges, they may need oral, intramuscular, or intravenous medications, and will be treated per study center standard of care. Trained personnel, including a physician, as well as medications and equipment (per PRACTALL recommendations and investigational site standard operating procedures), will be immediately available to treat any reaction. With these precautions, the rate of severe,

life-threatening, serious adverse events of anaphylaxis due to OIT is anticipated to be < 0.5% over the course of the ARC003 study.

There may be a risk that during participation in the trial the subjects may decrease their vigilance against accidental peanut ingestion because they believe they are protected from it. This phenomenon has been reported in previous trials. Subjects in the trial and their participating family will be warned that they should continue to practice their usual vigilance against accidental ingestion of peanuts or peanut-containing foods.

1.6.2 Benefits

There is no guarantee that participation in this study will help the subject. The subject may receive placebo during the double-blind treatment period of the study. Information from this study may help researchers to better understand peanut allergy or to develop future tests or treatments to help patients with this condition.

2 OBJECTIVES

2.1 Primary Objective

The primary objective is to demonstrate the efficacy of AR101, a pharmaceutical-grade peanut allergen formulation, through reduction in clinical reactivity to limited amounts of peanut allergen in peanut-allergic children (ages 4-17 years, inclusive).

2.2 Secondary Objective(s)

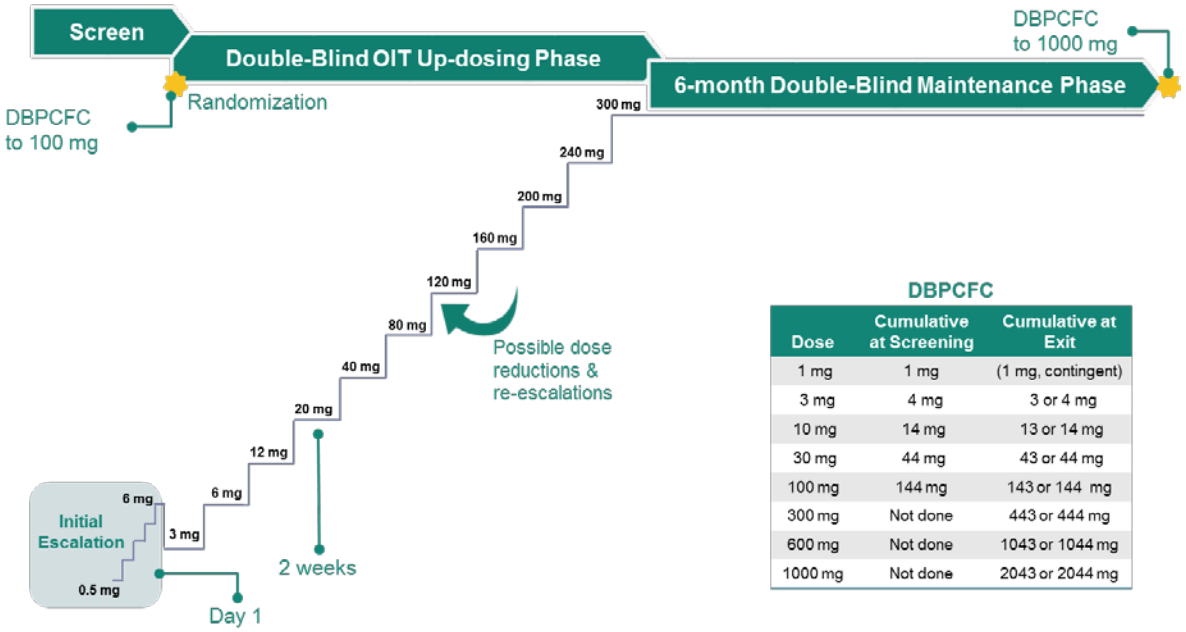
The secondary objectives are:

- To demonstrate the safety of AR101 as measured by the incidence of adverse events, including serious adverse events in children (ages 4-17 years, inclusive).
- To evaluate the immunological effects of peanut OIT therapy in children (ages 4-17 years, inclusive).

3 STUDY DESIGN

ARC003 is a multi-center, randomized, double-blind placebo-controlled study. The study design is illustrated in **Figure 3-1**.

Figure 3–1. Study Design



DBPCFC

Dose	Cumulative at Screening	Cumulative at Exit
1 mg	1 mg	(1 mg, contingent)
3 mg	4 mg	3 or 4 mg
10 mg	14 mg	13 or 14 mg
30 mg	44 mg	43 or 44 mg
100 mg	144 mg	143 or 144 mg
300 mg	Not done	443 or 444 mg
600 mg	Not done	1043 or 1044 mg
1000 mg	Not done	2043 or 2044 mg

3.1 Screening Period

Subjects aged 4 to 55 years must have a clinical history of peanut allergy, a serum IgE to peanut of ≥ 0.35 kU_A/L and/or a skin prick test (SPT) to peanut of ≥ 3 mm versus control at the time of screening. All eligible subjects will undergo an initial DBPCFC at the end of the screening period (refer to **Section 6.6.1**). This DBPCFC will include both a peanut challenge (defatted peanut flour) and a placebo challenge (artificially peanut-flavored oat flour) on separate days. The Screening DBPCFC will be an abbreviated version of the DBPCFC described in the PRACTALL guidelines, with top challenge doses of 100 mg (144 mg cumulative) of peanut protein and placebo.

For each subject, a "blinded" Evaluating Physician (Blinded Assessor) is to be designated to assess the tolerability of the challenge doses presented in the DBPCFC. The Blinded Evaluating Physician is not to be involved directly in the oversight of study product dosing (neither initial escalation, nor up-dosing, nor maintenance), nor the assessment or management of adverse events. To the extent practicable, the same Blinded Evaluating Physician who determines DLSs in the Screening DBPCFC should determine DLSs in the Exit DBPCFC.

Those subjects who have dose-limiting symptoms at or before the 100 mg (144 mg cumulative) challenge dose of peanut protein (measured as 200 mg of peanut flour) will be enrolled into the study. According to a logistical regression analysis performed by the VITAL 2.0 study group using food challenge data from multiple sources, this would select for roughly the more sensitive half of the peanut-allergic population (Remington, 2013; Allen et al., 2014). Those who successfully consume a 100 mg dose of peanut protein during the Screening DBPCFC, ie, without manifesting dose-limiting symptoms, will be considered screen failures and will not be randomized.

Any subject who is assessed to have had dose-limiting symptoms to the placebo part, or both parts, of the Screening DBPCFC (ie, to oat flour as well as peanut flour) will be considered a screen failure and will not be randomized.

Approximately 500 subjects who pass screening will be randomized 3:1 to either AR101 (active treatment) or placebo using a proprietary password-protected interactive response system. At least 80% of the subjects randomized will be children.

3.2 Treatment Phase

The Treatment Phase comprises 3 periods:

- **Initial Escalation Period** – 2 days in duration;
- **Up-dosing Period** (also referred to as the Buildup Period) – This is defined as the time from the subject's first home dose of study product at 3 mg to the subject's first in-clinic dose at 300 mg, ideally 20 weeks in duration, but may be extended to a maximum of 40 weeks to accommodate dose reductions and re-escalations, if necessary;
- **Maintenance Period** – The Maintenance Period starts with the first home dose of 300 mg. Ideally, it will be 24 weeks in duration, but it may be extended by up to an additional 4 weeks (for a maximum Maintenance Period duration of 28 weeks), or to a total Treatment Phase duration of 68 weeks, whichever occurs first, to accommodate dose reductions and re-escalations that may occur during the final weeks of the Maintenance Period.

The Treatment Phase starts with an initial escalation at the study center, followed by up-dosing for approximately 20 weeks, and then approximately 24 weeks of maintenance dosing at 300 mg/d. Treatment will be conducted in a double-blind fashion. The study products (AR101 or placebo) will be coded according to subject randomization number. The subjects and the investigational site personnel will be blinded to treatment assignment.

After the initial escalation period (comprising dose-escalation to a maximum of 6 mg on Day-1 and confirmation of the tolerability of a single 3 mg dose on Day-2), subjects will report to the study center every 2 weeks to escalate their OIT dose to an expected daily dose of 300 mg of peanut protein. This constitutes the Up-dosing Period. The dose-escalation schedule is described in detail in **Table 3-1** and **Table 3-2**.

Table 3-1. Initial Dosing Schedule for Peanut OIT

Initial Escalation Period, Day-1, Dosing Schedule		
Dose #	**Study Product Dose (mg peanut protein or**	**Cumulative Study Product Dose (mg peanut protein or placebo)**
1	0.5	0.5
2	1	1.5
3	1.5	3
4	3	6
5	6	12

Doses will be delivered at 20 to 30 minute intervals.

Subjects who are unable to tolerate a dose of 3 mg at the end of Day-1 will be considered an initial day escalation failure.

All subjects who tolerate a dose of at least 3 mg on Day-1 will return on Day-2 to receive a single confirmatory 3 mg dose under direct observation.

Subjects with either no symptoms or mild, non-dose-limiting symptoms after receiving 3 mg on Day-2 may start 2 weeks of daily dosing at 3 mg.

Subjects who experience moderate or severe symptoms after receiving the 3 mg dose on Day-2 will be considered escalation failures.

Future dose escalations will occur every 2 weeks with the initial dose increase administered in the clinical research center.

Table 3-2. Up-dosing Dosing Schedule for Peanut OIT

Up-dosing Period Dosing Schedule			
Up-dosing Dose #	**Study Product Dose (mg peanut protein or placebo)**	**Interval (weeks)**	**% Increase**
1	3	2	
2	6	2	100%
3	12	2	100%
4	20	2	67%
5	40	2	100%
6	80	2	100%
7	120	2	50%
8	160	2	33%
9	200	2	25%
10	240	2	20%
11	300	Enter Maintenance Period	25%

Capsules and sachets (introduced during the Maintenance Period) are to be opened, contents sprinkled over an age-appropriate food, and mixed thoroughly. 300 mg capsules will be used for at least the first 2 weeks of dosing during the 24-Week Maintenance Period.

All subjects who reach and tolerate 300 mg/d will continue at that dose level for the duration of the Maintenance Period. The first Maintenance visit occurs 2 weeks after the last Up-Dosing visit, with visits every 4 weeks thereafter. Any subject unable to achieve a dose of 300 mg/d of peanut protein by 40 weeks will be considered an escalation failure nonresponder and will not undergo Exit DBPCFC.

During the treatment period, the subjects will be monitored for the tolerability of study product, as described in **Section 6.7.2** and **Section 6.7.3**, and illustrated in **Figure 6-1** and **Figure 6-2** (**Section 6.7.5.2**).

If a subject discontinues therapy prematurely for any reason, the subject will be followed for safety and asked to return to the CRC 14 days following his or her last dose of study product to undergo an Early Discontinuation Visit (**Section 6.5**). In the event of ongoing AEs, subjects who have discontinued therapy should continue to be followed beyond the Early Discontinuation Visit until such time as the AE has resolved or is assessed to have reached a chronic stable state (a determination that may not be made sooner than 30 days after the Early Discontinuation Visit).

A Data Safety Monitoring Committee (DSMC) will be established and will meet approximately every 3 months to monitor the study for safety.

3.3 Exit DBPCFC

All subjects who reach the targeted daily dose of 300 mg and maintain that dose through the Maintenance Period will undergo an Exit DBPCFC. The Exit DBPCFC will be performed in accordance with PRACTALL guidelines, but starting at a dose of 3 mg of peanut protein (except for subjects who reacted to 1 mg in their Screening DBPCFC; these subjects will be required to start their Exit challenge at 1 mg; see also **Section 6.6.2**) and requiring progression in an unaltered sequence (**Table 6-1**), without repeating any dose. Also, the Exit DBPCFC will include a 600 mg penultimate challenge dose, and the top challenge dose will be capped at 1000 mg.

The same vehicle food should be used for the Exit DBPCFC as was used for the Screening DBPCFC.

Each subject will be unblinded after he/she completes the DBPCFC, provided regulatory and Institutional Review Board (IRB) / Ethics Committee (EC) approval for ARC004 have been received, the availability of IP for ARC004, and all major data queries for the subject have been resolved. If this is not the case, the subject shall remain on blinded treatment until these requirements are satisfied. The subject should continue his or her maintenance visits (completed as unscheduled visits) every 30 days, and complete all protocol procedures at each visit until study completion and rollover to ARC004. To maintain the study blind overall, individual unblinding information should only be distributed to designated team members on a need-to-know basis (refer to Masking Plan for details).

Subjects who do not reach the target dose by Week 40 are not eligible for the Exit DBPCFC, and will be considered escalation failure nonresponders. They will be unblinded no sooner than Week 64.

The ARC003 study will end with the last visit of the last subject.

3.4 Follow-on Study ARC004

All placebo subjects who complete ARC003 are eligible for rollover into the ARC004 protocol. Placebo subjects from ARC003 will, in ARC004, undergo an escalation schedule identical to that for active subjects in the ARC003 protocol. All subjects on active treatment in ARC003 who pass the DBPCFC at the 300 mg (443 mg cumulative) challenge dose level of peanut protein are eligible to proceed to ARC004. Those who do not pass DBPCFC at the 300 mg (443 mg cumulative) challenge dose level will be considered endpoint failures and nonresponders for the primary analysis. They will not be eligible for rollover into the ARC004 protocol due to safety concerns. Those subjects who pass DBPCFC at the 300 mg (443 mg cumulative) challenge dose level, but fail at the 600 mg (1043 mg cumulative) or 1000 mg (2043 mg cumulative) challenge dose level, will be considered endpoint failures and nonresponders for the primary analysis for North America or Europe, respectively; however, they will be eligible for rollover into the ARC004 protocol because tolerating a 300 mg (443 mg cumulative) dose of peanut protein is considered a clinically relevant level of desensitization in the event of accidental exposure.

Upon successful completion of Study ARC003, all subjects will be eligible to receive AR101 in Study ARC004. Subjects who received AR101 in Study ARC003 will continue on their maintenance dose of 300 mg/d, and subjects who had previously received placebo in Study ARC003 will undergo dose-escalation according to the same schedule and procedures used in ARC003, but in open-label fashion. At the end of the up-dosing period followed by a period of continued maintenance dosing at 300 mg/d, those subjects will be required to pass a DBPCFC by tolerating 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms to continue in the study. All subjects continuing maintenance therapy in ARC004 will be required to undergo a DBPCFC after at least 6 months of additional maintenance treatment.

3.5 Study Design Safety Considerations

The study design incorporates the following important safety considerations:

- All dose escalations will be performed under direct observation and medical supervision in the CRC
- The peanut OIT will start at 0.5 mg and will only escalate to a maximum single dose of 6 mg during the initial escalation on Day -1
- Adverse events, including dosing-related allergic symptoms, whether expected or not, will be captured throughout the study
- All subjects and/or their participating family (as appropriate for age and home circumstances) will be provided with an epinephrine auto-injector and will be trained in its use
- Subjects will be strongly cautioned against consuming any peanuts or peanut-containing foods other than the study product while on study, and will be instructed to remain on a peanut-free diet.

3.6 Primary Efficacy Endpoint

3.6.1 Primary Efficacy Endpoint, North America

The primary clinical efficacy endpoint is the proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC.

3.6.2 Primary Efficacy Endpoint, Europe

The primary clinical efficacy endpoint is the proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC.

3.7 Secondary Endpoints

3.7.1 Key Secondary Endpoints

North America: The key secondary endpoints are as follows:

- The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC
- The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC
- The maximum severity of symptoms in subjects aged 4 to 17 years occurring at any challenge dose of peanut protein during the Exit DBPCFC
- The proportion of subjects aged 18 to 55 years who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC

Europe: The key secondary endpoints are as follows:

- The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC
- The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC
- The maximum severity of symptoms in subjects aged 4 to 17 years occurring at any challenge dose of peanut protein during the Exit DBPCFC
- The proportion of subjects aged 18 to 55 years who tolerate a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC

3.7.2 Other Secondary Endpoints, North America and Europe

The other secondary endpoints are as follows:

- Maximum dose achieved with no or mild symptoms at Exit DBPCFC in subjects aged 4 to 17 years
- Change from baseline in maximum tolerated dose of peanut protein at DBPCFC in subjects aged 4 to 17 years
- Use of epinephrine as a rescue medication at Exit DBPCFC and comparison to its use at Screening DBPCFC in subjects aged 4 to 17 years
- Changes in peanut-specific serum IgE and IgG4 levels in subjects aged 4 to 17 years
- Changes in peanut skin prick test (SPT) mean wheal diameters in subjects aged 4 to 17 years
- Quality of life assessments using the food allergy related quality of life questionnaire (FAQLQ), and the food allergy independent measure (FAIM) questionnaire (van der Velde et al., 2010) in subjects aged 4 to 17 years

3.7.3 Secondary Safety Endpoints, North America and Europe

- The safety of peanut OIT based on adverse events (AEs) including serious adverse events (SAEs) in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
- Use of epinephrine as a rescue medication during OIT (Initial Escalation, Up-dosing, and Maintenance Periods) in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
- Frequency of anaphylaxis during OIT (Initial Escalation, Up-dosing, and Maintenance Periods) in in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
- Frequency of allergic reaction (hypersensitivity) AEs occurring during the Up-dosing versus the Maintenance Period, normalized for duration of treatment in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
- Frequency of accidental ingestions of peanut and other allergenic foods in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
- Severity of adverse events associated with accidental ingestions of peanut and other allergenic foods in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
- Frequency of premature discontinuation of dosing due to AEs; and frequency of premature discontinuation of dosing due to chronic/recurrent gastrointestinal (GI) AEs in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive

- Assessment of asthma control using the Asthma Control Test questionnaire in subjects with asthma in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive

3.8 Exploratory Endpoints, North America and Europe

- The primary endpoints identified above will be repeated in the following 3 age groups: 4 to 11 years, 12 to 17 years, and 4 to 55 years, inclusive
- The first 3 key secondary endpoints and all other secondary endpoints identified above will be repeated in the following 4 age groups: 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
- Treatment satisfaction assessment using the Treatment Satisfaction Questionnaire for Medication (TSQM-9), an exit questionnaire and palatability questions
- **(North America sites only)** Optional mRNA expression patterns in saliva obtained longitudinally from peanut-allergic participants undergoing OIT in ARC003 **(Appendix 6; Data will be reported separately)**

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects who meet all of the following criteria are eligible for enrollment as study subjects:

1. Age 4 through 55 years (inclusive)
2. Clinical history of allergy to peanuts or peanut-containing foods
3. Serum IgE to peanut of ≥ 0.35 kU_A/L [determined by UniCAP™ within the past 12 months] and/or a SPT to peanut ≥ 3 mm compared to control
4. Experience dose-limiting symptoms at or before the 100 mg challenge dose of peanut protein (measured as 200 mg of peanut flour) on Screening DBPCFC conducted in accordance with PRACTALL (Practical Issues in Allergology, Joint United States/European Union Initiative) guidelines
5. Written informed consent from adult subjects
6. Written informed consent from parent/guardian for minor subjects
7. Written assent from minor subjects as appropriate (eg, above the age of 7 years or the applicable age per local regulatory requirements)
8. Use of effective birth control by female subjects of child-bearing potential
9. Not be residing at the same address as another subject in this or any peanut OIT study

4.2 Exclusion Criteria

Subjects who meet any of these criteria are not eligible for enrollment as study subjects:

1. History of cardiovascular disease, including uncontrolled or inadequately controlled hypertension (see also **Section 5.10** Prohibited Medications)

2. History of severe or life-threatening episode of anaphylaxis or anaphylactic shock within 60 days of Screening DBPCFC
3. History of chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that is, or is at significant risk of becoming, unstable or requiring a change in chronic therapeutic regimen
4. History of eosinophilic esophagitis (EoE), other eosinophilic gastrointestinal disease, chronic, recurrent, or severe gastroesophageal reflux disease (GERD), symptoms of dysphagia (eg, difficulty swallowing, food "getting stuck"), or recurrent gastrointestinal symptoms of undiagnosed etiology
5. Current participation in any other interventional study
6. Subject is in "build-up phase" of immunotherapy to another allergen (ie, has not reached maintenance dosing)
7. Severe asthma (2007 NHLBI Criteria Steps 5 or 6, **Appendix 2)**
8. Mild or moderate asthma (2007 NHLBI Criteria Steps 1-4), if uncontrolled or difficult to control as defined by any of the following:
    - FEV1 < 80% of predicted, or ratio of FEV1 to forced vital capacity (FEV1/FVC) < 75% of predicted, with or without controller medications (only for age 6 or greater and able to do spirometry*) or
    - Inhaled corticosteroids (ICS) dosing of > 500 mcg daily fluticasone (or equivalent ICS based on NHLBI dosing chart) or
    - One hospitalization in the past year for asthma or
    - ER visit for asthma within six months prior to screening
9. History of steroid medication use (via intravenous [IV], intramuscular [IM] or oral administration) in any of the following manners:
    - history of daily oral steroid dosing for > 1 month during the past year or
    - burst oral (IM or IV) steroid course in the past 3 months prior to randomization or
    - > 2 burst oral (IM or IV) steroid courses in the past year of at least 1 week duration
10. Inability to discontinue antihistamines 5 half-lives before the initial day of escalation, skin testing or DBPCFC
11. Lack of an available palatable vehicle food to which the subject is not allergic
12. Use of any therapeutic antibody (eg omalizumab, mepolizumab, reslizumab, etc.), any investigational peanut immunotherapy (eg oral, sublingual, epicutaneous), or any other

* Spirometry is to be attempted in all subjects ≥ 6 years of age. For subjects aged 6-11 years: if valid spirometry results are not successfully obtained, the attempt is to be documented. Measures of peak flow will be acceptable for the entry criteria if results are > 80% of predicted. For subjects 4 or 5 years of age, peak flow rates are to be attempted, but reliable performance is not required for the subject to enter the study or undergo study procedures at the investigating physician's discretion. The attempt must be documented, and a clinical assessment is required.

immunomodulatory therapy excluding corticosteroids within the past 6 months (see also **Section 5.10** Prohibited Medications)

13. Use of beta-blockers (oral), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB) or calcium channel blockers (see also **Section 5.10** Prohibited Medications)
14. Pregnancy or lactation
15. Having the same place of residence as another subject in the study
16. Participation in another clinical trial within 30 days or 5 half-lives of the investigational product, whichever is longer, prior to randomization.
17. Developing dose limiting symptoms in reaction to the placebo part of the Screening DBPCFC
18. History of a mast cell disorder, including mastocytosis, urticaria pigmentosa, and hereditary or idiopathic angioedema
19. Allergy to oat
20. Hypersensitivity to epinephrine and any of the excipients in the product

4.3 Premature Subject Termination from the Study

4.3.1 Criteria

No subject randomized into this trial who discontinues treatment for any reason will be replaced.

Unless required for safety reasons (ie, medical treatment of SAEs), subjects eligible for an Exit DBPCFC will not be unblinded earlier than their scheduled DBPCFC. Subjects who are considered escalation failures will be unblinded no sooner than Week 64 (or when the last subject completes the Exit DBPCFC).

Any subject will be prematurely terminated from additional allergen exposures for the following reasons:

1. Life-threatening symptoms (CoFAR Grade 4; refer to **Table A4** in **Appendix 4**), including, but not limited to, anaphylaxis resulting in hypotension, neurological compromise, or mechanical ventilation secondary to peanut OIT dosing or any peanut food challenge
2. Severe symptoms (CoFAR Grade 3; refer to **Table A4** in **Appendix 4**), including, but not limited to, those that require intensive therapy (to be determined by the investigator, but may include such interventions as IV epinephrine, intubation, or admission to an intensive care unit) or those that are recurrent

Any subject may be prematurely terminated from additional allergen exposures for the following reasons:

3. Poor control or persistent activation of secondary atopic disease (eg, atopic dermatitis, asthma)

4. Started on angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, or other prohibited medications, with no alternative medications available per the prescribing doctor
5. Pregnancy
6. Non-adherence (non-compliance) with home peanut OIT (study product) dosing, as indicated by missing > 7 consecutive days on any 1 occasion, or 3 consecutive days on 3 or more occasions during the Up-dosing Period, as this could constitute a potential safety issue
7. Medically indicated circumstances (eg, as part of the treatment for intercurrent adverse events) that require missed peanut OIT (study product) dosing for >14 consecutive days

Any subject may also be prematurely terminated from the study if:

8. The subject elects to withdraw consent from all future study activities, including follow-up
9. The subject is "lost to follow-up" (ie, no further follow-up is possible because attempts to reestablish contact with the subject have failed)
10. The subject develops biopsy-documented eosinophilic esophagitis (EoE)
11. The subject's continued participation in the study is assessed by the investigator to constitute a threat to the safety of the subject or the safe conduct of the study
12. The subject dies (CoFAR Grade 5)

Subjects who discontinue study product prematurely due to AEs or other safety concerns should be encouraged to continue their participation in follow-up safety assessments. If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason.

4.3.2 Follow-up of Subjects Who Discontinue Treatment

Subjects who prematurely discontinue treatment will be brought in for an Early Discontinuation Visit approximately 14 days after their last dose of study product. To the extent possible, subjects will be monitored for safety until they come back for their Early Discontinuation Visit.

In the event of ongoing AEs, subjects who have discontinued therapy should continue to be followed beyond the Early Discontinuation Visit until such time as the AE has resolved or is assessed to have reached a chronic stable state (a determination that may not be made sooner than 30 days after the Early Discontinuation Visit).

Subjects under the age of 18 years who discontinue treatment due wholly or in part to GI AEs will be instructed to complete the Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS™ v2.0) questionnaire (Franciosi et al., 2011) monthly for 6 months (**Section 7.4.3.2**); adults will be given a modified version of the questionnaire. These subjects will also be asked to continue to fill out their daily diary for the same 6-month duration. Additional instructions for the follow-up of subjects who discontinue treatment due wholly or in part to GI AEs is contained in **Section 7.4.3.2.**

5 STUDY MEDICATION

5.1 Formulation, Packaging and Labeling

The active study product, AR101, is characterized peanut allergen in the form of peanut flour, formulated with a bulking agent and a flow agent in pre-measured graduated doses, comprising capsules containing 0.5, 1, 10, 20, and 100 mg each of peanut protein. AR101 is characterized by its HPLC fingerprint and by specific ELISAs performed against key allergenic proteins to demonstrate stability and lot-to-lot comparability. Placebos, containing only excipients that are color-matched to the peanut flour, will be provided as matching capsules, identical to the active capsules. For maintenance dosing, 300 mg of peanut protein are provided in sealed, foil-laminate sachets requiring one sachet/day. Matching placebo containing sachets are also provided.

Capsules containing study product will be provided in pre-packaged bottles or blister cards assembled into dosing kits. Each individual bottle or blister of a blister card will contain a single day's dose of study product; each 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 (**Section 3**).

All study products (both peanut allergen and placebos) will be packaged and labeled at the central packaging facility. The products will then be shipped to a drug depot where they will be labeled and inventoried for shipment to the clinical sites. Study products will be shipped by the drug depot to the investigational site or the investigational site pharmacy, according to site-specific institutional policies. Study products will then be distributed to subjects/subjects' parents or guardians by study site personnel. Study products will be dispensed to subjects on the basis of matching randomization code to ensure dosing according to their assigned treatment arm and dose level, without the blind being broken for the subjects or the study personnel.

All study products will be stored in a secure location and kept refrigerated between 2°C and 8°C. Sites will maintain temperature logs for all refrigerators storing study drug for the duration of the study.

5.2 Preparation, Administration and Dosage

The first dose at each new dose level is to be administered in the CRC under the direct supervision of an appropriately credentialed healthcare provider and the oversight of a physician. This dose, intended for in-clinic administration, is removed from the dosing kit for the assigned dose level. Once a dose is removed from a dosing kit, the kit must be dispensed to the subject or held at the site for documented destruction or return to the sponsor's designee (as instructed); dosing kits once opened cannot be used for any other dosing interval or any other subject. At each clinic visit, subjects will receive a kit of capsules to be taken at home according to their specific dose level. The subjects will be instructed to document capsules taken at home using electronic diary logs and to bring all unused capsules back to the clinic at the next visit. The subjects will be instructed to store the dosing kit in the refrigerator other than when it is removed to obtain the daily dose.

Procedures for preparation and administration of doses given in clinic or at home are the same. Dose preparation is to be completed by the subject or supervising adult, as age-appropriate. (For in-clinic dosing, dose preparation may be performed by clinic staff or by parent/subject under the

direct supervision of clinic staff for the purpose of teaching and reinforcing training.) The capsules should be pulled apart, and gently rolled between finger and thumb, followed by a light tap to the end of each half of the capsule to ensure full delivery of contents. The contents of the capsules are to be mixed with a vehicle food, such as apple sauce, yogurt, pudding, or other palatable, age-appropriate, food. Care must be taken not to inhale the powder as this could provoke worsening of asthma or induce an allergic reaction. Study product may not be added to food heated above room temperature before consumption. The vehicle food must be one to which the subject is not additionally allergic. The volume of the vehicle food should be such that the entire dose can be consumed in a few spoonfuls. The study product should be consumed as promptly after mixing as practicable. If not consumed within 4 hours of mixing into a vehicle, the study product-vehicle food mixture should be discarded and a new dose mixed prior to consumption. If preparing a new dose is not feasible, the study product may be stored for up to 24 hours under conditions appropriate for the food matrix in which the study product was prepared. If there is a delay of more than 24 hours in consumption, the study product is to be discarded and a new study product dose mixed and consumed. It is recommended that each dose of study product be taken at a consistent time (within a 4-hour time period) each day. A target interval of at least 8 hours should pass between doses.

Except for in-clinic dosing, the daily home dose should be taken as part of a meal. Dosing at the evening meal is recommended to permit children to be observed and supervised in the home setting by their parents or guardians for several hours after dosing. Subjects are to be cautioned against activities likely to increase allergic reactivity (eg, exercising or taking hot showers or baths within 3 h after dosing). Dosing should also not occur within 2 hours of bedtime. Additionally, if a subject has been engaged in strenuous exercise prior to dosing, dosing should be delayed until signs of a hypermetabolic state (eg, flushing, sweating, rapid breathing, and/or rapid heart rate) have abated.

Except as may be necessary in the course of treating an adverse event (**Section 6.7**), it is crucial that subjects take their dose every day. No attempt should be made to make up for a missed dose if greater than 6 hours have elapsed since usual time of dosing.

5.3 Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) and International Council for Harmonisation Good Clinical Practice Guideline (ICH E6), the investigator is required to maintain adequate records of the disposition of the investigational agent, including the date and quantity of the drug (study product) received, to whom the drug was dispensed (subject-by-subject accounting), and a detailed accounting of any drug accidentally or deliberately destroyed.

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each subject. This log will contain the identification of each subject and the date and quantity of drug dispensed.

All records regarding the disposition of the investigational product will be available for inspection by the clinical trial monitor.

5.4 Assessment of Compliance with Study Treatment and Monitoring

Families will document daily dosing and any reaction to at-home dosing by diary logs. Central monitoring of compliance will be performed by comparing returned unused study product against the daily dosing records. Families will be provided with 24-hr emergency contact information for the site.

Doses of study product lost or destroyed at home will also be recorded in the diary logs. All unused study product should be brought back to the clinic with each visit for reconciliation of remaining capsules/sachets.

5.5 Modification of Study Treatment

As described in the protocol (**Section 6.7**), peanut OIT doses may be adjusted by the study physician if the subject is unable to tolerate the scheduled dose level. If such a dose modification occurs, the subject will return all kits and unused capsules/sachets of study product during the dose adjustment visit, and be dispensed capsules at the adjusted dose level.

5.6 Concomitant Medications

Except as indicated in **Section 5.10**, all subjects may continue their usual medications, including those taken for asthma, allergic rhinitis, and atopic dermatitis, during the study. However, they must be able to discontinue antihistamines and other medications that could interfere with the assessment of an allergic reaction 5 half-lives prior to the initial day of escalation, skin prick testing (SPT), and oral food challenges. Usual topical steroid use is permitted following SPT.

5.7 Prophylactic Medications

None.

Although symptomatic treatments for chronic/recurrent AEs are permitted, as for example with H-1 or H-2 histamine blockers, proton pump inhibitors, or beta-adrenergic agonists, such medications should not be started in advance of symptoms; once started, their use should be minimized, and then discontinued, at the earliest medically appropriate opportunity.

5.8 Rescue Medications for Acute Allergic Reactions

Treatment of individual acute allergic reactions during peanut OIT therapy should be with either an antihistamine and/or epinephrine, along with IV fluids, beta-adrenergic agonist (eg, albuterol), oxygen, and/or steroids, as indicated. Subjects and parents/guardians are likely already to have an epinephrine auto-injection device, but for those who do not, an epinephrine auto-injection device will be provided. The expiry dates for the epinephrine auto-injectors will be tracked and subject/families resupplied as necessary. Study staff must document in each subject's medical record that the subject and parent/guardian have been provided with an epinephrine auto-injection device and have been trained in its proper usage including injection technique.

5.9 Symptomatic Treatment for Chronic and/or Recurrent Adverse Events

Symptomatic treatment for chronic/recurrent AEs is permitted (except for prohibited medications [**Section 5.10**]), but should be used to supplement dose reduction, not substitute for it. It is advised that an attempt to withdraw symptomatic therapy be made prior to dose re-escalation. If

unsuccessful, symptomatic therapy may be resumed and dose escalation proceed with the symptomatic therapy in place. However, any therapy instituted for treatment of symptoms (AEs) related to study product, must be withdrawn by 4 weeks prior to Exit DBPCFC. If a subject is unable to tolerate a daily maintenance of 300 mg of study product for at least the last 4 weeks of dosing prior to Exit DBPCFC, free of any symptomatic therapy that was initiated during the course of OIT, the subject will be considered a nonresponder.

5.10 Prohibited Medications

1. Omalizumab (Xolair)
2. Systemic (oral) corticosteroids used for any greater duration than a total of 3 consecutive weeks throughout the study. If used, subjects must not be up-dosed during the 3 days after ceasing the administration of oral steroids
3. Beta-blockers (oral)
4. Angiotensin-converting enzyme (ACE) inhibitors
5. Angiotensin-receptor blockers (ARB)
6. Calcium channel blockers
7. Tricyclic antidepressants

During the course of the study, subjects may be at increased risk for anaphylaxis, which, in severe form, can result in a drop in blood pressure. Additionally, the administration of epinephrine to treat anaphylaxis can result in a sudden rise in blood pressure. For these reasons, the risks accompanying the use of any medication with known cardiovascular side effects must be weighed against the potential benefits of peanut OIT. This assessment must be performed for any medications being taken at study entry or added during the course of the study. The use of medication with known cardiovascular side effects during the course of the study is discouraged; but if an investigator deems use necessary, it must be undertaken with caution. It is beyond the scope of this protocol to list all drugs with cardiovascular side effects. Classes of drugs with a high potential for cardiovascular side effects include antipsychotics, cyclooxygenase 2 inhibitors (chronic use), non-steroidal anti-inflammatory drugs (chronic use), antiarrhythmics, antihypertensives, and antineoplastics. Before a drug with cardiovascular side effects is used in conjunction with OIT, the investigator should discuss its use with 1 of the study's Medical Monitors.

Immunomodulatory (including immunosuppressive) medications constitute another class of drugs whose use during the course of the study is generally prohibited. It is beyond the scope of this protocol to list all immunomodulatory drugs; broadly, these include drugs to treat or prevent transplant rejection, autoimmune disease, and certain neoplasias - examples include cyclosporine, tacrolimus, anti-tumor necrosis alpha drugs, and anti-IgE drugs. If an investigator contemplates the use of a potentially immunomodulatory drug during the course of the study, the investigator should discuss this with 1 of the study's Medical Monitors.

6 STUDY PROCEDURES

6.1 Enrollment and Randomization

Subjects will have an initial Screening DBPCFC consisting of both a peanut challenge and a placebo challenge before randomization. The peanut and placebo challenges will be conducted in a double-blind fashion, using foodstuffs provided by an unblinded site pharmacist, nutritionist, or study coordinator. Those subjects reacting to ≤ 100 mg of peanut protein (≤ 144 mg cumulative) will be randomized in a 3:1 ratio to AR101 or placebo. Those able to successfully consume the 100 mg top challenge dose of peanut protein during their DBPCFC, ie, do not develop dose-limiting symptoms, will not be eligible for the study. In addition, those reacting with dose-limiting symptoms to ≤100 mg of the placebo challenge will not be eligible for the study. Because of the requirement for the peanut DBPCFC, the screening and baseline visits will need to be conducted over more than 1 day.

Randomization will be stratified to maintain balance between treatment groups and to ensure adequate representation of key demographic sub-populations. Stratification will be by broad geographic region (to include at a minimum North America and Europe) and age (children from ages 4 to 17, inclusive, and adults to age 55, inclusive). As the Phase 2 studies (ARC001 and ARC002) were enrolled exclusively in the United States and only 1 adult subject was enrolled, stratifying randomization for age and geographic region will ensure balanced representation of potentially relevant subpopulations in ARC003. It is anticipated that approximately 65% of subjects will be recruited from North America, 30% from Europe, and potentially up to 5% from other regions. Investigational centers from Southern as well as Northern Europe are expected to participate. At least 80% of the subjects randomized will be children. Analysis of the ARC001 data showed no interactive effect of age on treatment effect (ie, desensitization), so stratification by age will include only the 2 strata, children and adults. As there is male predominance on the order of 2 to 1 in the peanut-allergic population below the age of puberty, randomization may be regulated to ensure adequate representation of girls younger than 12 years. But since the proportion of males and females randomized to each arm of the ARC001, a relatively small study, adequately reflected the literature-reported breakdown of the peanut-allergic population by gender, and there was no apparent effect of gender on desensitization, it is assumed that in ARC003, a relatively large study, the two arms will be adequately balanced for gender without stratifying for this independent variable. Further, although the prevalence of peanut allergy tends toward parity between males and females after the age of puberty, social factors can play a significant role in clinical trial participation, such that a given clinical trial population may not match exactly the disease population. Taking this into account, a target for the proportion of males to females recruited from the adolescent and adult peanut-allergic populations is not being set.

Randomization will be performed using an interactive response system.

The study procedures are tabulated in **Appendix 1** and are listed per visit below.

6.2 Screening and Baseline

Screening may occur over several days and will include the following assessments/procedures:

- Informed consent and assent, as age appropriate

- Inclusion/exclusion criteria review
- Medical and allergy history review
- Concomitant medication review
- Diet (food allergen exposure) history review
- Completion of the food allergy related quality of life questionnaire (FAQLQ), and the food allergy independent measure (FAIM) questionnaire. Both questionnaires will be completed before the DBPCFC
- Assessment of asthma control using the Asthma Control Test questionnaire in subjects with asthma
- Physical examination, including weight and height
- Vital sign measurement (blood pressure, pulse rate, body temperature)
- Spirometry (FEV1) and/or Peak Expiratory Flow Rate (PEFR) prior to any DBPCFC; 3 attempts of FEV1 are performed and the best value is taken; 3 attempts of PEFR are to be performed, and the best value taken. PEFR should be measured at the same time for each visit assessment.
- Serum pregnancy test, for females of childbearing potential
- Blood draw to collect samples for:
    - Peanut-specific IgE, component-resolved IgE (including at screening determination of Ara h 1, Ara h 2, Ara h 3, Ara h 8 and Ara h 9) peanut IgE, total IgE, and peanut-specific IgG4 (immunoglobulin assays) The amount of blood to be taken for the immunoglobulin assays will be communicated from the central laboratory and included in the manual of procedures.
    - Complete blood cell count (CBC), obtained with the same venipuncture as the blood draw for the immunoglobulin assays
    - Optional exploratory immune cell characterization by the Immune Tolerance Network (ITN). Note that these samples can be obtained with the same venipuncture as the blood draw for the immunoglobulin assays and CBC, but will require an addition volume of blood to be collected. Separate informed consent is required.

The amount of blood to be taken in total for the above assays (required immunoglobulin assays, required CBC, and optional immune cell characterization assays) will not exceed a total volume of 0.67 mL/kg in children, to a maximum of 50 mL, total, in 8 weeks. Blood draw should be collected in compliance with local laboratory guidelines and testing regulations.

- Skin prick test to peanut extract
- DBPCFC conducted in accordance with PRACTALL guidelines, with assessments made by a Blinded Evaluating Physician (Blinded Assessor), as described in **Section 6.6**
- **(North America sites only)** Optional collection of saliva sample for exploratory biomarker development **(Appendix 6)**
- Monitoring for adverse events (AEs), including allergic symptoms (**Section 6.7**)

- Subjects will be instructed to continue to follow a peanut-avoidant diet for the duration of the study.
- Subjects and parents or guardians will additionally receive teaching about food/peanut allergy according to the investigational site's established standards. This is to include at a minimum the following topics (some or all of which may be addressed in a comprehensive anaphylaxis action plan):
  - Recognition of an allergic reaction and of the symptoms of anaphylaxis
  - When and how to administer epinephrine via auto-injector
  - Requirement to go to nearest emergency facility following use of epinephrine auto-injector
  - Ways to minimize the risk of accidental exposure to peanut in, and outside of, the home (may be supplemented by referral to recognized food allergy organizations for access to additional learning materials)

All screening procedures must be completed no later than 28 days from the signing of the informed consent/assent form. The Initial Escalation Day-1 visit should occur within 10 days of the Screening DBPCFC.

The laboratory values and clinical findings, including those from the Screening DBPCFC, will serve as the baseline measures for comparison to subsequent measures obtained during the course of the study.

6.2.1 Optional Post-DBPCFC Blood Draw Visit

This visit is only for subjects who consent to participate in the optional post-DBPCFC blood draw for exploratory immune cell characterization by the Immune Tolerance Network (ITN).

The visit is to occur 5-10 days after completion of the Screening DBPCFC and may coincide with an Initial Escalation Day Visit (**Section 6.3.1**).

The only procedure performed on this day is a blood draw. The amount of blood to be taken for the immune cell characterization assays will be provided in the manual of procedures and will be such that it will not cause the total blood volume collected to exceed 0.67 mL/kg in children, or maximum of 50 mL, total, in 8 weeks. Blood draw should be collected in compliance with local laboratory guidelines and testing regulations.

6.3 Study Treatment Visits

6.3.1 Initial Escalation

6.3.1.1 Initial Escalation, Day-1

The Initial Escalation Day-1 visit should occur within 10 days of the Screening DBPCFC and must occur within 6 weeks from the signing of the informed consent/assent form. If the Initial Escalation is not started in this time frame, written approval to rescreen the subject and/or to waive any of the screening procedures must be obtained from the Sponsor Medical Monitor.

A physician will be available at all times during the CRC peanut OIT dosing visits.

Subjects must be free from active wheezing or a flare of atopic disease (eg, atopic dermatitis), or suspected intercurrent illness prior to initiating study product dose escalation. Additionally, subjects must be fully recovered, ie back to their baseline state of health, from any preceding illness for at least 3 to 7 days, depending on the investigator-determined severity of the illness.

The following assessments/procedures will be performed during the Initial Escalation.

Day-1 visit in the CRC:

- Concomitant medication update
- Physical examination, including weight and height
- Diet (food allergen exposure) history update
- Pre-dose vital sign measurement (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time for each visit assessment.
- Administration of study product (AR101 or matching placebo), with dosing beginning at 0.5 mg and progressing in graduated doses (if tolerated) of 1, 1.5, 3, and 6 mg. Following the first dose, subsequent doses will be delivered at 20- to 30-minute intervals. The schedule for initial day dose escalation is also shown in **Table 3-1**.
- Post-dose vital sign measurements (blood pressure, pulse rate) within 15- to 30-minute postdose, and prior to next dose, and at 30 minute intervals thereafter, if the time between doses is extended, and for the duration of the postdose observation period.
- Monitoring for adverse events (AEs), including allergic symptoms (**Section 6.7** and **Section 7.2**)
- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study.

Subjects may have clear liquids or flavored gelatin (eg, Jell-O) during the day of the initial day escalation procedure while they are being given the desensitization doses.

At a minimum, subjects must be observed for 90 min. (1½ hours) after completion of dose escalation, with vital sign measurements and assessment for signs and symptoms of allergic reaction performed every 30 minutes. Any signs or symptoms of allergic reaction will be recorded in the CRF on the appropriate Dosing Symptom/AE form.

If Day-1 dose escalation is completed with no symptoms detected after 1½ hours of post-dose observation, the subject may be sent home from the CRC. If the subject exhibited mild symptoms, the duration of the observation period should be extended to a minimum of 1 hour after resolution of the symptoms. For moderate symptoms, the observation period should be extended to a minimum of 2 hours after resolution of the symptoms. And for severe symptoms, the subject should be observed for a minimum of 3 hours after resolution of the symptoms, either at the CRC or an emergency facility, as appropriate.

Any subject deemed to have severe symptoms that include hypoxia, hypotension, or change in mental status, stage 3 anaphylaxis defined in **Appendix 3**, or who receives intensive therapy (to be determined by the investigator, but may include such interventions as IV epinephrine, intubation, or admission to an intensive care unit) for an allergic reaction at any time should be discussed with the Medical Monitor and discontinued from the study.

If dose-limiting symptoms occur at or before the 3 mg single dose, there will be no further dosing of study product, and the subject will be classified as an escalation failure and a nonresponder for the purpose of primary and key secondary analyses. The subject will be asked to return to the CRC 14 days following the last dose of study product to undergo an Early Discontinuation Visit (**Section 6.5**). The subject will continue to be monitored for safety until the Early Discontinuation Visit is completed or any ongoing AEs are resolved, whichever is longer.

If no dose-limiting symptoms occur during Day-1 dose escalation, or if dose-limiting symptoms occur only with the 6 mg single dose, the subject is to return to the CRC on Day-2 to confirm the tolerability of a single 3 mg dose of study product.

6.3.1.2 Initial Escalation, Day -2

On Day -2, a single confirmatory 3 mg dose will be administered under medical supervision in the CRC.

Subjects must be free from active wheezing, a flare of atopic disease (eg, atopic dermatitis), or suspected intercurrent illness prior to continuing with Day -2 of the initial dose escalation. Consistent with the rules for missed doses (**Section 6.8**), Day -2 dosing may not be postponed for more than 2 weeks.

The following assessments/procedures will be performed during the Initial Escalation

Day -2 visit in the CRC:

- Symptom-directed physical examination
- Pre-dose vital sign measurement (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should, as far as possible, be measured at the same time for each visit assessment.
- Oral administration of a single 3 mg dose of study product
- Post-dose vital sign measurements (blood pressure, pulse rate) within 15 to 30 minutes postdose, and at 15- to 30- minute intervals thereafter for the postdose observation period
- Monitoring for adverse events (AEs), including allergic symptoms (**Section 6.7**)
- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study.

At a minimum, subjects must be observed for 1½ hours after dose administration, with vital sign measurements and assessment for signs and symptoms of allergic reaction performed every

30 minutes. Any signs or symptoms of allergic reaction will be recorded in the CRF on the appropriate Dosing Symptom / AE form.

If Day -2 dosing is completed with no symptoms detected after 1½ hours of post-dose observation, the subject may be sent home from the CRC. If the subject exhibited mild symptoms, the duration of the observation period should be extended to a minimum of 1 hour after resolution of the symptoms. For moderate symptoms, the observation period should be extended to a minimum of 2 hours after resolution of the symptoms. And for severe symptoms, the subject should be observed for a minimum of 3 hours after resolution of the symptoms, either at the CRC or an emergency facility, as appropriate.

Any subject deemed to have severe symptoms that include hypoxia, hypotension, or change in mental status (stage 3 anaphylaxis defined in **Appendix 3**), or who receives intensive therapy (to be determined by the investigator, but may include such interventions as IV epinephrine, intubation, or admission to an intensive care unit) for an allergic reaction at any time should be discussed with the Medical Monitor and discontinued from the study.

If dose-limiting symptoms occur on Day -2, there will be no further dosing of study product, and the subject will be classified as an escalation failure and a nonresponder for the purpose of primary and key secondary analyses. The subject will be asked to return to the CRC 14 days following the last dose of study product to undergo an Early Discontinuation Visit (**Section 6.5**). The subject will continue to be monitored for safety until the Early Discontinuation Visit is completed or any ongoing AEs are resolved, whichever is longer.

Those subjects who tolerate the single 3 mg dose of study product on Day -2 will be dispensed a 2-week supply of study product at the 3 mg/d dose level. They will be instructed to continue daily oral dosing at home, starting the following day (Study Day -3), and to continue daily home dosing at that dose level for 2 weeks until next escalation.

On Day -3, the site is to make telephone contact with the subject/subject's parent or guardian to enquire if any AEs (including allergic symptoms) occurred subsequent to the subject leaving the clinic, and to provide assistance in recording of, and responding to, any such events.

6.3.2 Up-dosing (also Referred to as Buildup or Escalation) Visits

The Up-dosing Period will last approximately 20 (to a maximum of 40) weeks and comprise 10 scheduled up-dosing visits (including the first 300 mg dose of the Maintenance Period), with the potential for unscheduled visits for assessment of dose tolerability, dose-reduction, dose re-escalation, or management of AEs.

Subjects will return to the clinic every 2 weeks for up-dosing to a maximum daily dose of 300 mg. The first dose of study product at each new dose level will be administered in the CRC under direct observation and medical supervision.

Subjects must be free from active wheezing, a flare of atopic disease (eg, atopic dermatitis), or suspected intercurrent illness prior to any dose escalation. Subjects should be maintained on their current, or a reduced, dose level of study product until their flare of asthma, atopic disease, or intercurrent illness has resolved.

Subjects should withhold their daily home dose of study product on in-clinic dosing days, but should take all other prescribed medications as scheduled.

The following assessments/procedures are scheduled for each up-dosing visit in the CRC:

- Concomitant medication review
- Diet (food allergen exposure) history update
- Return unused capsules to the clinic at each visit
- Symptom-directed physical examination
- Pre-dose vital sign measurement (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time for each visit assessment.
- Study product administration under observation in the clinic
- Post-dose vital sign measurements (blood pressure, pulse rate) within 15 to 30 minutes postdose, and at 15- to 30-minute intervals thereafter for the postdose observation period
- Take home capsules for daily dosing until next visit
- Monitoring for compliance
- Monitoring for adverse events, including allergic symptoms (see below and also **Section 6.7** and **Section 7.2**)
- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study.

Subjects enrolled in the optional saliva substudy **(North America sites only)** who are not experiencing gastrointestinal symptoms will have a saliva sample collected on the morning of an early up-dosing visit (6 weeks ± 2), according to **Table A6** in **Appendix 6**.

At a minimum, subjects must be observed for 1½ hours after dose administration, with vital sign measurements and assessment for signs and symptoms of allergic reaction performed every 30 minutes. Any signs or symptoms of allergic reaction will be recorded in the CRF on the appropriate Dosing Symptom/AE form.

If up-dosing is completed with no symptoms detected after 1½ hours of post-dose observation, the subject may be sent home from the CRC. If the subject exhibited mild symptoms, the duration of the observation period should be extended to a minimum of 1 hour after resolution of the symptoms. For moderate symptoms, the observation period should be extended to a minimum of 2 hours after resolution of the symptoms. And for severe symptoms, the subject should be observed for a minimum of 3 hours after resolution of the symptoms, either at the CRC or an emergency facility, as appropriate.

Any subject deemed to have severe symptoms that include hypoxia, hypotension, or change in mental status (stage 3 anaphylaxis defined in **Appendix 3**), or who receives intensive therapy (to be determined by the investigator, but may include such interventions as IV epinephrine,

intubation, or admission to an intensive care unit) for an allergic reaction at any time should be discussed with the Medical Monitor and discontinued from the study.

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

A dose escalation attempt may be postponed 1 to 2 weeks if, in the clinical judgment of the investigator, the current dose level has not been sufficiently well tolerated to proceed to the next dose level. Further, if an investigator suspects that a subject has not tolerated, or is not tolerating, his or her current dose level, the investigator should have the subject return to the clinic to determine whether a dose reduction is warranted, and if so, the magnitude of the reduction. Guidelines for setting the new, lower, dose are outlined in **Section 6.7.5**, with the dose adjustment depending on the severity of the dose-related symptoms.

Subjects who require dose reduction during a 2-week dosing period will have their escalation schedule reset, as necessary, to maintain the new dose level for a 2-week period prior to attempting to re-escalate.

Following a dose reduction, it is advised that an escalation attempt be made by 4 weeks, unless escalation is to be delayed further due to administration of epinephrine, as defined in **Section 6.7**. Failure to successfully escalate after 3 consecutive attempts, with each attempt spaced at least 2 weeks apart, will result in the cessation of dosing and the subject being considered an escalation failure and nonresponder. The subject will be asked to return to the CRC 14 days following the last dose of study product to undergo an Early Discontinuation Visit (**Section 6.5**) and is to be followed for safety in the interim.

For symptoms occurring during the Maintenance Period, the same study dosing rules and guidelines that apply for the Up-dosing Period will also apply.

6.3.3 Up-dosing Midpoint Visit

The first 80 mg in-clinic dosing visit is the approximate midpoint of the Up-dosing Period. At the up-dosing visit for the first administration of the 80 mg dose of study product the following procedures are to be performed in addition to those performed at the other up-dosing visits:

- Complete (not just symptom-directed) physical examination, including height and weight
- Assessment of asthma control in asthmatic subjects using the Asthma Control Test questionnaire
- Urine pregnancy test, for females of childbearing potential
- Review with subjects and parents or guardians teaching about food/peanut allergy according to the investigational site's established standards. This is to include at a minimum the following topics (some or all of which may be addressed in a comprehensive anaphylaxis action plan):
    - Recognition of an allergic reaction and of the symptoms of anaphylaxis

- When and how to administer epinephrine via auto-injector
- Requirement to go to nearest emergency facility following use of epinephrine auto-injector
- Ways to minimize the risk of accidental exposure to peanut in, and outside of, the home (may be supplemented by referral to recognized food allergy organizations for access to additional learning materials)

6.3.4 End of Up-dosing / Start of Maintenance Period Visit

The first 300 mg in-clinic dosing visit is the end of the Up-dosing Period; it is also the start of the Maintenance Period. At this visit the following procedures are to be performed in addition to those performed at the up-dosing visits:

- Complete (not just symptom-directed) physical examination, including height and weight
- Assessment of asthma control in asthmatic subjects using the Asthma Control Test questionnaire
- Urine pregnancy test, for females of childbearing potential
- Blood draw to collect samples for:
  - Peanut- and peanut-component specific IgE, total IgE, and peanut- and peanut-component specific IgG4 (immunoglobulin assays). The amount of blood to be taken for the immunoglobulin assays will be communicated from the central laboratory and included in the manual of procedures.
  - CBC, obtained with the same venipuncture as the blood draw for the immunoglobulin assays
  - Optional exploratory immune cell characterization by the Immune Tolerance Network (ITN). Note that these samples can be obtained with the same venipuncture as the blood draw for the immunoglobulin assays and CBC, but will require an addition volume of blood to be collected. Separate informed consent is required.

The amount of blood to be taken in total for the above assays (required immunoglobulin assays, required CBC, and optional immune cell characterization assays) will not exceed a total volume of 0.67 mL/kg in children, to a maximum of 50 mL, total, in 8 weeks. Blood draw should be collected in compliance with local laboratory guidelines and testing regulations.

- Skin prick test to peanut extract
- Review with subjects and parents or guardians teaching about food/peanut allergy according to the investigational site's established standards. This is to include at a minimum the following topics (some or all of which may be addressed in a comprehensive anaphylaxis action plan):
  - Recognition of an allergic reaction and of the symptoms of anaphylaxis
  - When and how to administer epinephrine via auto-injector

  - Requirement to go to nearest emergency facility following use of epinephrine auto-injector
- Ways to minimize the risk of accidental exposure to peanut in, and outside of, the home (may be supplemented by referral to recognized food allergy organizations for access to additional learning materials)

For the first 2-week dosing interval at the 300 mg/d maintenance dose, the dose will be administered from 300 mg capsules. Thereafter, 300 mg doses may be administered from foil-laminate sachets.

6.3.5 Maintenance Period Visits

The Maintenance Period begins with the first 300 mg in-clinic dosing visit.

The first visit in the Maintenance Period is to occur 2 weeks after the start of dosing at 300 mg/d; thereafter Maintenance Period visits will occur approximately every 4 weeks.

Subjects should withhold their daily home dose of study product on in-clinic dosing days, but should take all other prescribed medications as scheduled.

The following assessments/procedures are scheduled for each in-clinic dosing Maintenance visit in the CRC:

- Concomitant medication review
- Diet (food allergen exposure) history update
- Return unused sachets or capsules to the clinic at each visit
- Symptom-directed physical examination
- Pre-dose vital sign measurement (blood pressure, pulse rate, body temperature)
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should be measured at the same time for each visit assessment.
- Study product administration under observation in the clinic
- Postdose vital sign measurements (blood pressure, pulse rate) within 15 to 30 minutes postdose, and at 15- to 30-minute intervals thereafter if the postdose observation period is prolonged beyond the requisite 30 minutes (see below).
- Take home sachets (or capsules, as appropriate) for daily dosing until next visit
- Monitoring for compliance
- Monitoring for adverse events, including allergic symptoms (**Section 6.7** and **Section 7.2**)
- Subjects will be reminded to continue to follow a peanut-avoidant diet for the duration of the study.

In the event that dose reduction from the stable dose of 300 mg/d is required during the last weeks of the planned 24-week Maintenance Period, the Maintenance Period may be extended on

an individual basis up to an additional 4 weeks (to a maximum of 28 weeks) or to a maximum study duration of 68 weeks, whichever is shorter. The Exit DBPCFC must be performed by Study Week 68. Additionally, subjects must maintain a dose of 300 mg/d for at least the last 2 consecutive weeks of the Maintenance Period to qualify for the Exit DBPCFC. Failure to do so will result in the subject being discontinued from the study as a maintenance failure nonresponder for the primary and key secondary analyses.

If dosing is discontinued, the subject will be asked to return to the CRC 14 days following their last dose of AR101 to undergo an Early Discontinuation Visit (**Section 6.5**).

The procedures for dose reduction and re-escalating back to a dose of 300 mg/d in the Maintenance Period will follow the same guidelines as for the Up-dosing Period.

The procedure for monitoring subjects for safety after in-clinic dosing is the same as for up-dosing visits (**Section 6.7.3**), except that the initial period of required post-dose observation may be shortened to 30 min.

6.4 Unscheduled Visits / Unscheduled Blood Draws

The procedures performed at Unscheduled Visits may include any or all of those performed at Up-dosing Visits.

Additionally, if a subject (subject's parent/guardian) declares his or her intention to discontinue study product dosing, whether at a scheduled visit or an unscheduled visit, a blood draw should be performed to obtain a CBC, immunoglobulin assays, and optional exploratory immune cell characterization samples (if the subject is participating in the substudy). If a blood draw is performed at this time, it will take the place of the Exit Visit / Early Discontinuation Visit blood draw (**Section 6.5**).

6.5 Exit Visit / Early Discontinuation Visit

Subjects who tolerate 300 mg/d and are maintained at this dose for approximately 24 weeks will return to the clinic for an Exit Visit.

Subjects who fail initial escalation or up-dosing, or who prematurely discontinue treatment, will return to the site for an Early Discontinuation visit that consists of the same procedures as the Exit Visit, but without a DBPCFC. An Early Discontinuation Visit is to occur 14 days from the last dose of study product.

Subjects who withdraw from ARC003 wholly or in part due to intolerable gastrointestinal symptoms, who are not enrolled in the optional saliva study, may be approached at the time of their early termination visit to provide voluntary consent to enroll and participate in the saliva substudy **(North America sites only).** If this occurs, such subjects will provide a saliva sample as part of the early termination visit and then again during post-OIT follow-up (**Table A6** in **Appendix 6**).

The following procedures will be performed at the Exit/ Early Discontinuation Visit:

- Concomitant medication review

- Diet (food allergen) history
- Completion of the palatability questions
- Completion of the food allergy related quality of life questionnaire (FAQLQ), and the food allergy independent measure (FAIM) questionnaire after the completion of the exit DBPCFC and unblinding for all the patients
- Completion of the Treatment Satisfaction Questionnaire for Medication (TSQM-9) and the exit questionnaire after after the completion of the exit DBPCFC and unblinding for all the active subjects
- Assessment of asthma control in asthmatic subjects using the Asthma Control Test questionnaire
- Physical examination, including weight and height
- Vital signs (blood pressure, pulse rate, body temperature); if DBPCFC is to be conducted, these vital sign measurements should be taken shortly before the first challenge dose
- PEFR (3 attempts are to be performed, and the best value taken). PEFR should, to the extent possible, be measured at the same time as for prior visit assessments.
- Urine pregnancy test, for females of childbearing potential
- Blood draw to collect samples for:
    - Peanut-and peanut-component specific IgE, total IgE, and peanut- and peanut-component specific IgG4 measurement (immunoglobulin assays. The amount of blood taken for the immunoglobulin assays will be communicated from the central laboratory and included in the manual of procedures.
    - CBC, obtained with the same venipuncture as the blood draw for the immunoglobulin assays
    - Optional exploratory immune cell characterization by the Immune Tolerance Network (ITN). Note that these can be obtained with the same venipuncture as the blood draw for the immunoglobulin assays. Separate informed consent is required.

The amount of blood to be taken for the above assays (required immunoglobulin assays, required CBC, and optional immune cell characterization assays) be will not exceed a total volume of 0.67 mL/kg in children, to a maximum of 50 mL, total, in 8 weeks. Blood draw should be collected in compliance with local laboratory guidelines and testing regulations. (For subjects who are withdrawing prematurely from the study due to an AE, the blood draw at the Early Discontinuation Visit can be foregone if it was performed at the time that dosing with study product ceased.)

- Skin prick test to peanut extract
- Take home sachets (or capsules, as appropriate) for daily dosing until next visit (if enrollment in ARC004 does not happen at this visit)
- Monitoring for compliance
- Monitoring for AEs, including allergic symptoms (**Section 6.7** and **Section 7.2**)

In addition to the procedures listed above, eligible subjects will have an Exit DBPCFC performed. Eligible subjects are those who tolerate 300 mg/d and are maintained at this dose for the approximately 24-week Maintenance Period. The Exit DBPCFC is to be conducted in accordance with PRACTALL guidelines, with the protocol-specified modifications, as described in **Section 6.6.2**.

Each subject participating in the study will be unblinded when he/she completes the Exit Visit procedures (including the Exit DBPCFC for eligible subjects), provided regulatory and IRB/EC approval for ARC004 have been received, the availability of IP for ARC004, and all major data queries for the subject have been resolved (**Section 3.3**). If this is not the case, the subject shall remain on blinded treatment until these requirements are satisfied. The subject should continue his or her maintenance visits (completed as unscheduled visits), every 30 days, and complete all protocol procedures at each visit until study completion and rollover to ARC004.

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

All ARC003 placebo subjects who complete the study are eligible for rollover into the ARC004 protocol. Former ARC003 placebo subjects in ARC004 will undergo an escalation schedule identical to that for active subjects in the ARC003 protocol. All subjects on active treatment (AR101) in ARC003 who pass the DBPCFC at the 300 mg (443 mg cumulative) challenge dose level of peanut protein are eligible to proceed to ARC004. Those who do not pass DBPCFC at the 300 mg (443 mg cumulative) challenge dose level will be considered endpoint failures and nonresponders for the primary analysis. They will not be eligible for rollover into the ARC004 protocol due to safety concerns. Those subjects who pass DBPCFC at the 300 mg (443 mg cumulative) challenge dose level, but fail at the 600 mg (1043 mg cumulative) or 1000 mg (2043 mg cumulative) challenge dose level, will be also be considered endpoint failures and nonresponders for the primary analysis for North America or Europe, respectively; however, they will be eligible for rollover into the ARC004 protocol because tolerating a 300 mg (443 mg cumulative) dose of peanut protein is considered a clinically relevant level of desensitization.

6.6 Double-Blind, Placebo Controlled Food Challenge (DBPCFC)

Prior to performing DBPCFC, the subject must be off antihistamines and other medications that could interfere with the assessment of the DBPCFC for an appropriate length of time (5 half-lives of the antihistamine or other medication in question). Also prior to the DBPCFC, subjects will be assessed for an exacerbation of asthma as determined by active wheezing or a PEFR < 80% of predicted.

Subjects must be free from active wheezing, a flare of atopic disease (eg, atopic dermatitis), or suspected intercurrent illness prior to DBPCFC. Additionally, subjects must be fully recovered, ie back to their baseline state of health, from any preceding illness for at least 3 to 7 days, depending on the investigator-determined severity of the illness. Subjects should be maintained on their current, or a reduced, dose level of study product until their flare of asthma, atopic disease, or intercurrent illness has resolved.

Oral food challenges will be undertaken under direct medical supervision and with emergency medications and trained staff immediately available. The DBPCFC is performed by feeding gradually increasing amounts of a suspect allergenic food (in this case, peanut, presented as

defatted peanut flour) mixed in a vehicle (matrix) food under physician observation (Bock & Atkins, 1990; Burks et al., 2012). For this study, a uniform approach to food challenge, in accordance with the PRACTALL consensus guidelines for DBPCFC, will be used by all investigational sites. According to the PRACTALL guidelines, the challenge doses start at 1 mg and increase in semi-log increments to a maximum dose of 3000 mg. The DBPCFC dose escalation schedules used in the current study have been modified slightly from the PRACTALL recommendations, and are presented in **Table 6-1**.

Table 6-1. Modified PRACTALL DBPCFC Doses Using Peanut Flour with 50% Peanut Protein Content for Screening and Exit DBPCFC

	Challenge Doses			
	Amount of Peanut Protein at Each Challenge Dose (mg)	**Amount of Peanut Flour with 50% Protein Content (mg)**	**Cumulative Amount of Peanut Protein (mg) at Screening**	**Cumulative Amount of Peanut Protein (mg) at Exit**
Screening only	1	2	1	0 (or 1)*
Screening and Exit	3	6	4	3 (or 4)
Screening and Exit	10	20	14	13 (or 14)
Screening and Exit	30	60	44	43 (or 44)
Screening and Exit	100	200	144	143 (or 144)
Exit only	300	600	-	443 (or 444)
Exit only	600	1200	-	1043 (or 1044)
Exit only	1000	2000	-	2043 (or 2044)

*For explanation of contingent/optional doses indicated in parentheses refer to **Section 6.6.2**

For each subject, a "blinded" Evaluating Physician (Blinded Assessor) is to be designated to assess the tolerability of the challenge doses presented in the DBPCFC. The Blinded Evaluating Physician is not to be involved directly in the oversight of study product dosing (neither initial escalation, nor up-dosing, nor maintenance), nor the assessment or management of adverse events (for details refer to the Masking Plan). To the extent practicable, the same Blinded Evaluating Physician who determines DLSs in the Screening DBPCFC should determine DLSs in the Exit DBPCFC.

Vital signs (blood pressure and pulse rate) are to be measured just prior to each challenge dose of the DBPCFC or at 15 to 20 minute intervals post-dose, if the between challenge-dosing interval is prolonged. Assessment for signs and symptoms of allergic reaction is to be performed at the time that vital signs are checked.

The DBPCFC is halted when the investigator determines that dose-limiting symptoms have occurred. Dose-limiting symptoms, in the setting of the DBPCFC, are any symptoms that, in the investigator's assessment, indicate poor tolerability of the last challenge dose administered, and preclude safe advancement to the next challenge dose.

Dose-limiting symptoms, typically objective symptoms (signs), indicate a positive reaction and termination of dosing. The criteria for determining if symptoms are dose limiting during DBPCFC are the same as for determining whether a specific dose during up-dosing is tolerated (**Section 6.7**) with the exception that even mild symptoms, if they require pharmacological treatment, will be considered dose-limiting.

As with up-dosing, severe symptoms will always be assessed as dose limiting; and moderate symptoms, with only rare exceptions (requiring a documented explanation), will also be assessed as dose limiting. Mild symptoms, on the other hand, may or may not be assessed as dose-limiting (**Section 6.7**).

In general, if an investigator is unwilling to advance to the next challenge dose in a DBPCFC because of the emergence of allergic symptoms, the last symptom-eliciting challenge dose should be considered to have been not tolerated due to dose-limiting symptoms. There may, however, be exceptions to this, as for example if an emotional reaction to continuing the challenge dose escalation interferes with the ability to progress the dose escalation to the point where convincingly (typically objective) dose limiting symptoms occur. Any such instances must be accompanied by an explanation in the CRF.

On the days that subjects undergo DBPCFCs (Screening and Exit), they must, at a minimum, be observed for 2 hours after administration of the last challenge dose, with vital sign measurements and assessment for signs and symptoms of allergic reaction performed every 30 minutes. Any signs or symptoms of allergic reaction will be recorded in the CRF on the appropriate Dosing Symptom / AE form.

If DBPCFC is completed with no symptoms detected after 2 hours of observation following the last challenge dose, the subject may be sent home from the CRC. If the subject exhibited mild symptoms, the duration of the observation period should be extended to a minimum of 1 hour after resolution of the symptoms. For moderate symptoms, the observation period should be extended to a minimum of 2 hours after resolution of the symptoms. And for severe symptoms, the subject should be observed for a minimum of 3 hours after resolution of the symptoms, either at the CRC or an emergency facility, as appropriate.

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

6.6.1 Screening Double-Blind, Placebo Controlled Food Challenge (DBPCFC)

The initial (Screening) DBPCFC for eligibility will consist of administering gradually increasing challenge doses of a peanut flour mixture (containing ~50% peanut protein) or a placebo (oat) flour mixture, mixed in a vehicle food, at 20 to 30 min intervals. The placebo flour mixture will be supplied pre-mixed with a small amount of artificial peanut flavor to provide a reasonable degree of taste-matching of the final placebo/vehicle food mixture to the peanut/vehicle food mixture. Additional, non-allergenic, powdered flavoring agents have been added both to the peanut and placebo flour mixtures to help further mask the distinctive flavor of peanut. A small amount of oat flour has been added to the peanut flour mixture to help match its consistency to

the placebo flour mixture. Investigational sites will be provided with standardized recipes for preparation of the DBPCFC in a separate manual of procedures.

The Screening DBPCFC will be performed in accordance with PRACTALL guidelines, but requiring progression in an unaltered sequence without repeating any dose. The procedure will also be modified in that the top dose will be capped at 100 mg (144 mg cumulative) peanut protein or placebo, as shown in **Table 6-1.** Otherwise, the PRACTALL recommendations for maintaining safety and assessing symptom severity serve as useful guidelines.

The DBPCFC is to be conducted as 2 challenges, each on a separate day, using a placebo (artificially peanut-flavored oat flour) for one challenge and peanut (as defatted peanut flour) for the other. The 2 challenge days should be scheduled as closely together as practicable and should not be scheduled more than 7 days apart. The oral food challenge is to be performed under double-blind conditions so that neither the subject, nor the subject's caregiver, nor any of the clinic staff (save for the unblinded preparer of the challenge foods) knows which challenge contains the peanut or the placebo. The same vehicle food should be used for both parts of the DBPCFC. The clinic staff may not be unblinded as to the order of the two parts (peanut and placebo) of the DBPCFC until after completion of the observation period of the second part of the challenge.

6.6.2 Exit Double-Blind, Placebo Controlled Food Challenge (DBPCFC)

The Exit DBPCFC will be conducted in a manner similar to the Screening DBPCFC, but starting at a dose of 3 mg of peanut protein (except for subjects who failed their Screening DBPCFC at 1 mg), and with the last 3 challenge doses progressing from 300 mg (443 mg cumulative) to 600 mg (1043 mg cumulative) and then to 1000 mg (2043 mg cumulative) of peanut protein as shown in **Table 6-1**.

The same vehicle food should be used for the Exit DBPCFC as was used for the Screening DBPCFC.

Dosing with study product should continue on the days between the two parts of the Exit DBPCFC, according to the same dosing guidelines that apply throughout the Maintenance Period.

Subjects who failed their Screening DBPCFC at the 1 mg challenge dose of peanut protein will be required to start the Exit DBPCFC with a 1 mg dose. At the investigator's discretion, a 1 mg dose may be added at the beginning of the escalation (for a maximum cumulative dose of 2044 mg peanut protein) of any subject's Exit DBPCFC.

Subjects will be considered desensitization responders for the primary endpoint analysis for North America or Europe if they are able to tolerate an Exit DBPCFC challenge dose of 600 mg (1043 mg cumulative) or 1000 mg (2043 cumulative) of peanut protein with no, or only mild, symptoms, respectively.

6.7 Assessment and Treatment of Allergic Reactions to Peanut OIT

6.7.1 Assessment of the Severity of Acute Allergic Reactions to Peanut OIT

Subjects may develop allergic symptoms during the course of OIT, similar to those seen during other desensitization protocols (eg, venom immunotherapy, drug desensitization, desensitization to aeroallergens by subcutaneous injection). The severity of the reaction will be determined on the basis of the investigator's judgment. The following definitions, developed to be consistent both with the PRACTALL consensus report on DBPCFC, and with the CoFAR grading system for allergic reactions, are provided as a general guide.

Mild Symptoms:

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

Moderate Symptoms:

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

Severe Symptoms:

- Skin – severe generalized urticaria/angioedema/erythema
- Respiratory – laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea, stridor
- GI – severe abdominal pain/cramping/repetitive vomiting and/or diarrhea
- Neurological – change in mental status
- Circulatory – clinically significant hypotension **(Appendix 3)**

6.7.2 Assessment of the Tolerability of an Individual Dose of Study Product

Determination of the tolerability of any individual dose of study product should be based on an assessment of acute symptoms occurring in close temporal succession to dosing.

In general, the severity of allergic symptoms elicited at a particular dose of study product will define the tolerability of that dose of study product. The place where there is the greatest need for

clinical judgment in determining the tolerability of a dose is when the dose elicits mild allergic symptoms. The following **Table 6-2** illustrates the likely combinations of symptom severity and tolerability:

Table 6-2. Allergy Symptom Severity and Study Product Dose Tolerability

Symptom Severity	Assessed Tolerability
None	Tolerated
Mild, oropharyngeal symptoms only	Tolerated
Mild, meeting pre-defined tolerability criteria (**Section 6.7.1**)	Tolerated
Mild, *not* meeting pre-defined tolerability criteria (**Section 6.7.1**)	Not tolerated
Moderate (except for rare exceptions, **Section 6.7.1**)	Not tolerated
Severe	Not tolerated

In general, the severity of an allergic reaction will correspond to the maximum severity of any of its symptoms.

No Symptoms: If a dose elicits no symptoms, the dose will be assessed as tolerated.

Mild Symptoms: When dosing with study product elicits an acute reaction characterized by the appearance of only a mild symptom or symptoms, the investigator will be required to assess whether the dose was or was not tolerated. The determination of tolerability must be made on the basis of clinical judgement. The following are presented as guidelines for determining whether a dose associated with the emergence of a mild symptom or symptoms was tolerated. A dose eliciting only mild symptoms may be considered to be tolerated if the symptoms are:

- Isolated to a single organ system
- Resolve with no pharmaceutical intervention or with a single oral administration of an H1 antihistamine
- Do not require administration of epinephrine
- Are not worsening in intensity or distribution over time
- Resolve, or shows definite signs of resolving, in under 1 hour
- Do not include objective wheezing

Based on experience from Phase 2, most acute allergic responses to dosing that are characterized by mild symptoms would be anticipated to meet the above criteria. If, however, an allergic response to dosing is characterized by mild symptoms that do not meet all of the above criteria (eg, has mild symptoms occurring in 2 or more organ systems, requires treatment with 2 doses of antihistamine or 1 dose epinephrine, shows progression in severity or distribution over time, is protracted in duration, or includes objective wheezing), then even though the allergic symptoms may be mild, the dose should be assessed to be not tolerated. If a dose elicits mild symptoms that do not fit all of the above criteria and the dose is assessed to be tolerated, then a brief explanation as to why the dose was considered tolerated must be recorded in the CRF.

Moderate symptoms: In general, if a dose elicits moderate symptoms, the dose will be assessed as not tolerated. There may, however, be rare occasions when a dose eliciting moderate symptoms could be assessed as tolerated. Generally, this would only be the case for a transient, self-limited (requiring no intervention and resolving completely) symptom occurring in a single organ system. In addition, typically the symptom would be subjective only. Any dose associated with moderate symptoms and assessed as tolerated must be accompanied by a brief explanation in the CRF as to why the dose was considered tolerated.

Severe symptoms: In nearly all cases, if a dose elicits severe symptoms, the dose will be assessed as not tolerated. Whenever a dose elicits an allergic response characterized by 1 or more severe symptoms, the crucial decision, after adequate treatment for the allergic reaction has been administered, will be to determine whether the subject should continue in the study, dosing at a reduced dose level, or be discontinued early from the study.

The determination of tolerability will decide the course of action to be taken in response to dose-related reactions (**Section 6.7.3**).

6.7.3 Assessment of the Tolerability of a Dose Level

6.7.3.1 Assessment of Acute Symptoms Occurring after Dosing

The assessment of the tolerability of a single dose forms the foundation for assessing the tolerability of a dose level during home-dosing when acute symptoms arise in close temporal succession to dosing. With the report of moderate or severe symptoms occurring during home-dosing, the dose level should be considered not tolerated and the subject brought to the clinic the day after the emergence of such symptoms for administration of the next dose of study product under medical supervision. If a dose administered at home is suspected to have been not tolerated, even on the basis of mild symptoms, the subject should also return to the CRC for dosing under medical supervision.

The recurrence of a mild symptom or symptoms over the course of several days of home-dosing should suggest that the dose level is not tolerated, even if each individual occurrence of symptoms could be assessed as tolerated on the basis of the criteria listed above. If the investigational site is notified of mild dose-related symptoms on 4 or more occasions during a single week, the subject should be brought to the CRC for dosing under direct observation for assessment of the tolerability of the dose level. If mild dose-related symptoms are noted on 7 or more occasions during a 2-week dosing interval at a given dose level, that dose level should be considered not tolerated and appropriate action taken (**Section 6.7.5.2**).

Because of the reduced reliability inherent in the second-hand reporting of symptoms, investigators are strongly encouraged to have subjects return to the clinic to undergo dosing under direct observation whenever acute allergic symptoms associated with dosing are reported.

6.7.3.2 Assessment of Chronic / Recurrent Symptoms

GI symptoms were the most common potentially allergic symptoms to occur on a subacute, chronic, and/or recurrent basis during Phase 2 clinical trials with AR101. Atopic dermatitis, seasonal allergies, or asthma are other potentially non-acute allergic reactions that could be brought on or exacerbated by OIT. The absence of a clear temporal relationship between dosing

and the emergence of recurrent symptoms may help to distinguish these from acute dosing-related symptoms.

If symptoms arise that suggest a chronic/recurrent reaction to study product, the dose level should be reduced. As with acute symptoms, the level of the dose reduction should be guided by the severity of the symptoms. Symptomatic treatment is permitted (refer to **Section 6.7.5**), but should be used as a supplement to dose reduction, not a substitute for it.

For chronic/recurrent GI symptoms, especially upper GI symptoms, investigators are advised to have a low threshold for instituting a dose reduction and/or for considering early discontinuation of affected subjects from the study, owing to the potential for EoE.

For subjects determined to be having dose-limiting chronic/recurrent GI symptoms up to and including the 20 mg/d dose level, it is advised that dosing of study product be suspended for 4 weeks and resumed at a dose level of 3 mg/day for a minimum of 4 weeks, with the first dose given in the CRC under medical supervision. If tolerated, up-dosing may resume, with caution, according to the usual schedule, as tolerated, (Note – The 4-week suspension of dosing in response to chronic/recurrent GI symptoms occurring up to and including the 20 mg/d level is the only protocol-specified exception to the rules for missed OIT delineated in **Section 6.8**.)

For subjects who develop dose-limiting chronic/recurrent GI symptoms at the 40 mg/d dose level or above, dose reduction and re-escalation is to proceed as described in **Section 6.7.5**.

6.7.4 Treatment of Acute Reactions to Peanut OIT during Initial Escalation

The process algorithm for responding to acute allergic symptoms during OIT is shown in **Figure 6-1** in **Section 6.7.5.**

Investigator judgment will be required to determine the best course of action, with possible actions being the following:

- Extending the time interval between dosing (up to an additional 30 min) without any additional treatment
- Instituting enhanced clinical monitoring. This could include (though is not limited to) more frequent vital sign monitoring (including respiratory rate), auscultation, and/or the addition of pulse oximetry
- Treating with antihistamine and then resuming dose escalation within 60 minutes of last dose, if assessed as safe
- Treating additionally with epinephrine, beta-agonist, oxygen, IV fluids, and/or glucocorticosteroids, as necessary, and discontinuing dose-escalation
- Discontinuation of desensitization protocol

Mild symptoms: For *oral/pharyngeal pruritus* occurring in isolation, a specific type and commonly occurring mild allergic reaction, the recommended action is to advance to the next dose in 30 min (though the action taken is, as always, at the investigator's clinical discretion).

For other *mild symptoms*, the action to be taken, at the investigator's discretion, should be to either:

- Advance to next dose in 30 to 60 minutes *or*
- Treat with antihistamine and then resume dose escalation within 60 minutes of last dose, provided that symptoms have resolved to the point where the investigator assesses the subject to be safe to continue dosing (ie, having no or only minimal residual signs or symptoms)

In general, if a subject requires only 1 or two doses of antihistamine to treat mild symptoms occurring during the course of the initial escalation, then the initial escalation may continue. If, however, the subject requires a second medication (eg, epinephrine or a beta-agonist) to treat the symptoms, or more than 2 doses of an antihistamine, the initial escalation is to be terminated and the subject is to receive no further OIT, even if the symptoms were assessed to be mild. Use of epinephrine to treat dose-related symptoms, even in the unlikely event that the symptoms are graded as mild, will be cause to terminate the initial escalation.

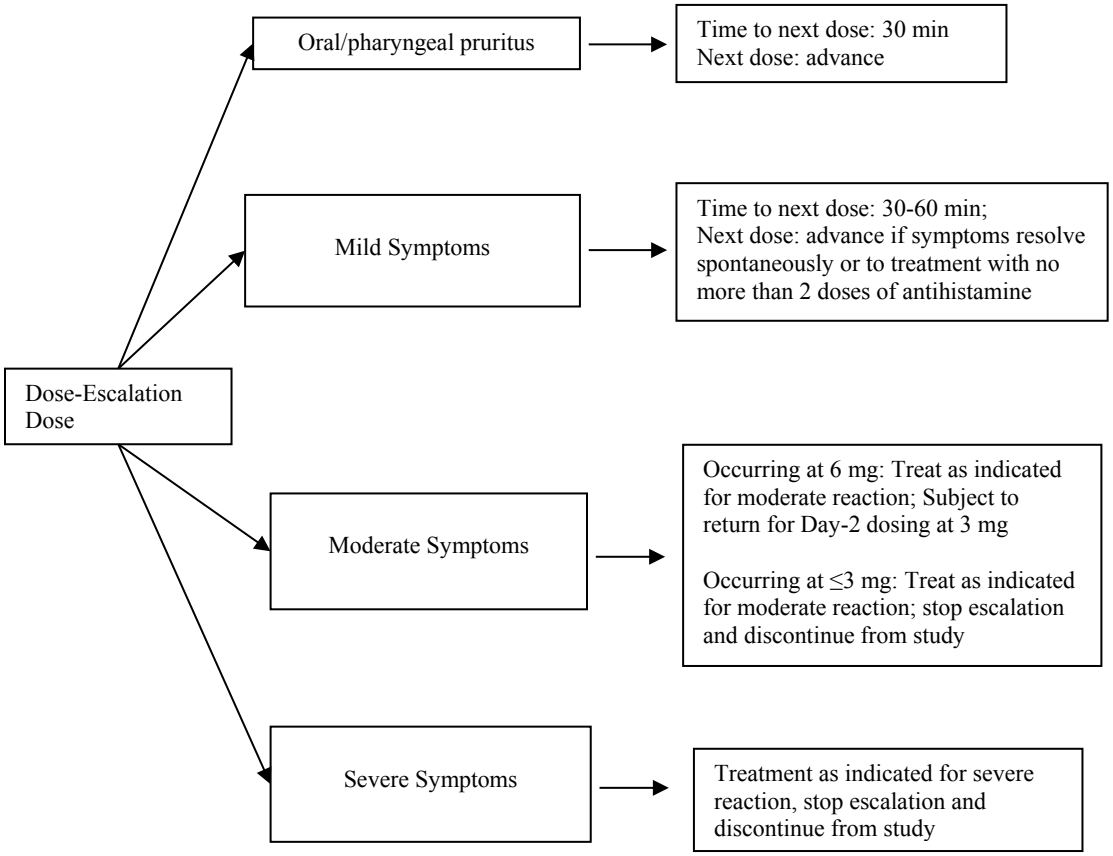
Moderate symptoms: For *moderate symptoms*, if the symptoms are not worsening or amassing at a rapid pace, then a stepwise approach to treatment may be taken at the discretion of the investigator. If the first action undertaken is to implement an observation period, the observation period should not exceed 30 min before either the symptoms are noted to be resolving or therapy is instituted. Whether treatment is initiated immediately or after an observation period, the subject may be treated first with antihistamines or immediately with epinephrine, as deemed appropriate by the investigator. Other therapies may be added either sequentially or simultaneously, per investigator judgment.

If moderate symptoms occur at any of the doses below 6 mg (ie, up to and including 3 mg), then the desensitization procedure will be discontinued and the subject considered an escalation failure and desensitization nonresponder. The decision to discontinue escalation is to be based solely on the determination of whether the allergic reaction was of moderate severity. Although it is generally the case that some form of treatment will be instituted for moderate symptoms, treatment is not a requirement for assessing an allergic reaction as being of moderate severity.

Severe symptoms: For *severe symptoms*, the actions taken should be to discontinue the initial escalation and administer the appropriate rescue medications. The desensitization procedure will be discontinued regardless of the dose at which the severe symptom or symptoms occurred, and the subject will be considered an escalation failure and desensitization nonresponder.

A Medical Monitor (from INC or Aimmune) is to be available at all times to answer any questions or to assist in any decisions related to the study protocol.

Figure 6-1: Schematic for Initial Escalation Day-1



6.7.5 Treatment for Reactions During the Up-dosing Period: Dose Adjustment

If a dose or dose level is assessed *as not tolerated*, the action taken will depend on the type and severity of the dose-related reaction and the investigator's clinical judgement. The following possible actions are at the investigator's disposal and are considered in greater detail in subsequent sections (**Section 6.7.5.1**, **Section 6.7.5.2**, and **Section 6.7.5.3**, and **Figure 6-2**):

- Dosing the subject under medical supervision in the CRC – this is encouraged whenever there is question as to the tolerability of a dose level. It may be performed at the current dose level or at a reduced dose level, if there is already a high index of suspicion that the current dose level has not been tolerated.
- Holding dose level at current level for an additional 1 to 2 weeks before attempting dose escalation – this may be done at the discretion of the investigator if there is concern that the current dose level has not been sufficiently well tolerated to attempt up-doing to the next dose level.
- Reducing dose by 1 or 2 dose levels and maintaining the reduced dose level for at least a 2- to 4-week period before attempting dose re-escalation – Generally, this should be the

action taken when a dose that has been observed in the CRC is assessed as not tolerated, if a dose elicits moderately severe symptoms, if a single dose of epinephrine has been administered to treat a dosing reaction, or if the investigator is convinced of the intolerability of the current dose level. In short, it should be considered the default action whenever a dose or dose level is assessed *as not tolerated*.

- Reducing dose level for less than the usual 2-week period – this may be instituted as treatment for an intercurrent AE, to aid the investigator in determining if a dose level is or is not tolerated, or if a pattern of decreased study product tolerability during menses is discerned. The level of the reduction in dose, ranging from a 1-step reduction to a 50% reduction will be at the investigator's discretion, based on clinical judgement. The manner in which dose escalation may resume will depend on the level and the duration of the dose reduction.
- Temporarily withholding study product dosing – this may be instituted as treatment for an intercurrent AE or to aid the investigator in determining if a dose level is or is not tolerated, but the duration of withholding study product may not exceed 14 consecutive days, or the subject will be discontinued from the study. The manner in which dosing may resume after withholding dosing of study product depends on the duration for which dosing was withheld.
- Reducing dose by 2 dose levels and maintaining the reduced dose level for at least 6 weeks – continuing dosing at a reduced dose level for at least 6 weeks prior to attempting re-escalation is mandatory if 2 doses of epinephrine are given to treat a single AE.
- Stopping dosing and discontinuing the subject early from the study – this is an option that the subject may elect at any time and for any reason. The investigator must discontinue the subject from further dosing and continuation in the trial under circumstances that could jeopardize the health of the subject or the integrity of the trial.

6.7.5.1 Reactions to In-Clinic Dosing

If symptoms arise in the clinic after up-dosing, the investigator is to determine whether or not the dose was tolerated (**Section 6.7.3**). The process algorithm for continued dosing after dose-related symptoms occur is described below and shown in **Figure 6-2**.

If a subject has a dose escalation in the CRC without symptoms, the action should be to continue, per protocol, with daily home dosing at the tolerated dose level and return to the CRC for the next scheduled dose escalation visit 2 weeks later.

If the subject experiences only *oral/pharyngeal pruritus* following the administration of the first dose at a new dose level, the dose will generally be *assessed as tolerated*, and the same dose can be repeated the next day at home and continued throughout the 2-week home-dosing interval, unless other symptoms begin to develop (see below).

If other *mild symptoms* occur with the first dose at a new dose level and the dose is *assessed as not tolerated*, the action taken should be to have the subject return to the CRC the next day for dosing at the last tolerated dose (ie, a 1-step dose reduction) under medical supervision (if the subject is unable to return to the CRC on the day specified, the investigator may initiate an

approximate 1 dose-level reduction at home, with the subject coming to the CRC at the earliest date possible). If the reduced dose is *assessed as tolerated*, the subject is to continue on that daily home dose for the ensuing 2 weeks. (**Section 6.7.5.2** for actions to be taken in the event that symptoms develop during home-dosing.) If the reduced dose is again *assessed as not tolerated*, the subject is to return to the CRC the next day for supervised dosing at a 1- or 2-step reduction in dose (per investigator judgment, based on severity of reaction). If this further reduced dose is *assessed as tolerated*, the subject will continue at that dose level for daily home-dosing over the ensuing 2 weeks. If, however, the reduced dose is *assessed as not tolerated*, the subject is to be considered an escalation failure nonresponder.

If *mild symptoms* occur with the first dose at a new dose level and the dose is *assessed as tolerated*, the action taken should be to repeat the same dose the next day. It is advised that the repeat (next day's) dose be administered in the CRC, but it may be given at home, at the investigating physician's discretion. If the second dose at the new (increased) dose level is tolerated without symptoms, then the subject is to continue on that dose level for the requisite 2 weeks and return to the CRC for up-dosing at the next scheduled visit. If the dose again causes mild symptoms, but is *assessed as tolerated*, the subject may continue at that dose level or return to the last tolerated dose (at the investigator's discretion) and continue dosing at home for the next 2 weeks at the investigator-determined dose level. (**Section 6.7.5.2** for actions to be taken in the event that symptoms develop during home-dosing.) If, following the first dose at a new dose level, the second dose at the new (increased) dose level is again accompanied by mild symptoms, but is *assessed as not tolerated*, the procedures outlined in the paragraph above should be followed.

If *moderate symptoms* occur with the first dose at a new dose level, except for rare instances, the dose will be *assessed as not tolerated*. The action taken should be to have the subject return to the CRC the next day for dosing at the last tolerated dose under medical supervision. If this reduced dose elicits no allergic symptoms, ie, is well tolerated, the subject will continue on that daily home dose level for an additional 2 weeks. If the subject experiences mild symptoms at the reduced dose, the procedures for responding to a dose with mild symptoms should be followed (see above and **Figure 6-2**. If the subject experiences moderate symptoms at the reduced dose level, the subject should return to the CRC the next day and receive a further 1- or 2-step dose reduction (per investigator judgment). If this reduced dose is well tolerated, it will be continued as the daily home dose for at least 2 weeks before re-escalation is attempted in the CRC. If the dose is not well tolerated, but elicits mild symptoms, then the treatment procedures for responding to mild symptoms should be followed (see above, and **Figure 6-2**. If, however, the subject again experiences moderate symptoms at the reduced dose level, a discussion with the Medical Monitor is to ensue to reach a decision as to whether to continue the subject in the study.

In the rare instance that a dose eliciting moderate symptoms is *assessed as tolerated*, then the actions taken should be the same as for a dose with mild symptoms *assessed as tolerated* (see above).

If *severe symptoms* occur, the action should be to treat the subject for the allergic reaction, and then, in consultation with the Medical Monitor, decide whether or not to discontinue the subject from the study. If it is determined that it is safe to allow the subject to continue in the study, the

subject should return to the CRC the next day for dosing at a 2-step reduction in dose under observation. If the subject tolerates the dose reduction (ie, shows no or only mild symptoms that are assessed as tolerated), then the subject is to remain at the reduced dose level for at least 2 weeks before returning to the CRC to attempt dose re-escalation. If the subject does not tolerate the reduced dose, then the subject is to be considered an escalation failure nonresponder.

For specific questions related to dose-escalation or continuation of the same dose that are not answered in the above protocol, the Medical Monitor will be available for consultation.

6.7.5.2 Reactions to Dosing at Home

With the occurrence of symptoms of an acute reaction to study product after home-dosing, or any acute allergic reaction, subjects/parents or guardians are instructed to call the study site. The investigator must then determine whether or not the dose was tolerated (**Section 6.7.3**). Because of the reduced reliability inherent in the second-hand reporting of symptoms, investigators are strongly encouraged to have subjects return to the clinic to undergo dosing under direct observation whenever acute allergic symptoms associated with dosing are reported.

When symptoms of a dose-related allergic reaction are reported during the course of daily home-dosing, the investigator must assess the severity of the reaction and whether the dose associated with the reaction was tolerated. The appropriate intervention will depend on the type and severity of symptoms (**Section 6.7.5.2** and **Figure 6-2**).

In general, moderate or severe symptoms will be considered clinically significant, and any dose eliciting such symptoms *assessed as not tolerated*; however, mild symptoms may also be considered clinically significant, eg, if affecting multiple organ systems, increasing in intensity, occurring with increasing frequency, or affecting a larger area over time, and *assessed as not tolerated*. Whenever there is question as to the clinical significance of mild signs or symptoms, the investigator should have the subject return to the CRC for observed dosing under medical supervision.

For home-doses *assessed as not tolerated* on the basis of acute dose-related symptoms, the same procedures described in **Section 6.7.5**, above, for adjusting up-dosing should be followed.

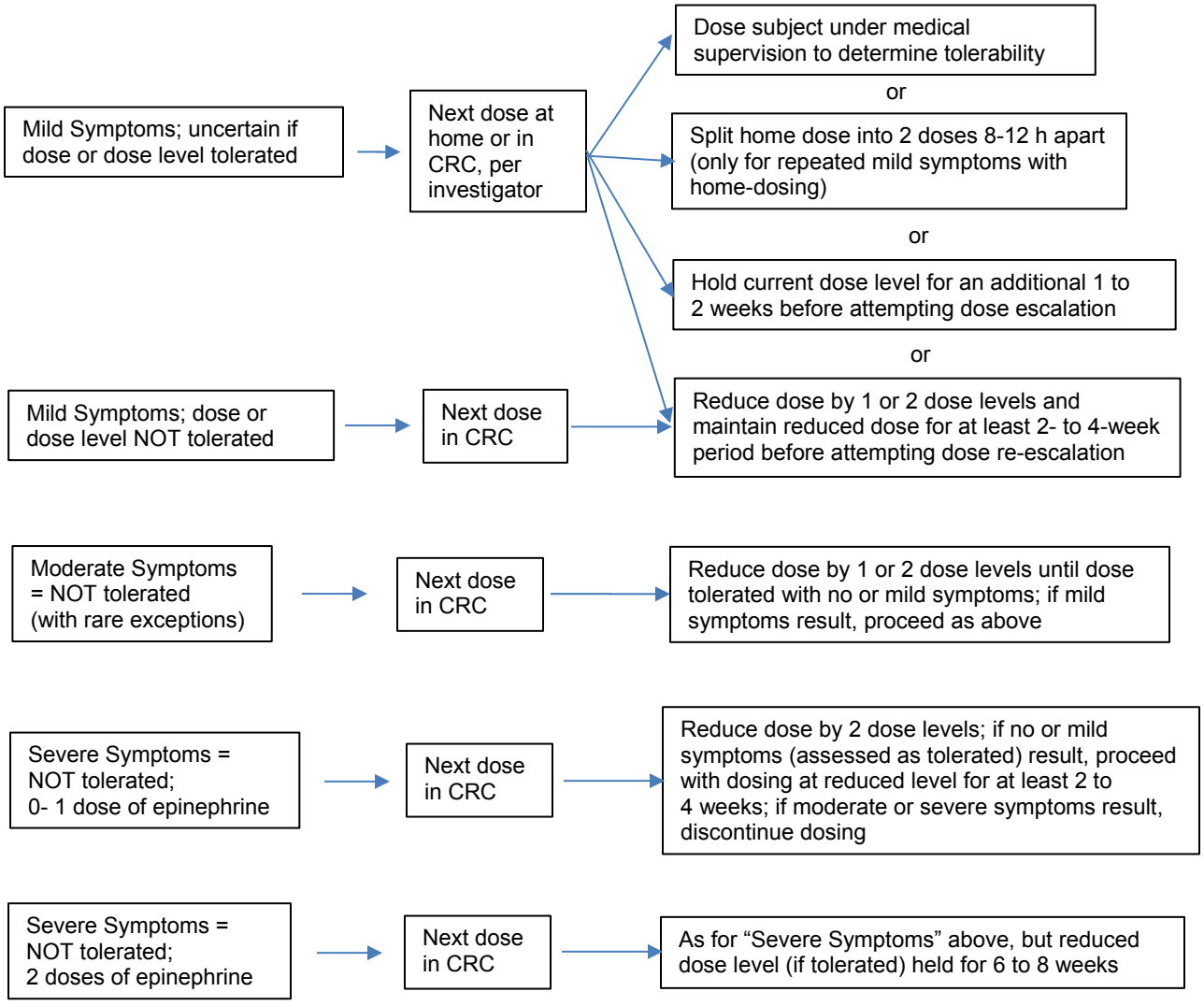
The recurrence of mild symptoms over the course of several days of home-dosing should suggest that the dose level is not tolerated, even if each individual occurrence of symptoms could be assessed as tolerated on the basis of the criteria listed above. In this circumstance, investigator judgment will be required to determine the best course of action with the possible actions being the following:

- Continue with daily home dosing at the current dose level
- Continue the same daily dose for the rest of the 2-week interval, with the dose split into 2 fractional doses given 8 to 12 hours apart (the 2 fractional doses need not be equal)
- Return to the CRC for repeat dosing at the current dose level under direct observation to confirm whether or not the dose level is tolerated

- Return to the CRC for dosing of a previously tolerated dose level, either a 1- or 2-step reduction (per investigator judgment, based on severity of reaction) and follow the procedures described in **Section 6.7.5.2** above
- Institute the 4-week hiatus from dosing, with resumption of dosing at the 3 mg/d dose level, as permitted for recurrent GI symptoms occurring at or before the 20 mg, as described in **Section 6.7.3.2**.
- Discontinuation of dosing

Any subject who discontinues build-up dosing due to severe or repeated allergic reactions to study product should have his/her mechanistic blood draw and CBC **(Section 8)** at, or as nearly as possible to, the time of the last dose and no later than at their Early Discontinuation Visit.

Figure 6-2: Schematic for Up-dosing Period Dose Adjustment



6.7.5.3 Dose Adjustment in Response to Adverse Events

At the investigating physician's discretion, temporary dose reductions, ranging from a 1-step decrement (ie, to the previous dose) to approximately half of the current dose level (to the nearest feasible available whole dose), can be instituted as part of the treatment regimen for an intercurrent AE. Also, if a pattern of decreased tolerability of study product during menses is discerned, then a temporary dose reduction can be instituted during this time. Temporary dose reductions for intercurrent AEs may be instituted as follows:

- For dose reductions of ≤ 4 consecutive days, whether dose re-escalation is to occur at home or in the CRC is at the investigator's discretion. If the reduction in dose is maintained for ≤ 4 consecutive days, then the prereduction dose level may be resumed, with the biweekly escalation schedule kept unaltered.
- If a reduction in dose is maintained for 5 to 7 consecutive days, then the subject is to return to the CRC to undergo dosing under medical supervision. At the investigator's discretion, the prereduction dose level may be resumed or dosing may continue at the reduced dose level. The biweekly escalation should be reset so that the subject receives at least 2 consecutive weeks of treatment at the dose level assigned (either the reduced or the prereduction dose level).
- If a reduction in dose is maintained for 8 to 14 consecutive days, then the next escalation attempted must be conducted in the clinic, and it should only be to 1 dose level above the reduced dose. If the escalation is successful, the subject should continue home-dosing for a minimum of 2 weeks, with his or her biweekly escalation schedule reset as necessary.

Doses of study product may also be withheld at the investigator's discretion, in response to an intercurrent AE. Doses withheld as part of the treatment for an AE constitute a special category of missed peanut OIT doses (**Section 6.8**).

6.7.6 Treatment for Reactions During the Up-dosing Period: Pharmacological and Supportive Treatments

Treatment of acute reactions should be with either an antihistamine and/or epinephrine, along with IV fluids, a beta-agonist (eg, albuterol, by inhaler or nebulizer), oxygen, and/or glucocorticosteroids, as indicated.

Many mild acute allergic reactions can be transient and self-limiting, requiring no therapeutic intervention. Others, however, may require treatment. Generally, for mild symptoms requiring treatment, the subject should receive antihistamines.

Acute allergic reactions manifesting with moderate symptoms will generally require therapeutic intervention, although some, even moderate, symptoms may on rare occasion be so transient as to require no specific treatment. Generally, for moderate symptoms requiring treatment, the subjects should receive antihistamines and/or epinephrine, as indicated. If there is uncertainty as to the severity of the reaction, administering epinephrine would be considered the most appropriate course of action.

Generally, severe symptoms will require treatment with epinephrine at a minimum. If severe symptoms that qualify as stage 3 anaphylaxis (defined in **Appendix 3)** occur at any time, dosing with study product will stop and the subject will be discontinued from the study as an escalation failure nonresponder.

Antihistamines

If a subject receives antihistamines only, the dose escalation can be continued. If symptoms during a build-up day require administration of more than 2 doses of an antihistamine or of an antihistamine in combination with other medications (except epinephrine), there should be a dose reduction of 1 or 2 dose levels, with the next dose given in the CRC. If epinephrine is administered, then a different course of action is to be taken (see below).

Epinephrine - General

Any reaction to study product (in clinic or at home) that requires more than two doses of epinephrine will halt all further dosing of study product for the individual. The subject will be asked to return to the CRC 14 days following the last dose of study product to undergo an Early Discontinuation Visit (**Section 6.5**).

Epinephrine - Clinic

If a single administration of epinephrine is required during, or after, a dose-escalation in the clinic, no further dosing of study product is to occur at that visit. The next dose of study product is to be reduced by two dose levels and administered in the CRC, but biweekly dose escalation should continue.

If a single administration of epinephrine is required a second consecutive time during, or after, 1 escalation attempt, the dose should be reduced by two dose levels, and the subject continued at that dose level for 6 to 8 weeks. After 6 to 8 weeks at the reduced dose, an escalation attempt may be tried in clinic.

If a single administration of epinephrine is required a third consecutive time during an escalation attempt, no further dosing should be attempted. Dosing in these subjects will be discontinued. They will be asked to return to the CRC 14 days following their last dose of study product to undergo an Early Discontinuation Visit (**Section 6.5**).

Epinephrine - Home

If a single administration of epinephrine is given during dosing at home, this epinephrine use is not counted as 1 of the uses described above, unless severe anaphylaxis is assessed to have occurred at home. Administration of epinephrine outside of the clinic should be followed immediately by the subject being taken to the nearest emergency department. The subject should return to clinic for an observed dose under medical supervision prior to resuming any dosing at home.

6.7.7 Reactions Occurring During the Maintenance Period

This phase consists of the subject receiving the 300 mg/d dose of study product for approximately 24 weeks. For any noted symptoms during the Maintenance Period, the same study product dosing guidelines and procedures will be followed as for the Up-dosing Period.

6.8 Missed Peanut OIT (Study Product) Doses during Up-dosing:

Missed doses of study product at any phase of the study can pose a significant risk to the enrolled subjects, but the risk is believed to be highest during the Up-dosing Period. The algorithm for missed consecutive doses of study product is as follows:

- Miss 1 dose – The next dose would be at the current dose level and could be given at home
- Miss 2 doses in a row – The next dose would be the current dose level and could be given at home
- Miss 3 doses in a row – The next dose would be the current dose and would be given under supervision in the CRC
- Miss 4 doses in a row – The next dose would be the current dose and would be given under supervision in the CRC
- Miss 5-7 doses in a row – Initiate the next dose at approximately 50% of the last tolerated dose (to the nearest feasible available whole dose that is ≤50% of the last tolerated dose). This dose is to be administered under supervision in the CRC. If tolerated, dose escalation may resume with dose increases of 1 dose level occurring no more frequently than weekly and generally no less frequently than every 4 weeks until the subject has returned to the dose level at which the lapse in dosing occurred. If symptoms occur, the dosing guidelines for the up-dosing period apply.
- Missing > 7 consecutive days of dosing due to non-compliance, ie, for any reason other than treatment of an AE or a study product dispensing error, constitutes an individual stopping rule and the subject is to stop taking study product. The subject will be considered an escalation failure nonresponder, and will be asked to return to the CRC 14 days following their last dose of study product to undergo an Early Discontinuation Visit (**Section 6.5**).
- Additionally, excessive missed dosing, defined as 3 consecutive days of missed doses on 3 occasions during the Up-dosing Period or on 3 occasions during the Maintenance Period, for any reason other than treatment of an AE, constitutes an individual stopping rule and the subject is to stop taking study product. The subject will be considered an escalation failure nonresponder, and will be asked to return to the CRC 14 days following their last dose of study product to undergo an Early Discontinuation Visit (**Section 6.5**).
- If study product has been withheld for 8 to 14 consecutive days as treatment for an AE or due to a study product dispensing error, dosing may be reinitiated at approximately 25% of the last tolerated dose (to the nearest feasible available whole dose that is ≤ 25% of the last tolerated dose) if the lapse in dosing occurred during the Up-dosing Period. If the lapse in dosing occurred during the Maintenance Period, dosing may, at the investigator's discretion, be reinitiated at 50% of the last tolerated dose (to the nearest feasible available

whole dose that is ≤ 50% of the last tolerated dose). The reduced dose is to be administered under supervision in the CRC. If tolerated, dose escalation may resume with dose increases of 1 dose level occurring no more frequently than weekly and no less frequently than every 4 weeks until the subject has returned to the dose level at which the lapse in dosing occurred. If symptoms occur, the dosing guidelines for the Up-dosing period apply.

- If study product has been withheld for ≥ 15 consecutive days for any reason, at any point in the study (with the exception of a dosing hiatus instituted for chronic/recurrent GI AEs at or before the 20 mg dose level, as per **Section 6.7.3.2**), the subject will be considered an escalation failure nonresponder, and will be asked to return to the CRC 14 days following their last dose of study product to undergo an Early Discontinuation Visit (**Section 6.5**).

No attempt should be made to make up for a missed dose if greater than 6 hours have elapsed since usual time of dosing.

6.9 Skin Prick Test

Subjects will have skin prick tests performed using investigational site- and sponsor-approved procedures for food allergens. Detailed instructions for performance of the SPT will be provided in a manual of operating procedures. In brief, while the subject is off antihistamines for an appropriate length of time (5 half-lives of the antihistamine that is being used), a skin test probe is pressed through a commercial peanut allergen extract into the epidermis. Positive (histamine) and negative (saline-glycerin) controls are placed to establish that the response is not blocked and to determine if there is dermatographism, respectively.

6.10 Assessment of Asthma Control Using the Asthma Control Test Questionnaire

Subject or subject and parental assessment of asthma control will be performed at the specified visits using the Asthma Control Test questionnaire for subjects with asthma.

6.11 Visit Windows

Dosing schedule should be adhered to strictly. Two days before, or 2 days after a planned dosing visit, is an acceptable window with continued daily dosing of the current dose level. Study visits for scheduled blood draws or DBPCFC should take place within 2 weeks of the scheduled visit.

Early Discontinuations Visits are to occur 14 days after the last dose of study product. The permissible window is minus 3 days to plus 7 days.

6.12 Study Blinding Procedures

This is a double-blind study. The study as a whole will not be unblinded until after the last subject exits ARC003 and the database is locked.

After undergoing the Exit DBPCFC, most subjects will, however, become de facto unblinded to their on-study treatment assignment on the basis of their experience with the food challenge; ie, subjects who fail 1 part of the Exit DBPCFC early on may reasonably deduce that they had been in the placebo arm of the study, and those who tolerate both parts of the Exit DBPCFC (or fail

1 part only at the highest dose levels tested) may reasonably deduce that they had been in the AR101 arm. Hence, the study is double-blinded on an individual subject basis only up to completion of the Exit DBPCFC. It is for this reason that assessment of reactions to DBPCFC will be made by a Blinded Evaluating Physician (Blinded Assessor).

Although the unblinding of subjects after completion of the Exit DBPCFC cannot influence the manner in which they are assessed or treated by the investigational site personnel (as their participation in ARC003 will have concluded at that time), knowledge of subjects' treatment assignments could potentially influence the investigational site personnel's conduct toward other subjects who have not yet reached the conclusion of the study. The risk of bias being introduced into the determination of DLSs during DBPCFCs due to knowledge of the treatment assignments of other subjects will be substantially reduced by having the assessment of the DBPCFC results made by a Blinded Evaluating Physician (Blinded Assessor) who is not otherwise directly involved with the treatment of the subjects he or she is evaluating. Additionally, the duration of the study and the anticipated rate of recruitment are such that that enrollment should not be influenced by the Exit DBPCFC, as enrollment should be completed before the first subjects exits the study.

Additionally, to ensure that allocation of subjects to their appropriate analysis populations is not biased by knowledge of their treatment assignments, specific masking procedures have been put in place to shield study team members who could be involved in determining allocation of the subjects to the analysis populations from knowing subject treatment assignments (refer to Masking Plan). To further ensure that allocation of subjects to their appropriate analysis populations is performed in an unbiased way, subjects will not be informed of their on-study treatment assignments or rollover into the open-label follow-on study, ARC004, until all major data queries, ie queries that could influence allocation to 1 or another analysis population, have been resolved (as detailed in the Masking Plan), regulatory and IRB/EC approval for ARC004 have been received, and IP for ARC004 is available.

Those subjects who are not eligible for the DBPCFC at Week 68 of their projected up-dosing schedule, may be unblinded at this time (their projected study Week 68) or when the last subject completes the Exit DBPCFC, provided all major data queries for the subject have been resolved.

6.12.1 Securing Blinding and Randomization Information

Aimmune or one or more of its contractors will manufacture, package, label, store, and distribute the study products. During site visits, the site monitor will check the clinic and/or pharmacy logs to ensure that appropriate randomization assignments are received, recorded, and maintained.

6.12.2 Requirements for an Unblinding

Prior to the Exit DBPCFC assessment, a subject can be unblinded only when needed for making medical decisions regarding the care of a subject. The decision to unblind should, if at all possible, be made in collaboration with the sponsor's Medical Monitor. If a life-threatening event occurs, the subject should be treated as if the subject received active study product. For all unscheduled non-life-threatening events that require unblinding, the investigator will contact the clinical monitor who will coordinate with the sponsor's representatives.

6.12.3 Breaking the Blind

Site personnel or other study team members (such as a Medical Monitor) may request emergency unblinding as described above. If it is specifically necessary to provide a treatment assignment to the Sponsor, this information will be provided to a Medical Monitor and/or Clinical Operations Designee.

In case emergency unblinding is necessary, the interactive response system allows study personnel with appropriate permissions to request unblinding for a specific subject. An automated notification is then sent to the sponsor and the sponsor's safety designees to inform them of the unblinding. A built-in audit trail documents the unblinding process and the persons involved.

6.12.4 Documenting and Unblinding

Any premature unblinding requires a full written account by the site study physician of the event(s) that necessitated unblinding of the study medication for an individual participant. This account includes the reason(s) for unblinding, the name of the sponsor's medical monitor who was notified of the unblinding, the names of the unblinded individual staff members and the date and time the unblinding occurred. The treatment assignment is confidential and should not be provided to blinded team members, as detailed in the Masking Plan.

7 SAFETY MONITORING

This section defines the types of adverse events that should be reported and outlines the procedures for appropriately collecting, grading, recording, and reporting them.

7.1 Definitions for Recording of Safety Events

All safety events observed under this protocol are reported through the electronic data capture system for the duration of the study. Some safety events arising under certain defined conditions are recorded on specific forms as follows.

- Any allergic symptoms observed during in-clinic dosing will be recorded directly on the Escalation / In-Clinic Dosing form (also referred to as a Study Product Administration form), and are not recorded on an adverse event form (to avoid duplicate reporting) unless the event is considered a serious adverse event. These symptoms are, however, by definition, adverse events (**Section 7.2**) and will be reported as such in the database.
- Safety events related to accidental food exposure are recorded on an Accidental Food Exposure form. They are not to be reported on an adverse event form (to avoid duplicate reporting) unless the event is considered a serious adverse event, as defined below (**Section 7.3** and **Section 7.4.2**).
- For any event occurring after a subject has signed the informed consent form that meets the definition of anaphylaxis, an Anaphylaxis Episode form will be completed and forwarded to the CRO's Reporting Center within 24 hours of its occurrence and/or the site's being notified of the event (**Section 7.7.2**), if the event is associated with any of the following:
    - An emergency room visit;

  - Hospitalization;
  - More than 2 doses of epinephrine being given as treatment for the same episode;
  - Assessment of the anaphylaxis as severe, as defined in **Appendix 3**.
- If any safety event meets the definition of a serious adverse event (whether or not related to dosing), it will also be recorded on an adverse event (AE)/serious adverse event (SAE) form.
- Skin prick test reactions are not considered adverse events unless the reaction, or a complication from the procedure, is considered a serious adverse event, as defined below (**Section 7.4.2**).
- Food challenge reactions that occur in the clinic are captured on study specific forms and are not reported on an adverse event form (to avoid duplicate reporting) unless the event is considered a serious adverse event, as defined below (**Section 7.4.2**).
  - As study product is not used in the DBPCFCs, no AEs occurring from Screening DBPCFC can be treatment-related (referring to treatment with study product).
  - For food challenge reactions that occur at the Exit DBPCFC, it will also usually be the case that study product was not the cause of the reaction, as study product is not used in the challenge. There is, however the possibility that dosing with study product in the days prior to Exit DBPCFC could contribute to a reaction encountered during the challenge. The investigator must determine if dosing with study product in the days prior to Exit DBPCFC likely contributed to any observed reaction. If so, the investigator should indicate the level of the relatedness, and provide a brief explanation as to the manner in which prior dosing with study product was thought to be contributory.
- All serious adverse events are reported on the AE/SAE form set in addition to the Skin Prick form or an Oral Food Challenge form if the event occurred during 1 of these procedures. All other safety events that occur throughout the study are reported on the AE/SAE form set.

7.2 Dosing Symptoms as Adverse Events

Although signs and symptoms of allergic reaction, especially those that are mild in severity, are frequent and expected occurrences in response to dose escalation during OIT, they still constitute AEs. As such, the start and stop times of dose-related allergic reactions, as well as any therapeutic interventions, and relatedness to study product will need to be recorded **(Section 7.7.1)**.

It is common for allergic reactions, especially allergic reactions to food allergens, to manifest with multiple symptoms. Investigator sites will record each individual symptom as an AE and indicate the symptom is part of an allergic reaction by checking the “allergic reaction” box on the AE form.

7.3 Accidental Food Exposures

In order to report the occurrence of a safety event associated with accidental food ingestion, subjects will be instructed to contact the site study coordinator or investigator for any adverse event. The subject may be asked to return to the site. These events will be reported as follows:

- Accidental Food Exposure form will be completed for each of these events in addition to events where consumption of peanut without a reaction occurs.
- If the accidental food ingestion safety event meets the definition of a serious adverse event, as defined below (**Section 7.4.2**), the AE/SAE form will be completed as well.

7.4 Definitions

7.4.1 Adverse Event (AE) or Medical Event

An **adverse event** is any untoward medical occurrence in humans, whether or not considered drug related which occurs during the conduct of a clinical trial. Any change in clinical status, ECGs, routine labs, x-rays, physical examinations, etc., that is considered clinically significant by the study investigator is considered an AE.

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. A reasonable possibility implies that there is evidence that the drug caused the event.

Adverse reaction is any adverse event caused by the drug.

7.4.2 Serious Events (Serious Adverse Events, Serious Suspected Adverse Reactions or Serious Adverse Reactions)

A serious adverse event including a serious suspected adverse reaction or serious adverse reaction as determined by the investigator or the sponsor is any event that results in any of the following outcomes:

1. Death
2. Life-threatening AE (Life-threatening means that the study subject was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred.)
3. Inpatient hospitalization or prolongation of existing hospitalization
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. Congenital abnormality or birth defect
6. Important medical event that may not result in 1 of the above outcomes, but may jeopardize the health of the study subject or require medical or surgical intervention to prevent 1 of the outcomes listed in the above definition of serious event.

It is anticipated that the most likely cause of SAEs in this study will be anaphylaxis; however, not all occurrences of anaphylaxis are necessarily SAEs. Guidance for determining when anaphylaxis should be reported as an SAE is provided in **Appendix 5**.

7.4.3 AEs of Special Interest

7.4.3.1 Anaphylaxis

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

With respect to the inclusion of being "potentially life-threatening" in the definition of anaphylaxis and how that relates to the assessment of anaphylaxis as an SAE, reference is made to the 2012 FDA Guidance for Industry and Investigators, "Safety Reporting Requirements for INDs and BA/BE Studies," that states, "An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death." Thus, for the reporting of anaphylaxis as an SAE, the severity of the reaction, assessed according to the EAACI system for grading the severity of anaphylactic reactions (Muraro et al., 2007), is also to be taken into account (**Section 7.6** and **Appendix 5**).

When the diagnosis of anaphylaxis is made, the basis for having suspected the diagnosis must be documented, using the criteria established by the Second Symposium on the Definition and Management of Anaphylaxis (Sampson et al., 2006) (**Appendix 3**). These criteria were again affirmed in the recently published "International consensus on (ICON) anaphylaxis" (Simons et al., 2014).

7.4.3.2 Gastrointestinal Adverse Events Resulting in Prolonged Disruption of Dosing

Gastrointestinal AEs, typically chronic/recurrent GI AEs, that result in a prolonged disruption of dosing will be considered AEs of special interest and will be assessed longitudinally according to the procedures described below. For the purpose of delineating these AEs of special interest, prolonged disruption of dosing is defined as withholding study product 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 (**Section 6.7**)
- 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 (**Section 6.7.3.2**);
- Any subject who permanently discontinues dosing who had experienced GI AEs (**Section 4.3.2**).

Subjects under the age of 18 years who fall into any of these 3 categories will be asked to fill out the PEESS™ v2.0 questionnaire (Franciosi et al., 2011), with the assistance of a parent or guardian, as appropriate, every month for 6 months; adults will be given the same questionnaire. It should, however, be noted that the PEESS™ v2.0 was not designed to establish a diagnosis of EoE, and has not been validated for use in patients with GI symptoms of other etiologies. Furthermore, the discriminant validity of the questionnaire has not been reported in either longitudinal natural history or interventional studies. For these reasons, the use of the PEESS™ v2.0 to monitor the clinical course of GI symptoms must be considered exploratory. Nevertheless, the PEESS™ v2.0 has shown good content and construct validity (Franciosi et al., 2011; Martin et al., 2015) and so holds promise for being a valuable tool to follow the clinical course of EoE or an EoE-like immune-mediated GI syndrome. Thus, the PEESS™ v2.0, could reveal trends toward symptomatic improvement or worsening that might otherwise go undetected.

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

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

If a subject who discontinued dosing with the investigational product prematurely due to chronic/recurrent GI AEs is unable to discontinue the use of symptomatic therapies that may have been initiated to treat the GI AEs (eg, H1 or H2 histamine blockers or proton pump inhibitors) by 12 weeks from the time that study product was withdrawn, the subject should be referred to a (pediatric) gastroenterologist.

As is the case for any AE occurring during the study, so it is for chronic/recurrent GI AEs that the investigator may, at any time, and at his or her discretion, request consultation from an outside physician or additional testing to assist in the diagnosis or management of the AE.

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

Subjects signing the optional consent to participate in the saliva substudy **(North America sites only)** will provide a saliva sample as close as possible to the time that they complete the first PEESS™ v2.0 questionnaire, and another saliva sample at the end of their post-OIT follow up period.

7.4.4 Unexpected Adverse Event

An adverse event is "unexpected" when its nature (specificity) or severity is not consistent with applicable product information, such as safety information provided in the package insert, the investigational plan, the investigator's brochure or the protocol.

7.5 Adverse Event Monitoring

7.5.1 Data Safety Monitoring Committee

Although the safety of peanut OIT overall is well established, a Data Safety Monitoring Committee (DSMC) will monitor the study for safety. The DSMC will meet periodically to review accruing safety data. The committee will consist of individuals with extensive multi-center clinical study experience drawn from the fields of clinical immunology (specifically food allergies) and biostatistics. These individuals will be entirely independent of the conduct of the study. Further details will be provided in the DSMC Charter.

7.5.2 Adjudication Committee

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

7.6 Severity Grading

The investigator is to assign severity grades to adverse events (AEs). Depending on the type of AE, different severity grading systems will be used in this study.

- The severity grading of allergic reactions will be according to the definitions developed the CoFAR group **(Appendix 4)**.
- The severity of anaphylactic reactions will be graded according to the EAACI system for grading the severity of anaphylactic reactions **(Appendix 3)**.
- For grading the severity of all other AEs, the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) system will be used. The purpose of using the NCI-CTCAE system is to provide standard language to describe AEs ("toxicities") and to facilitate tabulation and analysis of the data and for assessment of the clinical significance of treatment-related toxicities. The NCI-CTCAE provides a term and a grade that closely describes the adverse event. Each participating site will receive copies of the grading scales and event descriptions. For additional information and a printable version of the NCI-CTCAE v. 4.03 manual, consult the NCI-CTCAE website, http://ctep.cancer.gov/reporting/ctc.html.

For adverse events not included in the NCI-CTCAE listing, they are also to be graded on a scale from 1 to 5, according to the General Grade Definition provided below:

Grade 1	Mild	Transient or mild discomforts (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, eg, aspirin for simple headache, acetaminophen for post-surgical pain).
Grade 2	Moderate	Mild to moderate limitation in activity, some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.
Grade 4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical/therapy intervention required, hospitalization, or hospice care probable.
Grade 5	Death	Death

For additional information and a printable version of the NCI-CTCAE v. 4.03 manual, consult the NCI-CTCAE website, http://ctep.cancer.gov/reporting/ctc.html.

7.6.1 Guidelines for Determining Causality of an Adverse Event

The investigator will use the following question when assessing causality of an adverse event to study product: Is there a reasonable possibility that the study product caused the event?

An affirmative answer designates the event as a suspected adverse reaction.

7.7 Adverse Event Collection Procedures

Any new event or experience that was not present at Screening, or worsening of an event present at Screening, is considered to be an AE. Unchanged, chronic conditions are not AE's and should not be recorded on the AE page of the CRF. Adverse events will be evaluated from the onset of the event until the time the event is resolved or medically stable, or until 44 days after the subject completes study treatment, whichever comes first. Adverse events ongoing at the time that study treatment is discontinued may not be determined to be medically stable until 30 days after the Exit or Early Discontinuation Visit has been conducted, in which case additional visits after the Exit or Early Discontinuation Visit will be required. Investigators should also report AEs discovered after cessation of dosing and prior to the Early Discontinuation.

AEs may be discovered through any of these methods:

- Observing the subject
- Questioning the subject, which should be done in an objective manner
- Receiving an unsolicited complaint from the subject
- Review of medical records/source documents
- Review of home dosing symptom logs (provided to record symptoms between visits)

7.7.1 Recording and Reporting Procedures

A multi-screen adverse event eCRF will be used allowing all adverse events to be submitted through a single reporting mechanism. Serious adverse events will require additional information reported on additional screens within the electronic data capture (EDC) system. Source documents, with subject identifiers redacted, can be scanned and attached to the adverse event form as well. The investigator will treat subjects experiencing adverse events appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

7.7.2 SAE Recording and Reporting Procedures

Serious adverse events will be recorded on the adverse event case report form (CRF). All centers are obligated to report SAEs within 24 hours of their occurrence and/or the site's knowledge of the event to the Reporting Center. The following attributes will be assigned:

- Description
- Date of onset and resolution (if known when reported)
- Severity
- Assessment of relatedness to test article
- Action taken

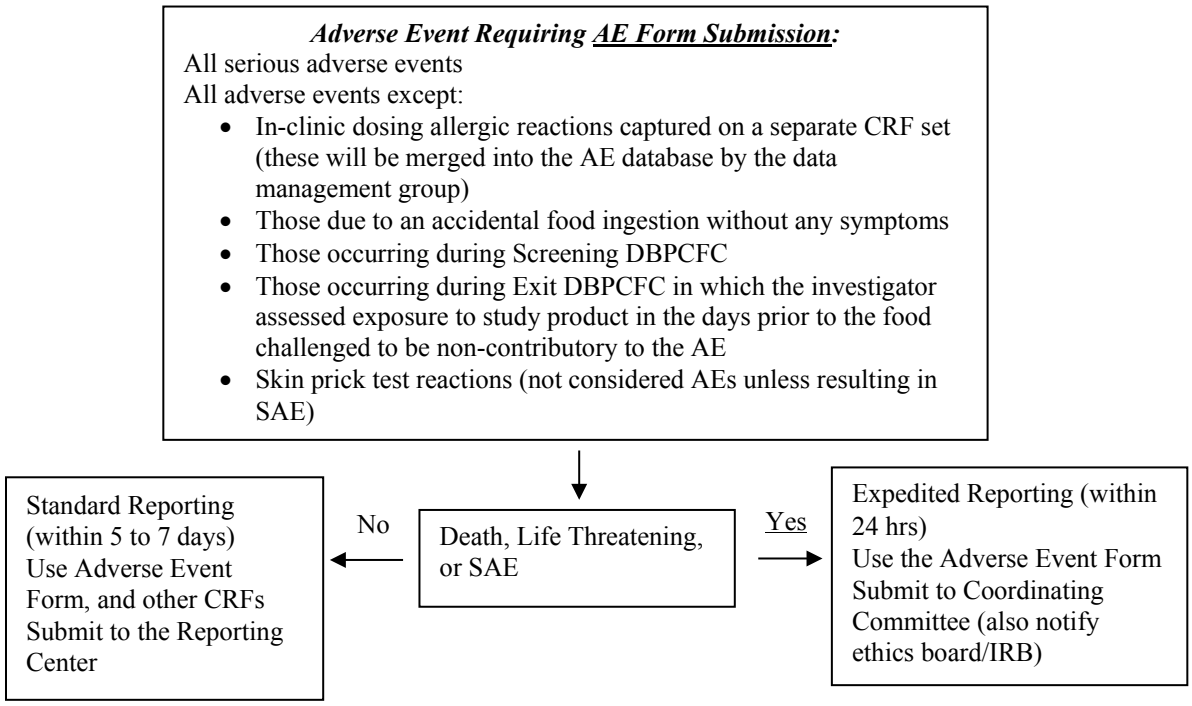
The site investigator will apply his/her clinical judgment to determine whether an adverse event is of sufficient severity to require that the subject be removed from treatment. If necessary, an investigator will suspend any trial procedures and institute the necessary medical therapy to protect a subject from any immediate danger.

Subsequent review by regulatory health authority(ies), the DSMC, IRB/EC, or the sponsor(s) may suspend further trial treatment or procedures at a site. The study sponsor(s) and the regulatory health authorities retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

A subject may voluntarily withdraw from treatment due to what he/she perceives as an intolerable AE, or for any other reason. If voluntary withdrawal is requested, the subject should be asked to continue (at least limited) scheduled evaluations, complete a study termination form, and be given appropriate care under medical supervision until the symptoms of any AE resolve or their condition becomes stable.

7.7.2.1 Reporting Criteria

Figure 7-1: Reporting Decisions for Adverse Events



1. Notify the site's investigator.
2. Complete and transmit an AE Form through the Internet data entry system. Information regarding a SAE report must be recorded in the subject's medical chart.
3. SAE follow-up reports should include hospital admittance notes, hospital discharge summary, clinical notes, resolution date, treatment and any other pertinent information regarding the event. Reporting should not be delayed in order to provide these documents.
4. In the event of a death, the SAE Form must be completed and transmitted along with other supporting data (eg, death certificate, medical notes, etc.).

7.8 Serious Adverse Event Notification

7.8.1 Notifying the Sponsor

Study investigators will provide the Reporting Center with data of all SAEs as defined per the protocol on an ongoing basis.

The CRO Medical Monitor is responsible for notifying the sponsor and will do so simultaneously with the reporting to the clinical database. As noted above, this should be within 24 hours of site awareness of the event.

7.8.2 Expedited SAEs Reporting to Regulatory Health Authorities and DSMC

The sponsor's Medical Monitor will review each SAE report and will determine whether the SAE must be reported to regulatory health authorities on an expedited basis. The final decision for disposition regarding expedited reporting to the regulatory health authorities rests with the sponsor's Medical Monitor. The Study Sponsor and Clinical Research Organization (CRO) will provide the DSMC and the Reporting Center with copies of any expedited SAE reports submitted to regulatory health authorities.

The Reporting Center will provide these expedited reports to the individual site investigators. Events that are serious, related to therapy, and unexpected will be reported to regulatory health authorities within 15 days or for deaths and life-threatening events within 7 days (as per applicable regulatory reporting requirements).

7.8.3 Notifying the Data Safety Monitoring Committee

The Reporting Center will provide the DSMC with listings of all SAEs on an ongoing basis. Furthermore, the DSMC will be informed of expedited reports of SAEs. Periodic reports from the DSMC as to the overall safety of the ongoing study, and recommendations regarding continuation will be sent to the investigators for forwarding to their IRBs/ECs if requested.

Investigational sites are instructed to report episodes of anaphylaxis within 24 hours of their occurrence and/or the sites being notified of the event to the Reporting Center for forwarding to the DMSC if the event is associated with any of the following:

- An emergency room visit;
- Hospitalization;
- More than 2 doses of epinephrine being given as treatment for the same episode;
- Assessment of the anaphylaxis as severe, as defined in **Appendix 3**.

An initial Anaphylaxis Episode form containing the information known to the site at this time will be transmitted to the Reporting Center. The Reporting Center will then relay to the sponsor and DSMC the individual anaphylaxis reports as they are obtained. The investigational site will supplement the initial Anaphylaxis Episode report with additional information pertaining to an event as it becomes available and will forward the information to the Reporting Center.

7.8.4 Notifying the Institutional Review Board and Ethics Committee

The investigator will ensure the timely dissemination of all AE information, including expedited reports and DSMC safety reviews, to the IRB in accordance with applicable local regulations and guidelines.

7.9 Other Safety Assessments and Precautions

7.9.1 Physical Examination and Vital Signs

Physical examinations will be conducted at visits indicated in **Appendix 1** Schedule of Events. Height and weight will also be recorded at specified visits. Vital signs will be measured, including blood pressure (BP), pulse rate (PR), and body temperature. Except where a full, age

appropriate, physical examination is specifically indicated, a symptom-directed physical exam may be performed.

7.9.2 Prior and Concomitant Medications

Prior and concomitant medications will be duly documented in the CRF.

7.9.3 Pregnancy Testing and Contraception

7.9.3.1 Pregnancy Testing

All female subjects of child-bearing age will undergo a serum pregnancy test at screening and then urine pregnancy test at subsequent visits.

7.9.3.2 Contraception

Subjects undergoing OIT are at increased risk for experiencing allergic reactions and may be at increased risk for experiencing anaphylaxis. Anaphylaxis can cause a dangerous drop in blood pressure; and if this were to occur during pregnancy, it could result in compromised placental perfusion and significant risk to the fetus.

Pregnancy is a time when the mother's immune system undergoes complex and incompletely understood changes that are believed to reduce the risk of a maternal immune reaction directed against the fetus. It is also a time when the fetus's immune system is developing. OIT, at its core, entails repeated stimulation of the immune system to affect changes in its makeup and function. What effects OIT-induced changes in the immune system might have on the course of pregnancy or fetal development are currently unknown. Accordingly, female subjects of child-bearing potential are required to practice effective birth control for the duration of the current study.

Female subjects are to use either:

- A highly effective method of birth control, defined as 1 that results in a low failure rate (ie, less than 1 percent per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices (IUDs), sexual abstinence, or a vasectomized partner; or
- Alternatively, if a highly effective method of birth control is not used, an effective, double barrier method of contraception (eg, male condom with female condom, cervical cap, diaphragm, or contraceptive sponge) may be used.

7.10 Stopping Rules

7.10.1 Overall Stopping Rules

The study will be suspended at any time if a treatment-associated death occurs in a subject on active therapy, or that the second of two subjects is admitted to the hospital, within 6 months of the first, as a direct consequence of dosing with study product. Suspension of the study will entail halting the enrollment of subjects and refraining from any dose increases, but will not entail cessation of dosing unless so directed by the FDA or other regulatory agency, or advised by the DSMC and agreed to by the sponsor. The suspension will not be lifted and dose escalation will not be resumed until the information has been discussed with regulatory authorities and the

regulatory authorities either concur with resumption of up-dosing or direct discontinuation of the study in their jurisdictions.

The DSMC will also be continually reviewing safety data, and can also recommend, in its judgment, halting the study for any substantial imbalance in adverse events, apart from anticipated allergic dosing symptoms.

Aimmune Therapeutics additionally reserves the right to discontinue the study at any time for any reason. The regulatory health authority(ies) and IRBs/ECs will be notified in the event of study discontinuation.

7.10.2 Individual Stopping Rules

Individuals may stop the study at any time if they experience subjectively intolerable adverse events or dosing symptoms. They must halt up-dosing and re-start with a reduced dose if more than 3 days of dosing are missed. Seven or more consecutive days of missed dosing due to non-compliance constitutes an individual stopping rule, as does a significant number of episodes of missed dosing (ie, 3 or more consecutive days on at least 3 occasions) during the Up-dosing Period. Missing 15 or more consecutive days of dosing for any reason also constitutes an individual stopping rule. For additional individual stopping rules, the reader is referred back to **Section 4.3.1**.

Occurrence of any of the following will result in the cessation of dosing and the subject being discontinued from the study as an escalation failure nonresponder:

- Failure to accomplish up-dosing of study product after 3 attempts
- Failure to identify a tolerated dose of study product after 3 attempts at dose reduction
- Administration of 3 or more doses of epinephrine for the treatment of any dose-related allergic reaction.

8 MECHANISTIC ASSAYS

Assays will be performed to measure humoral (immunoglobulin; antibody) immune responses at Screening/Baseline, at the end of the Up-dosing Period, and at the Exit or Early Discontinuation visit. The blood samples for these serum-based assays can and should be collected with the same blood draw as the CBC. This is mandatory blood draw is to be performed at Screening, the End of Up-dosing / Start of Maintenance Period Visit, and the Exit Visit.

Additionally, subjects will be asked to participate in an optional substudy to characterize cellular immune responses in allergy. The characterization of immune cells, including lymphocytes and basophils, based on their surface markers and responses to in vitro stimulation, performed by the Immune Tolerance Network (ITN) and consequently will require an additional consent/assent form to be signed.

8.1 Peanut-Specific Antibody (Immunoglobulin) Assays

Antigen immunotherapy has been shown to induce antigen-specific humoral responses. The balance of isotypic response may play a role in allergen sensitivity (eg, an increase of IgG / IgE).

The blood sample for antibody analysis should be collected with the same blood draw as the CBC. Collection of a sample for antibody analysis, like the CBC, is mandatory.

At each of the specified points, a sample of serum will be stored for assessment of peanut specific antibody levels (immunoglobulin assays). Total IgE and specific IgE and IgG4 will be measured using UniCAP™. Peanut specific IgE and IgG4 (included in the immunoglobulin assays) will be measured at Screening/Baseline, the end of the Up-dosing Period, and the Exit/Early Discontinuation visit. Additionally, as part of the Screening/Baseline immunoglobulin assays, component-resolved (Ara h1, Ara h2, Ara h3, Ara h8, and Ara h9) peanut IgE testing will be performed. The amount of blood to be drawn will be determined on the basis of the requirements of the test and individual laboratory protocols, in compliance with local regulations.

8.2 Optional Immune Cell Characterization

This exploratory characterization of the mechanism of action of OIT at the cellular level will be conducted by the Immune Tolerance Network (ITN). Immune cells, including lymphocytes, monocytes, and potentially basophils, and eosinophils, will be analyzed for their cell surface markers by flow cytometry. Additionally, in vitro stimulation of lymphocytes and potentially basophils, or other immune cell types will be performed.

8.2.1 Optional Additional Blood Volume

Subjects who consent to participate in the optional substudy to characterize immune cell responses, conducted by the ITN, will have an additional volume of blood collected at the same time as the immunoglobulin assay blood draws (**Section 8.1**; full procedures will be provided in the manual of procedures). Participation in the substudy to characterize immune cell responses does not require an additional venipuncture.

8.2.2 Optional Post-DBPCFC Blood Draws

Additionally, subjects will be given the option to volunteer for to characterize immune cell changes following an allergic reaction, the optional post-DBPCFC blood draw. Participation would require 2 additional venipunctures, 1 after the Screening DBPCFC and 1 after the Exit DBPCFC (the blood draw after the Exit DBPCFC will be included in the ARC004 protocol). The same types of in vitro assays will be performed on these samples as will be performed in the immune cell characterization substudy, but on cells collected after a controlled allergic challenge. Because participation requires 2 additional blood draws, separate informed consent is required.

8.3 Optional Oral Biomarker Substudy

Subjects will also be given the option to participate in a companion substudy to examine the relationship between food allergy and other gastrointestinal disorders. The study, coordinated by researchers at Cincinnati Children's Hospital Medical Center, will involve the collection of saliva to measure gene expression products (including ribonucleic acids) that may reflect susceptibility to eosinophilic esophagitis or other potentially IgE-related GI diseases. This substudy will require subjects/parents to undergo a separate informed consent (and assent, as age appropriate) process.

9 STATISTICAL CONSIDERATIONS

This section outlines the major statistical consideration for the ARC003 study, a randomized evaluation of peanut OIT versus placebo therapy and baseline for individuals with peanut allergy. A comprehensive statistical analysis plan (SAP) will be finalized prior to the first subject undergoing Exit DBPCFC.

Data will be summarized descriptively by treatment arm and overall. The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include means, medians, standard deviations and minimum and maximum values.

All data will be listed for all subjects.

9.1 Analysis Populations

The ITT population (ie, the Full Analysis Set) will consist of all randomized subjects who received at least 1 dose of randomized study treatment. Subjects will be analyzed according to randomized treatment. The ITT population will be used as the primary analysis population for all analyses of efficacy endpoints.

The Completer population includes all subjects in the ITT population who complete treatment and have an evaluable Exit DBPCFC, where an evaluable Exit DBPCFC is defined as completion of at least the peanut part of the food challenge. Sensitivity analyses and supportive analyses of the primary endpoint, and key secondary endpoints, and other secondary endpoints will be performed using the Completer population. These supportive analyses are considered important because they will provide the basis for informing patients and their families of their chances of achieving a clinically relevant level of desensitization if Up-dosing and maintenance therapy are achieved.

The Per Protocol (PP) population will be a subset of the Completer population, limited to subjects who have no major protocol deviations that may influence the desensitization response. Additional criteria to exclude subjects from the PP population may be added. Any changes will be documented in a SAP amendment or other supporting document. Exclusions will be determined by blinded review before database lock and overall study unblinding. Subjects will be analyzed according to randomized treatment.

The Safety population will consist of all subjects who receive randomized study treatment. The Safety population will be used for summaries of safety parameters. Subjects will be analyzed according to treatment received.

The modified ITT (mITT) population will consist of all randomized subjects who received at least one dose of randomized study treatment and who have sufficient data to assess treatment success or failure for the primary efficacy endpoint. Subjects who withdraw early for reasons unrelated to treatment success or failure will be excluded as there are no data to suggest they are a treatment success or failure. Withdrawals for escalation failure, treatment-related AEs, and deaths will not be excluded and these will be counted as treatment failures. Exclusions will be determined by blinded review prior to database lock and overall study unblinding. Subjects will be analyzed according to randomized treatment. The mITT population may be used for

sensitivity analyses of the primary and key secondary endpoints if the mITT population differs from ITT population by > 5% in either treatment arm. Sensitivity analyses of selected endpoints may, however, be performed if the mITT population differs from the ITT population by ≤ 5% in both treatment arms.

The decision to conduct analyses in the mITT population and other subsets of the ITT population will be made before database lock and overall study unblinding.

9.2 Study Endpoint Assessment

9.2.1 Primary Endpoint

North America: The primary endpoint is the proportion of subjects aged 4 to 17 years who achieve desensitization as determined by tolerating a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC (ie, responders).

The primary efficacy analysis will test for a treatment difference in the response rate in the ITT population. All individuals failing to achieve the success definition described above will be considered treatment failures, as will subjects who fail to achieve and maintain a 300 mg daily dose of study product (escalation failure nonresponders). All individuals who drop out of the study or discontinue OIT prior to undergoing the Exit DBPCFC will be considered treatment failures (ie Missing = Failure). The Farrington-Manning test will be used to test that the difference in response rates (AR101 minus Placebo) is not equal to 0.15 at the 0.05 significance level. AR101 is considered to have met primary efficacy endpoint if the lower bound of the corresponding test-based 95% confidence interval is greater than the pre-specified margin of 0.15.

Europe: The primary endpoint is the proportion of subjects aged 4 to 17 years who achieve desensitization as determined by tolerating a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC (ie, responders).

The primary efficacy analysis will test for a treatment difference in the response rate in the ITT population. All individuals failing to achieve the success definition described above will be considered treatment failures, as will subjects who fail to achieve or maintain a 300 mg daily dose of study product (escalation failure or nonresponders, respectively). All individuals who drop out of the study or discontinue OIT prior to undergoing the Exit DBPCFC will be considered treatment failures (ie Missing = Failure). The Farrington-Manning test will be used to test that the difference in response rates (AR101 minus Placebo) is not equal to 0 at the 0.05 significance level. AR101 is considered to have met primary efficacy endpoint if the lower bound of the corresponding test-based 95% confidence interval is greater than 0.

9.2.2 Secondary Endpoints

The secondary endpoints are defined in **Section 3.7**, and a full description of the analyses planned for each will be provided in the statistical analysis plan (SAP). A brief description of the planned analyses for the key secondary endpoints and other selected secondary endpoints is provided below.

9.2.2.1 Analysis of Key Secondary Endpoints

North America:

- The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC: The statistical analysis to be conducted for this key secondary endpoint will be similar to that used for the primary endpoint.
- The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC: The statistical analysis to be conducted for this key secondary endpoint will be similar to that used for the primary endpoint.
- The maximum severity of symptoms in subjects aged 4 to 17 years occurring at any challenge dose of peanut protein during the Exit DBPCFC: The objective of analysing this key secondary endpoint is to show that subjects from the AR101 group will have less chance of developing more severe levels of symptom severity compared to subjects from the placebo group. Symptom severity will be recorded at 4 levels: 0-None, 1-Mild, 2-Moderate, 3-Severe or higher. Symptom severity data will be collected at each challenge dose of peanut protein during the Exit DBPCFC – 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, and 1000 mg; the maximum severity at any dose will be used for each subject in the analysis.

  The analysis of this key secondary endpoint will be conducted in the ITT population. The number and percent of subjects by maximum severity at the Exit DBPCFC will be tabulated by treatment arm. The Cochran-Mantel-Haenszel statistic (with equally spaced scores) will be used to test for a treatment difference. The test will be stratified by region. Subjects without an Exit DBPCFC will have their maximum severity during the Screening DBPCFC used, which equates to no change from screening.

- The proportion of subjects aged 18 to 55 years who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC. The statistical analysis to be conducted for this key secondary endpoint will be similar to that used for the primary endpoint.

The key secondary endpoints will be tested in the ITT population in the hierarchical order specified in **Section 3.7.1**. If the primary efficacy analysis is significant at the 0.05 level, then the proportion of subjects who tolerate a single highest dose of at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at Exit DBPCFC will be tested with a Type I error rate of 0.05; if this test is significant, then the proportion of subjects who tolerate a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at Exit DBPCFC will be tested with a Type 1 error rate of 0.05; if this test is significant, then the maximum severity of symptoms occurring at any challenge dose of peanut protein during the Exit DBPCFC will be tested with a Type I error rate of 0.05. This closed testing procedure maintains the overall Type I error rate at 0.05 (EMEA CPMP, 2002; Cook et al., 2008).

Europe:

- The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC: The statistical analysis to be conducted for this key secondary endpoint will be similar to that used for the primary endpoint.
- The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC: The statistical analysis to be conducted for this key secondary endpoint will be similar to that used for the primary endpoint.
- The maximum severity of symptoms in subjects aged 4 to 17 years occurring at any challenge dose of peanut protein during the Exit DBPCFC: The objective of analysing this key secondary endpoint is to show that subjects from the AR101 group will have less chance of developing more severe levels of symptom severity compared to subjects from the placebo group. Symptom severity will be recorded at 4 levels: 0-None, 1-Mild, 2-Moderate, 3-Severe or higher. Symptom severity data will be collected at each challenge dose of peanut protein during the Exit DBPCFC – 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, and 1000 mg; the maximum severity at any dose will be used for each subject in the analysis.

  The analysis of this key secondary endpoint will be conducted in the ITT population. The number and percent of subjects by maximum severity at the Exit DBPCFC will be tabulated by treatment arm. The Cochran-Mantel-Haenszel statistic (with equally spaced scores) will be used to test for a treatment difference. The test will be stratified by region. Subjects without an Exit DBPCFC will have their maximum severity during the Screening DBPCFC used, which equates to no change from screening.

- The proportion of subjects aged 18 to 55 years who tolerate a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC. The statistical analysis to be conducted for this key secondary endpoint will be similar to that used for the primary endpoint.

The key secondary endpoints will be tested in the ITT population in the hierarchical order specified in **Section 3.7.1**. If the primary efficacy analysis is significant at the 0.05 level, then the proportion of subjects who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at Exit DBPCFC will be tested with a Type I error rate of 0.05; if this test is significant, then the proportion of subjects who tolerate a single highest dose of at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at Exit DBPCFC will be tested with Type 1 error rate of 0.05; if this test is significant, then the maximum severity of symptoms occurring at any challenge dose of peanut protein during the Exit DBPCFC will be tested with a Type I error rate of 0.05. This closed testing procedure maintains the overall Type I error rate at 0.05 (EMEA CPMP, 2002; Cook et al., 2008).

9.2.2.2 Analysis of Other Selected Secondary Endpoints

- Maximum dose achieved with no or mild symptoms at Exit DBPCFC: The probability estimates for tolerating each challenge dose or higher of the Exit DBPCFC will be calculated based on the discrete hazards model in the ITT population with terms for treatment group effect, region (North America and Europe) and the MTD at the Screening DBPCFC (baseline) in the $\log_{10}$ scale (Chinchilli et al., 2005). The extreme value hazard function will be used for the model. The probability estimates will be tabulated by treatment group and adjusted for their Screening MTD. The values for MTD for subjects who do not undergo the Exit DBPCFC will be imputed using the maximum doses of peanut protein tolerated in their Screening DBPCFC. The treatment effect hazard ratio and its 95% confidence interval (95% CI) and p-value will be based on the Wald statistic.
- Change from baseline in maximum tolerated dose (MTD) of peanut protein at DBPCFC: Analyses of change from baseline MTD will be performed using change calculated on the $\log_{10}$ scale. An analysis of covariance (ANCOVA) model of change from baseline MTD at Exit DBPCFC ($\log_{10}$ mg) will be fit with terms for treatment group, region, and the MTD at baseline ($\log_{10}$ mg). The values for MTD for subjects who do not undergo the Exit DBPCFC will be imputed using the maximum doses of peanut protein tolerated in their Screening DBPCFC. The baseline adjusted least squares means with 95% CIs by treatment group and for the treatment group difference will be tabulated. The p-value is based on the F-test for treatment group effect adjusted for the MTD at baseline ($\log_{10}$ mg). Residuals for ANCOVA will be assessed for non-normality using the Shapiro-Wilk test. If significant at the 0.05 level, then the Wilcoxon rank sum statistic will be used to test for a treatment group difference to examine the robustness of the ANCOVA F-test.

The statistical methods used for testing the remaining secondary endpoints are described in the Statistical Analysis Plan (SAP).

9.2.3 Supportive Analyses of Primary and Secondary Endpoints

All analyses described in **Sections 9.2.1** and **9.2.2** will be repeated in the Completers and Per Protocol (PP) populations. Sensitivity analyses, using different methods to handle missing data, will be described in the SAP. In addition, a tipping point analysis to determine at what point may a variation in missing data handling overturn the primary efficacy analysis will be conducted. Details will be described in the SAP.

9.3 Subject and Demographic Data

9.3.1 Study Disposition

The number and percent of subjects in each analysis population will be summarized. The number of subjects who complete the study, discontinue prematurely, and their reason for study discontinuation will be tabulated. Total duration on treatment and total duration on study will also be summarized.

9.3.2 Baseline Characteristics and Demographics

Summary descriptive statistics for baseline and demographic characteristics will be provided for all enrolled subjects. Demographic data will include age, race, sex, body weight and height. Baseline characteristics include total IgE, peanut-specific IgE, peanut-specific IgG4, peanut-specific IgE/IgG4 ratio, results from SPT, and MTD of peanut protein at Screening DBPCFC.

Baseline and demographic characteristics may also be summarized by baseline peanut-specific serum IgE level and by baseline SPT peanut wheal size.

9.3.3 Use of Medications

All medications used will be coded using the World Health Organization drug dictionary. The number and percentage of subjects receiving concomitant medications or therapies will be summarized by treatment group.

9.4 Sample Size and Power Calculations

As of the writing of Amendment 4, 554 subjects, 495 of which are between the ages of 4 and 17 years, have been enrolled and enrollment has been completed.

The sample size of 495 subjects between the ages of 4 and 17 years, randomized at a ratio of 3:1, provides sufficient power to detect a treatment effect for the primary efficacy analysis. The set of assumptions and calculations that follow are provided to show this sample size is adequate to demonstrate the AR101 response rate is significantly higher than placebo with at least a 15% margin for the primary efficacy endpoint analysis in North America, and the sample size is adequate to demonstrate the AR101 response rate is significantly higher than placebo for the primary efficacy endpoint analysis in Europe. Additionally, with a trial of this size, there would be an 80% probability of observing at least 1 AE among 375 subjects assigned to AR101 when the background rate of the AE is 4.3 per 1,000 subjects. With the completion of the ARC004 study and the ongoing ARC002 study (for a total of approximately 550 subjects treated with AR101), it is estimated that there would be an 80% probability of observing at least 1 AE when the background rate of the AE is 2.9 per 1,000 subjects.

While natural history of peanut allergy desensitization is not fully understood, significant short-term improvements in consumption amounts are believed to be uncommon. Nevertheless, the sensitivity thresholds to peanut allergen are known to vary day to day based on numerous intrinsic and extrinsic factors. The inherent variability in the sensitivity threshold for allergic reaction to peanut as measured by oral food challenge has been demonstrated in peanut-allergic patients not undergoing immunotherapy (Glaumann et al., 2013), as well as in the placebo arms of several peanut immunotherapy trials (Sampson et al., 2011; Varshney et al., 2011; Fleischer et al., 2013; Sampson et al., 2015). The publication by Glaumann et al. (2013) showed that the threshold for responding in oral food challenge can vary up or down by two orders of magnitude. The placebo response rates reported across therapeutic trials also vary widely, ranging anywhere from 11 to 55%, and are dependent on multiple factors, including the level of peanut protein set as a target response, the specific procedures for oral food challenge employed, the dose level of maintenance therapy, and the duration of immunotherapy.

The literature on peanut OIT, though sparse, also suggests that there could be a high degree of variability in the magnitude of the treatment effect. Only 2 randomized controlled trials of peanut OIT (Varshney et al., 2011; Anagnostou et al., 2014) have been reported to date, and these employed significantly different study designs. In the Varshney study, 16 of 19 (84%) subjects randomized to active treatment demonstrated a high degree of desensitization (although baseline sensitivity to peanut had not been established). This stands in contrast to the Anagnostou study, wherein only 24 of 49 (49%) subjects randomized to active treatment achieved the predefined level of desensitization.

North America: In the Phase 2 ARC001 study the primary endpoint was determined at the 300 mg (443 mg cumulative) level of peanut protein in the Exit DBPCFC, whereas in the current Phase 3 study, ARC003, the primary endpoint will be determined at the 600 mg (1043 mg cumulative) dose level of peanut protein in the Exit DBPCFC, a level that was studied as an additional endpoint in ARC001. For the purpose of calculating statistical power for the ARC003 study, the response rates at both the 443 mg (primary) and 1043 mg (additional) cumulative dose endpoints from ARC001 have been taken into consideration.

In the Phase 2 ARC001 study, the placebo response rate for the primary endpoint in the ITT population of tolerating 443 mg cumulative of peanut protein at Exit DBPCFC was 19% (95% CI of 7% to 39%), and it was 0% (95% CI of 0% to 13%) in the post-hoc analysis of tolerating 1043 mg cumulative of peanut protein at Exit DBPCFC. Thus, the Phase 2 results suggest that the point estimate for the placebo response rate in the primary endpoint of ARC003 is likely to fall between 0 and 19% (based on point estimates), although it could be as high as 13 to 39% (based on upper bound of the 95% CIs). Taking into account the wide range of placebo response rates evident from the literature, a placebo response rate of 20% for the primary endpoint is assumed for power calculations in this study.

The response rate in the AR101 arm of the ARC001 study was 79% (95% CI of 60% to 92%) and 62% (95% CI of 42% to 79%) for endpoints based on tolerating 443 mg and 1043 mg cumulative of peanut protein, respectively, at Exit DBPCFC in the ITT population. Thus, the Phase 2 results suggest that the point estimate for the active treatment response rate at the primary endpoint in ARC003 is likely to fall between 62 and 79% (based on point estimates), although it could be as low as 42 to 60% (based on lower bound of 95% CIs). Given that dropouts accounted for the majority of desensitization failures in ARC001, a 6-month study, and the opportunity for dropout increases as the duration of the trial increases, a 50% AR101 response rate at the primary endpoint is assumed for the purpose of power calculation for ARC003, a 12 month study. This approach is consistent with published recommendations for adjusting assumptions about Phase 3 response rates based on Phase 2 results (Wang, Hung, & O'Neill, 2006; Kirby et al., 2012).

An additional 15% margin in the separation between the placebo response and the response to AR101 will be included in defining the success criteria for the primary endpoint. This will help to ensure that the number of peanut-allergic patients spared moderate or severe allergic reactions at Exit DBPCFC (a model for accidental exposure) after treatment with AR101 represents a clinically meaningful benefit, and not just a statistically significant non-zero difference from placebo. The primary efficacy analysis is based on the Farrington-Manning test with a two-sided alternative hypothesis at the 5% level of significance (Farrington and Manning, 1990). Given

placebo response rates of at most 20%, a 2-tailed 5% level test would have approximately 89% power to detect an AR101 response rate of at least 50% and rule out treatment differences (AR101 minus placebo) that are 15% or less for the primary endpoint.

Europe: Based on preliminary data from ARC002, 40 out of 55 subjects treated in ARC001 and ARC002 with AR101 underwent an Exit DBPCFC with a single dose of 1000 mg (2043 mg cumulative) of peanut protein after approximately 12 or more weeks of maintenance dosing at 300 mg/d. Of these, 24 subjects tolerated a single dose of 1000 mg (2043 mg cumulative) of peanut with no more than mild symptoms. This corresponds to an AR101 response rate of 44% (95% CI of 30% to 58%). We assume a placebo response rate of 15% at a single dose of 1000 mg (2043 mg cumulative) of peanut protein (two-thirds of what we assumed for the placebo response rate at a single dose of 600 mg [1043 mg cumulative]). A sample size of 495 children, aged 4 to 17 years, provides at least 93% power to detect an AR101 response rate of at least 30% at a single dose of 1000 mg (2043 mg cumulative) of peanut protein when the placebo response rate is at most 15%.

10 IDENTIFICATION AND ACCESS TO SOURCE DATA

10.1 Web-Based Data Collection and Management System

Data collection will occur via a web-based data entry system to allow easy access to enrollment 24 hours a day, 7 days a week. Upon enrollment, a form submission schedule is generated for each subject and displayed as a grid of forms by study visit that permits direct access to each electronic CRF for data entry. As data are entered, they are validated through range and within-form consistency checks. The investigator must ensure that all web-based CRFs are completed in a timely fashion for each subject in the study.

10.2 Certification in the Use of Web-Based Data Entry System

The clinic and laboratory staff will be trained in the use of the data entry and specimen-tracking systems. Once certified, users are permitted to enter data into the production system. Access is password controlled. Certification for use of the web-based data entry system will be completed via telephone and/or web-cast training.

10.3 Data Management

Information regarding the subject's history, laboratory tests, nutritional intake, evaluation of allergic response and follow-up status will be stored and processed through the data center. Quality control procedures and a feedback system between the data center and the sites will be instituted to ensure the accuracy and completeness of the data collected.

10.4 Access to Data

The investigational sites shall periodically permit authorized representatives of the Study sponsor, and/or regulatory health authorities to examine clinical records and other source documents for the purpose of safety monitoring, quality assurance reviews, audits and evaluation of the study progress throughout the entire study period. The investigator is required by law and applicable guideline (21 CFR 312.62, EU Clinical Trials Directive 2001/20/EC and ICH E6) to keep accurate case records for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing application in an ICH

region. These documents should be retained for a longer period however if required by the applicable local regulatory requirements or by an agreement with the sponsor.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Statement of Compliance

This study will be conducted using good clinical practice (GCP), as delineated in the United States Code of Federal Regulations (CFR) – 21 CFR Parts 50, 54, 56 and 312 and in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) "Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance", and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate IRB/EC and other applicable health authorities. Any amendments to the protocol must also be approved by Aimmune Therapeutics, IRB/EC and other applicable health authorities before they are implemented. Any amendments to the consent materials must also be approved by Aimmune Therapeutics and IRB/EC before they are implemented.

11.2 Informed Consent/Assent

The informed consent/assent form is a means of providing information about the study to a prospective adult subject or a pediatric subject's parent/guardian and allows for an informed decision about participation in the study. Because the study population will comprise a significant percentage of children, parents or legal guardians will be asked to read, sign and date a consent form before a child enters the study, takes study product, or undergoes any study-specific procedures. Children will sign an assent as appropriate. Consent materials for parents/guardians who do not speak or read English will be translated into the appropriate language. The informed consent/assent form will be evaluated for revision whenever the protocol is amended. A copy of the informed consent/assent will be given to a prospective adult subject or a pediatric subjects' parent/guardian for review. The investigator (or designee), will review the consent/assent and answer questions, as well as emphasize the need to avoid allergen exposure other than to AR101, and the necessity to continue exposure to AR101 to maintain desensitization. The prospective adult subject or a pediatric subject's parent/guardian will be told that being in the study is voluntary and that he or she may withdraw his/her child from the study at any time, for any reason.

In the optional saliva substudy **(North America sites only)** in which samples will be obtained noninvasively from ARC003 participants, only subjects enrolled in ARC003 and providing additional consent for this substudy are eligible to participate **(Appendix 6)**.

11.3 Privacy and Confidentiality

A subject's privacy and confidentiality will be respected throughout the study. Each subject will be assigned a sequential identification number and these numbers rather than names will be used to collect, store and report subject information.

12 RESOURCE SHARING

All data derived from this study will be sent to the Reporting Center for storage and analysis. Subject data will be anonymized to maintain subject confidentiality. All data derived from these

studies will be published in peer-reviewed scientific journals in a timely manner. The sponsor will review all manuscripts prior to submission to journals for publication and all abstracts prior to submission to national and international meetings. All data sets will be archived by the Reporting Center and may be made available to interested, outside investigators with the approval by the sponsor.

13 PROTOCOL DEVIATIONS

The investigators and site staff will conduct the study in accordance to the protocol. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. Whenever applicable, corrective actions will be developed by the site and implemented promptly as a result of protocol deviations.

13.1 Major Protocol Deviation (Protocol Violation)

A Protocol Violation is a deviation from the IRB approved protocol 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.

13.2 Nonmajor Protocol Deviation

A nonmajor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol 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.

13.3 Reporting and Managing Protocol Deviations

Non-major protocol deviations related to data entry or visit adherence are captured within the data system and are not additionally reported on a separate CRF.

The study site Principal Investigator has the responsibility to identify, document and report protocol violations/deviations and appropriate corrective action plans which are described above. However, protocol violations/deviations may also be identified during site monitoring visits or during other forms of study conduct review. All protocol violations will be reported in the data system on a specific CRF.

14 REFERENCE LIST

Allen KJ, Remington BC, Baumert JL, Crevel RW, Houben GF, Brooke-Taylor S, et al. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. J Allergy Clin Immunol. 2014;133(1):156-164.

Alpan O, Miehlke S, Straumann A. Oral immunotherapy for egg allergy in children. N Engl J Med. 2012;367(15):1472; author reply 1472-1473.

Altschul AS, Scherrer DL, Muñoz-Furlong A, Sicherer SH. Manufacturing and labeling issues for commercial products: relevance to food allergy. J Allergy Clin Immunol. 2001;108(3):468.

American Academy of Pediatrics. Feeding and Nutrition: Your 4- to 5-Year-Old. 2013 http://www.healthychildren.org/English/ages-stages/preschool/nutrition-fitness/Pages/Feeding-and-Nutrition-Your-4-to-5-Year-Old.aspx.

Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet. 2014;383(9925):1297-1304.

Arias A, Lucendo AJ. Dietary therapies for eosinophilic esophagitis. Expert Rev Clin Immunol. 2014;10(1):133-142.

Avery N, King R, Knight S, Hourihane J. Assessment of quality of life in children with peanut allergy. Ped Allergy Immunol. 2003;14:378–382.

Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, de Oliveira LC, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol. 2010;126(1):83-91.

Bock SA, Atkins FM. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. J Pediatr. 1990;117(4):561-567.

Bousquet J. Primary and secondary prevention of allergy and asthma by allergen therapeutic vaccines. Clin Allergy Immunol. 2004;18:105-114.

Branum AM, Lukacs SL. Food allergy among U.S. children: trends in prevalence and hospitalizations. NCHS Data Brief. 2008;Oct(10):1-8.

Buchanan AD, Green TD, Jones SM, Scurlock AM, Christie L, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy, J Allergy Clin Immunol. 2007;119:199-205.

Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, et al. for the Consortium of Food Allergy Research. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med. 2012;367:233-243.

Burks AW, Jones SM, Plaut M, et al. Oral immunotherapy for egg allergy in children. N Engl J Med. 2012;367(15):1472-1473.

Campbell DE. A review of the induction of tolerance of IgE-mediated food allergy – past, present and future. Curr Allergy Clin Immunol. 2014;27(3):162-168.

Cashdan E. A sensitive period for learning about food. Hum Nat. 1994;5(3):279-291.

Chinchilli VM, Fisher L, Craig TJ. Statistical issues in clinical trials that involve the double-blind, placebo-controlled food challenge. J Allergy Clin Immunol 2005;115:592-7.

Clark AT, Islam S, King Y, Deighton J, Anagnostou K, Ewan PW. Successful oral tolerance induction in severe peanut allergy. Allergy. 2009;64(8):1218-1220.

Cook, Thomas D, and David L DeMets. Introduction to Statistical Methods for Clinical Trials. Boca Raton, FL: Chapman & Hall/CRC, 2008, p374.

Cronin JA, Wisniewski J, Commins SP. Low Dose Maintenance Peanut OIT Can Produce Sustained Unresponsiveness. J Allergy Clin Immunol. 2014;133(2):AB103.

EMEA. Points to Consider on Multiplicity Issues in Clinical Trials, London (UK), EMEA CPMP 2002.

Fallon AE, Rozin P, Pliner P. The child's conception of food: the development of food rejections with special reference to disgust and contamination sensitivity. Child Dev. 1984;55(2):566-575.

Farrington, C. P. and Manning, G. 'Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-Zero Risk Difference or Non-Unity Relative Risk.' Statis Med. 1990;9:1447-1454.

Farrow C, Blissett J. Stability and continuity of parentally reported child eating behaviours and feeding practices from 2 to 5 years of age. Appetite. 2012;58(1):151-156.

Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, Sicherer, SH, Liu AH, Stablein D, Henning AK, Mayer L, Lindblad R, Plaut M, Sampson HA; Consortium of Food Allergy Research (CoFAR). Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol. 2013;131(1):119-127.e1-7.

Franciosi JP, Hommel KA, DeBrosse CW, Greenberg AB, Greenler AJ, Abonia JP, Rothenberg ME, Varni JW. Development of a validated patient-reported symptom metric for pediatric eosinophilic esophagitis: qualitative methods. BMC Gastroenterol. 2011;18;11:126.

Frew AJ. 25. Immunotherapy of allergic disease. J Allergy Clin Immunol, 2003;111(2 Suppl):S712-S719.

Glaumann S, Nopp A, Johansson SG, Borres MP, Nilsson C. Oral peanut challenge identifies an allergy but the peanut allergen threshold sensitivity is not reproducible. PLoS One. 2013;8(1):e53465.

Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology. 2012 Jun;142(7):1451-9.e1.

Greenhawt M, Aceves SS. Non-IgE Medicated Food Allergy: Eosinophilic Esophagitis Update on the Pathogenesis, Clinical Features, and Management of Eosinophilic Esophagitis in Children. Curr Pediatr Rep. 2014 Jun;2(2):127-134.

Greenhawt MJ. STOPping peanut allergy: the saga of food oral immunotherapy. Lancet. 2014 Apr 12;383(9925):1272-4.

Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy, J Allergy Clin Immunol. 2009;124:286-291, 291 e281-286. PMCID: PMC2731305.

Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, Steele PH, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. J Allergy Clin Immunol. 2009;124(2):286-291, 291.e1-6.

Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004;113(5):832-836.

Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol. 2009;124(2):292-300, 300 e1-97.

Joshi P. Mofidi S, Sicherer SH. Interpretation of commercial food ingredient labels by parents of food-allergic children. J Allergy Clin Immunol. 2002;109(6):1019-1021.

Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2006;4(9):1097-1102.

Kapsenberg ML, Hilkens CM, Wierenga EA, Kalinski P. The paradigm of type 1 and type 2 antigen-presenting cells. Implications for atopic allergy. Clin Exp Allergy. 1999;29Suppl 2:33-36.

Kim EH, Bird JA, Kulis M, Laubach S, Pons L, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. 2011;127(3):640-646 e1.

Kirby S, Burke J, Chuang-Stein C, Sin C. Discounting phase 2 results when planning phase 3 clinical trials. Pharm Stat. 2012;11(5):373-385.

Le UH, Burks, AW. Oral and Sublingual Immunotherapy for Food Allergy. World Allergy Organ J. 2014;7:35.

Lehrer SB, Wild LG, Bost KL, Sorensen RU. Immunotherapy for food allergies. Past, present, future. Clin Rev Allergy Immunol. 1999;17(3):361-381.

Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann Allergy Asthma Immunol. 2014;113(6):624-629.

Maggadottir SM, Hill DA, Ruymann K, Brown-Whitehorn TF, Cianferoni A, Shuker M, et al. Resolution of acute IgE-mediated allergy with development of eosinophilic esophagitis triggered by the same food. J Allergy Clin Immunol. 2014;133(5):1487-1489.

Martin LJ, Franciosi JP, Collins MH, Abonia JP, Lee JJ, Hommel KA, et al. Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease. J Allergy Clin Immunol. 2015;135(6):1519-1528.

McKenna C, Klontz KC. Systemic allergic reaction following ingestion of undeclared peanut flour in a peanut-sensitive woman. Ann Allergy, Asthma Immunol. 1997;79:234-236.

Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29-322.

Muraro A. Roberts G. Clark A. Eigenmann PA, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. Allergy. 2007;62(8):857-871.

Narisety, SD, Skripak JM, Steele P, Hamilton RG, Matsui EC, et al. Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. J Allergy Clin Immunol. 2009;124(3):610-612.

Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. J Allergy Clin Immunol. 1997;99(6 Pt 1):744-751.

Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. N Engl J Med. 2004;351(9):940-941.

Nurmatov U, Devereux G, Worth A, Healy L, Sheikh A. Effectiveness and safety of orally administered immunotherapy for food allergies: a systematic review and meta-analysis. Br J Nutr. 2014;14;111(1):12-22.

Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol. 1992;90(2):256-22.

Primeau M, Kagan R, Joseph L, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. Clin Exp Allergy. 2000;30:1135–1143.

Remington BC. Chapter in Risk Assessment of Trace and Undeclared Allergens in Processed Foods. Dissertations & Theses in Food Science and Technology. University of Nebraska, Lincoln, Nebraska. 2013;May:1-281. http://digitalcommons.unl.edu/foodscidiss/32/

Rea F, L. E. D'Urbano LE, R. Luciano R, M. Muraca M, L. Dall'Oglio L. Eosinophilic Esophagitis and IgE-Mediated Allergy in Children: Specific IgE by Component-Based-Allergen Microarray. J Allergy Ther. 2014;5(4):180.

Ridolo E, Montagni M, Olivieri E, Rogkakou A, De' Angelis GL, Canonica GW. Eosinophilic esophagitis: which role for food and inhalant allergens? Asia Pac Allergy. 2012;2(4):237-241.

Rimbaud L, Héraud F, La Vieille S, Leblanc, JC, Crépet A. Quantitative Risk Assessment Relating to the Inadvertent Presence of Peanut Allergens in Various Food Products. Int. Food Risk Anal. 2013;J(3):1-11.

Sampson H, et al. Epicutaneous Immunotherapy (EPIT) Is Effective and Safe to Treat Peanut Allergy: A Multi-National Double-Blind Placebo-Controlled Randomized Phase IIb Trial. AAAAI Annual Meeting 2015; Abstract L28 (American Academy of Allergy, Asthma & Immunology Meeting DBV Investor Update - February 2015)

Sampson HA, Leung DY, Burks AW, Lack G, Bahna SL, Jones SM, Wong DA. A phase II, randomized, double‐blind, parallel‐group, placebo‐controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. J Allergy Clin Immunol. 2011;127(5):1309-1310.

Sampson HA, Muñoz-Furlong A, Bock SA, Schmitt C, Bass R, et al. Symposium on the definition and management of anaphylaxis: summary report. J Allergy Clin Immunol. 2005;115(3):584-591.

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-397.

Sampson HA, van Wijk RG, Bindslev-Jensen C, Sicherer S, 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(8):1260-1274.

Sánchez-García S, Rodríguez Del Río P, Escudero C, Martínez-Gómez MJ, Ibáñez MD. Possible eosinophilic esophagitis induced by milk oral immunotherapy. J Allergy Clin Immunol. 2012 Apr;129(4):1155-7.

Secrist H DeKruyff RH, Umetsu DT. Interleukin 4 production by CD4+ T cells from allergic individuals is modulated by antigen concentration and antigen-presenting cell type. J Exp Med. 1995. 181(3): p. 1081-1089.

Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. Pediatrics. 1998. 102(1): p. e6.

Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol. 2014 Feb;133(2):291-307.

Sicherer SH, Wood RA, Stablein D, Burks AW, Liu AH, et al. Immunologic features of infants with milk or egg allergy enrolled in an observational study (Consortium of Food Allergy Research) of food allergy). J Allergy Clin Immunol. 2010, 125:1077-1083 e1078. PMCID: PMC2868273

Simons FE, Ardusso LR, Bilò MB, El-Gamal YM, Ledford DK, Ring J, et al.; World Allergy Organization. World Allergy Organization anaphylaxis guidelines: summary. J Allergy Clin Immunol. 2011 Mar;127(3):587-93.e1-22.

Simons FE, Ardusso LR, Bilò MB, Cardona V, Ebisawa M, El-Gamal YM, et al. International consensus on (ICON) anaphylaxis. World Allergy Organ J. 2014;30;7(1):9.

Skripak, JM, Nash SD, Rowley H, Brereton NH, Oh S, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol. 2008;122(6):1154-1160.

Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, Liacouras CA. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunol. 2012;130(2):461-467.

Trendelenburg V, Beyer K, Blumchen K. Efficacy and safety balance of oral and sublingual immunotherapy in food allergy. Curr Treat Options Allergy 2014;1:117-132.

van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Oude Elberink JN, DunnGalvin A, Hourihane JO, et al. Development, validity and reliability of the food allergy independent measure (FAIM). Allergy. 2010;65(5):630-635.

Varshney P, Jones SM, Scurlock AM, Perry TT, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol. 2011;127(3):654-660.

Vickery B. et al. High Rate of Sustained Unresponsiveness with Early-Intervention Peanut Oral Immunotherapy. AAAAI Annual Meeting 2015; Abstract 506 (https://aaaai.confex.com/aaaai/2015/webprogram/Paper20251.html#).

Vickery BP, Scurlock AM, Steele P, Kamilaris J, Hiegel AM, Carlisle SK, et al. Early and Persistent Gastrointestinal Side Effects Predict Withdrawal from Peanut Oral Immunotherapy (OIT). J Allergy Clin Immunol. 2011;127(2):AB26.

Vierk K, Falci K, Wolyniak C, Klontz KC. Recalls of foods containing undeclared allergens reported to the US Food and Drug Administration, fiscal year 1999. J Allergy Clin Immunol. 2002;109(6):1022-1026.

Vierk KA, Koehler KM, Fein SB, Street DA. Prevalence of self-reported food allergy in American adults and use of food labels. J Allergy Clin Immunol. 2007;119(6):1504-1510.

Wang SJ, Hung HM, O'Neill RT. Adapting the sample size planning of a phase III trial based on phase II data. Pharm Stat. 2006;5(2):85-97.

Wasserman RL, Sugerman RW, Mireku-Akomeah N, Gallucci AR, Pence DM, Long NA. Peanut oral immunotherapy (OIT) of food allergy (FA) carries a significant risk of eosinophilic esophagitis (EoE). J Allergy Clin Immunol. 2011;127(2):AB28.

Wen T, Stucke EM, Grotjan TM, Kemme KA, Abonia JP, Putnam PE, et al. Molecular diagnosis of eosinophilic esophagitis by gene expression profiling. Gastroenterology. 2013;145(6):1289-1299. doi: 10.1053/j.gastro.2013.08.046. Epub 2013 Aug 23. PubMed PMID: 23978633.

Wechsler JB, Schwartz S, Amsden K, Kagalwalla AF. Elimination diets in the management of eosinophilic esophagitis. J Asthma Allergy. 2014;24;7:85-94.

Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. Allergy. 2005;60(1):4-12.

Wolf WA, Jerath MR, Dellon ES. De-novo onset of eosinophilic esophagitis after large volume allergen exposures. J Gastrointestin Liver Dis. 2013;22(2):205-208.

Yu GP, Weldon B, Neale-May S, Nadeau KC. The safety of peanut oral immunotherapy in peanut-allergic subjects in a single-center trial. Int Arch Allergy Immunol. 2012;159(2):179-182.

Appendix 1: Schedule of Events

Visit		Screening/ Baseline	Initial Escalation		Up-dosing Period			Maintenance Period		Un-scheduled [c]
					CRC Dosing	Interim (80 mg) Visit	End of Period (300 mg) Visit	CRC Dosing	Exit/Early Discontinuation Visit	
			Days 1-2[a]	5-10 days post-DBPCFC	~every 2 weeks for 20-40 weeks[b]	Approx. Week 10	≤ Week 40	At 2 wks & every 4 wks thereafter for ~24 wks		
Informed consent/assent		X								
Inclusion/Exclusion		X								
Medical/allergy history		X								
Diet (food allergen) history		X	X		X	X	X	X	X	X
Concomitant medications		X	X		X	X	X	X	X	X
Physical exam[d]		X	X		X	X	X	X	X	X
Vital signs (BP, PR, temp)		X	X		X	X	X	X	X	X
Spirometry (FEV1) or PEFR[e]		X	X		X	X	X	X	X	X
Pregnancy test[f]		Serum				Urine	Urine		Urine	
FAQLQ & FAIM questionnaires		X[p]							X[p]	
Palatability questions									X[q]	
TSQM-9 and Exit questionnaire									X[r]	
Blood draw	Peanut-specific IgE, IgG4[g]	X					X		X	X
	CBC	X					X		X	X
	Optional extra vol. for ITN[h]	X					X		X[i]	X
Optional saliva collection, and packaging/shipping										
	No GI symptoms (controls)	X			X[j]		X			
	GI symptoms (cases)	X			X[j]				X	
Optional additional blood draw for post-DBPCFC ITN sample				X[k]						
Skin prick test		X					X		X	
Administration of OIT at site			X		X	X	X	X		X
Dispense / return unused study drug			X		X	X	X	X	X	X
DBPCFC (2 parts within 7 days)		X[l]							X[m]	
Monitor AEs / allergic symptoms[n]		X	X		X	X	X	X	X	X
Monitor for compliance					X	X	X	X	X	X

Visit	Screening/ Baseline	Initial Escalation		Up-dosing Period			Maintenance Period		Un-scheduled [c]
				CRC Dosing	Interim (80 mg) Visit	End of Period (300 mg) Visit	CRC Dosing	Exit/Early Discontinuation Visit	
		Days 1-2[a]	5-10 days post-DBPCFC	~every 2 weeks for 20-40 weeks[b]	Approx. Week 10	≤ Week 40	At 2 wks & every 4 wks thereafter for ~24 wks		
Assessment of Asthma	X				X	X		X	
Subject reminder to avoid all peanut	X	X	X	X	X	X	X	X	X
Telephone Follow-up[o]		X		X	X	X			X
PEESS™ v2.0 questionnaire									X[s]

Footnotes:

a) The Initial Escalation Visit will be scheduled within 10 days after the Screening DBPCFC. See **Table 3-1** for dose escalation schedule. Subjects will begin home dosing at dose 3 mg/d.
Day-1: Escalation to at least 3 mg or 6 mg, as tolerated (subjects who cannot tolerate 3 mg are escalation failures).
Day-2: Confirm tolerance of 3 mg.

b) Subjects return to clinic every 2 weeks for up-dosing to a maximum of 300 mg, following the dose escalation schedule in **Table 3-2** , unless up-dosing is delayed due to allergic reaction.

c) Any of the procedures performed at CRC Dosing Visits may be performed at Unscheduled Visits.

d) Physical exam to include height and weight. At the investigator's discretion, symptom-directed physical exams may be completed at up-dosing visits during the Up-dosing Period, and CRC Dosing visits during the Maintenance Period. Full physical exams are to be conducted at the Screening/Baseline, the first 80 mg up-dosing, the first 300 mg up-dosing, and the Exit/Early Discontinuation (Termination) visits.

e) Peak expiratory flow rate (PEFR): To be conducted prior to any DBPCFC, 3 attempts should be made with the best value recorded. PEFR should be measured at the same time for each visit assessment. If a subject's pulmonary status is in question at any time during the study, performance of pulmonary function testing (spirometry) is suggested.

f) For females of childbearing potential.

g) Blood for peanut specific IgE, IgG4 is to be drawn prior to DBPCFC.

h) Optional blood draw for subjects ≥ 30 kg only. No more than 5 mL/kg may be drawn, up to a maximum of 50 mL total; analysis by Immune Tolerance Network (ITN).

i) Blood draw to be collected prior to the Exit DBPCFC (a second draw, 5-10 days post-DBPCFC, will be collected in ARC004; for subjects not continuing to ARC004, specimen collection should be as an Unscheduled ARC003 visit).

j) Subjects withdrawing early from ARC003 with GI symptoms who were not already enrolled in the optional saliva substudy will be allowed to enroll upon early termination **(North America sites only).**

k) Blood draw to be collected 5-10 days after the Screening DBPCFC.

l) Eligible subjects, those who satisfy all other screening requirements, will undergo a DBPCFC at the end of the Screening Period to a maximum challenge dose of 100 mg.

m) Eligible subjects, those who up-dose to 300 mg and maintain for ~24 weeks, will undergo a DBPCFC at the end of Maintenance Period Visit to a maximum challenge dose of 1000 mg.

n) AEs will be evaluated from the onset until the event is resolved or medically stable, or until 30 days after the subject completes study treatment, whichever comes first.

o) Phone calls will occur 1 day after each escalation visit to inquire about allergic symptoms and promote compliance

p) FAQLQ and FAIM to be filled up prior to screening DBPCFC and after exit DBPCFC and unblinding

q) Palatability questions to be answered before the exit DBPCFC for all patients

r) TSQM-9 and Exit questionnaire to be answered after exit DBPCFC and unblinding for all active patients

s) Subjects under the age of 18 years who fall into any of these 3 categories will be asked to fill out the PEESS^{TM}v2.0 questionnaire (Franciosi et al., 2011), with the assistance of a parent or guardian, as appropriate, every month for 6 months:
   - Any subject whose dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level (**Section 6.7**)
   - 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 (**Section 6.7.3.2**)
   - Any subject who permanently discontinues dosing who had experienced GI AEs (**Section 4.3.2**)

Note: BP = blood pressure; PR = pulse rate; temp = body temperature; OIT = oral immunotherapy; DBPCFC = double-blind, placebo-controlled food challenge

Appendix 2: Evaluation of Asthma

The evaluation of asthma severity will be assessed using the NHLBI classification published August 28, 2007 as described in the table below.

Classification	Symptoms	Nighttime awakenings	Lung Function	Interference with normal activity	Short acting beta-agonist use
Intermittent (Step 1)	≤ 2 days per week	≤ 2x /month	Normal FEV_1 between exacerbations FEV1 > 80% predicted FEV1/FVC normal*	None	≤ 2 days /week
Mild Persistent (Step 2)	> 2 days per week but not daily	3-4x /month	FEV1 ≥ 80% predicted FEV1/FVC normal*	Minor limitation	> 2 days /week but not > 1x/day
Moderate Persistent (Step 3 or 4)	Daily	> 1x /week but not nightly	FEV1 ≥ 60% but < 80% predicted FEV1/FVC reduced 5%*	Some limitation	Daily
Severe Persistent (Step 5 or 6)	Throughout the day	Often 7x /week	FEV1 < 60% predicted FEV1/FVC reduced > 5%*	Extremely limited	Several times per day

*Normal FEV1/FVC: 8-19 yr = 85%; 20-39 yrs = 80

Appendix 3: Criteria for Suspected Diagnosis, and Severity Grading, of Anaphylaxis

Criteria for Suspected Diagnosis

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

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

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

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

Criteria for Severity Grading (Muraro et al., 2007)

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

Appendix 4: Allergic Reaction Severity Grading

The CoFAR grading system for allergic reactions as displayed in **Table A4.**

Table A4: CoFAR Specific Grading System for Allergic Reactions

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

Appendix 5: Guidance for Determining When an Episode of Anaphylaxis Should Be Reported as a Serious Adverse Event (SAE)

For an episode of anaphylaxis to be considered an SAE, Aimmune advises that the event satisfy one of the outcome-based definitions of SAE specified in **Section 7.4.2** of the

Protocol, with the stipulations (denoted in *italics*) indicated. These stipulations follow from, and are consistent with, the criteria for DSMC reporting (**Section 7.7.2**):

1. Death – *No further stipulation.*
2. Life-threatening AE (Life-threatening means that the study subject was, in theopinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred.): *For anaphylaxis to be considered life-threatening it should be assessed to have been severe, as defined in Appendix 3 and of a Grade 4 allergic reaction, as defined in **Table A4** of **Appendix 4**.*
3. Inpatient hospitalization or prolongation of existing hospitalization: *The hospital admission should not have been solely for the sake of providing an extended period of observation, as, for example, might be implemented to watch for a delayed or biphasic reaction.*
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions: *No further stipulation.*
5. Congenital abnormality or birth defect: *No further stipulation.*
6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study subject or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event:
    - *In general, for an anaphylactic episode to be classified as an SAE on the basis of being an "important medical event," it should have resulted in an emergency room visit, and the emergency room visit should have been associated with intensive therapy. What constitutes intensive therapy is to be determined by the investigator, but may include such interventions as IV epinephrine, intubation, or admission to an intensive care unit.*
    - *One or 2 intramuscular injections of epinephrine should ordinarily not be construed as intensive therapy*
    - *If an investigator assesses an episode of anaphylaxis to be an "important medical event" when the episode was of mild or moderate severity and did not require intensive therapy, the rationale for the assessment must be explained in detail in the narrative of the event.*

Appendix 6: (North America sites only) Exploratory Biochemical and Molecular Study of Peanut-Allergic Children and Adults with Oral Immunotherapy-Related Gastrointestinal Symptoms in ARC003

Background

A strong association exists between food allergy and eosinophilic esophagitis (EoE) (Noel 2004; Spergel 2012; Greenhawt 2014). Instituting an elemental diet free of potential allergens is the most reliably effective treatment for spontaneously occurring EoE (Arias 2014; Wechsler 2014). In some cases of EoE, if a specific allergy-provoking food can be identified, then dietary avoidance of the offending food can result in resolution of the esophageal symptoms (Spergel 2012). Alternatively, elimination from the diet of the most common food allergens, including milk, egg, peanut/tree nuts, soy, wheat, and shellfish/fish, can also result in resolution of the esophagitis (Kagalwalla 2006; Gonsalves 2012). When reintroduction of a suspected allergenic food is associated with the return of symptoms, this strongly implicates the food as a likely causative agent of the EoE (Gonsalves 2012).

IgE-mediated hypersensitivity to food allergens, but also aeroallergens (Alpan 2012; Ridolo 2012; Wolf 2013; Rea 2014), figures prominently in the pathogenesis of EoE, but other factors besides the induction of an immediate hypersensitivity reaction also appear important. One circumstance in which multiple factors pertaining to food exposure are controlled at the time that EoE becomes symptomatic is when EoE occurs in the setting of oral immunotherapy (OIT). The inciting food is known, as is the amount and timing of its consumption. Moreover, EoE occurs only in a minority of patients undergoing OIT. Thus, studying EoE when it arises during the course of OIT may provide a unique opportunity to gain insights into its pathogenesis.

In OIT studies, gastrointestinal (GI) adverse events (AEs) are typically prominent (Anagnostou 2014; Yu 2012; Blumchen 2010; Jones 2009) and account for a substantial proportion of premature discontinuations of study treatment (Burks 2012; Varshney 2011; Jones 2009; Vickery 2011). This was also observed in the completed ARC001 study and the ongoing ARC002 study. In the ARC001 study, 6 out of 29 subjects (21%) receiving active treatment discontinued prematurely. Four of the early discontinuations were attributed by the principal investigators to have been the consequence of recurrent GI AEs; and in one of these cases the diagnosis of EoE was subsequently established by endoscopic biopsy. In the other two discontinuations, at least one GI AE had occurred in each subject. In the ongoing ARC002 study, an open-label follow-on to the ARC001 study, 6 of the 26 subjects (22%) who had been assigned to the placebo group in ARC001 discontinued therapy prematurely. Four of these early discontinuations were due to recurrent GI AEs and two were due to study visit scheduling difficulties.

Repeated bouts of abdominal pain and vomiting are common to both EoE and chronic/recurrent OIT-related GI symptoms, suggesting a common, or at least a similar, etiology in at least a proportion of patients. To date, at least 20 occurrences of OIT-related GI AEs have been confirmed histopathologically to be EoE as reported in the medical literature (Hofmann 2009; Vickery 2011; Wasserman, 2011; Sánchez-García 2012; Lucendo 2014), and in still other cases the symptomatology and clinical course (with or without concomitant blood eosinophilia) have been highly suggestive of EoE (Narisety 2009; Vickery 2011; Stein 2012). A recent review of

the literature (Lucendo, 2014) has indicated that the incidence of confirmed EoE in OIT is on the order of 3% (ranging from approximately 1% to 5%), but the incidence of suspected EoE on clinical grounds may be in the vicinity of 15 to 25%.

Establishing the association between OIT and the subsequent development of EoE is not always straight forward. The time to onset of EoE during the course of OIT may vary depending on the allergen and OIT regimen. Many (Vickery 2011; Wasserman 2011), though not all (Hofmann 2009), of the reported cases of EoE with peanut OIT had developed GI symptoms early in the course of oral desensitization, whereas with milk OIT the occurrence of EoE has tended to be after reintroduction of milk into the diet (Sánchez-García 2012; Maggadottir 2014; Nowak-Wegrzyn 2014). Not all EoE occurring during OIT is necessarily caused by the OIT, however. Food allergies often occur to more than one type of food and allergies to foods often coexist with allergies to airborne and contact allergens.

Chronic GI AEs affecting participants in ARC003 have been designated as Adverse Events of Special Interest (AESI) in the ARC003 protocol document, Amendment 1. The goal of the current substudy is to explore the biology of these GI AESIs occurring during our Phase 3 trial using a readily available and noninvasive sampling method (saliva) in an attempt to overcome some of the difficulties in assessing intolerable GI AEs in subjects undergoing OIT.

Rationale for the Proposed Study

The overall aims of this substudy are to collect biospecimens through a noninvasive technique, and to analyze them to develop a better understanding of the biochemical and molecular changes that occur when OIT participants develop GI adverse events significant enough to require discontinuation of the OIT protocol. We will obtain preliminary information regarding these biological changes in biospecimens from symptomatic individuals, as well as controls, using methods that have been developed for the study of eosinophilic GI disorders at Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA.

Specifically, this substudy of ARC003, Amendment 3 will enroll all willing volunteers at screening, prior to dosing, in ARC003 and then collect further information from those subjects who go on to experience GI side effects during OIT and controls. To overcome the obstacles limiting traditional EoE evaluations in this context (eg, performance of an esophagogastroduodenoscopy [EGD]), an easily collected biospecimen will be analyzed to determine whether patterns can be detected that correlate with patterns seen in other subjects with known bona fide EoE. As there are no known clinical predictors of EoE, all ARC003 participants will be approached about participating in this substudy. Further analyses will be conducted on those subjects who develop GI symptoms during the course of OIT and controls who do not develop GI symptoms. While all subjects will provide baseline saliva specimens (collected at screening), we will be opportunistic about the collection of esophageal specimens, which may provide additional supportive data. Specifically, if subjects in the study withdraw from OIT and undergo a clinically-indicated EGD, we will, whenever possible, collect biopsy material from the site for further analysis, as per the ARC003 protocol.

In addition to addressing the detection of biomolecular signatures in subjects having adverse events, it is possible that specific biomolecular signatures could emerge from the planned study

that associate with treatment success or treatment withdrawal. Thus, a possibility exists that the proposed biospecimen testing could yield biomarkers predictive of an individual subject's response to OIT and the collection of biospecimens in this substudy could facilitate these future analyses.

Known and Potential Risks and Benefits to Human Participants

Risks

The principal potential risk associated with this substudy is the potential for emotional or psychological distress related to the discovery of uncertain information that is not itself diagnostic but may suggest a new clinical diagnosis (ie, EoE). To mitigate against this risk, and because the assays run in this substudy are experimental, exploratory, and not part of standard care EoE diagnostics, the results of these studies will not be shared with participants. Clinical management of these individuals will be at the judgment of the site investigator, per the current standard of care. The ARC003 protocol document also contains specific recommendations about the clinical follow-up of subjects developing AESIs. All study candidates entering ARC003 will undergo an informed consent procedure detailing the potential risk of OIT-associated gastrointestinal symptoms, including the possibility of EoE.

There are no known physical risks to the saliva collection procedure.

Benefits

Individual subjects are not expected to benefit from participation in this study. Information from this study may help researchers to better understand peanut allergy and its relationship to EoE or to develop future tests or treatments to help patients with one or both of these conditions.

Objectives

Primary Objective

The primary objective is to analyze biomolecular expression patterns in saliva samples obtained longitudinally from peanut-allergic participants undergoing OIT in ARC003. These studies will target the salivary RNA transcriptome, and if necessary further validate, with molecular-, cellular-, and/or protein-based approaches, the expression profile of gene pathways that are likely relevant to intolerable GI side effects in ARC003 subjects.

Secondary Objectives

The key secondary objective is to examine the relationship of the RNA expression profile to selected clinical variables from ARC003, including:

- The frequency and severity of AEs related to the gastrointestinal tract
- The frequency of dosing interruptions (reductions and/or discontinuations) directly related to GI AEs
- Peripheral blood eosinophil counts

- PEESS v2.0 scores
- Immunoglobulin levels (IgE, IgG4, and their subclasses)

Further secondary objectives include the correlation of salivary RNA transcriptome data to histopathologic and molecular analyses of the esophagus, when available.

Substudy Design

This is an optional substudy in which samples will be obtained from ARC003 participants according to the Schedule of Events in **Table A6**. Only subjects enrolled in ARC003 and providing additional consent for this substudy are eligible to participate. Subjects enrolled in both ARC003 and this substudy will undergo saliva collection coordinated at the designated ARC003 study visits. Otherwise these subjects will be treated according to the ARC003 study protocol.

Table A6: Schedule of Events

	Screening	Early Build-Up Visit	At PEESS v2.0 #1	End of Up-Dosing Visit	Post-OIT Follow-up[b]
Study Week[a]	**0**	**6 (±2 wk)**	**varies**	**20**	**Varies**
Informed consent/assent	X		X[c]		
Eligibility assessment	X				
Saliva collection and packaging/shipping:					
No GI symptoms (controls)	X	X		X	
GI symptoms (cases)	X		X[c]		X

[a] Minimum study weeks are shown. Actual duration may be longer depending on subject's actual up-dosing in ARC003.
[b] For subjects who terminate dosing and enter observational follow-up, as per **Section 7.4.3.2** of the ARC003 protocol. This sample is to be collected at the sixth monthly visit after study withdrawal or as close as practicable.
[c] Subjects withdrawing early from ARC003 with GI symptoms that were not already enrolled in this substudy will be consented to enroll upon early termination.

Subjects in this substudy will undergo 3 protocol-specified collections of saliva. All subjects will have a baseline saliva sample collected at Screening (before the Screening DBPCFC). Because the GI adverse events of special interest are unpredictable and treatment-emergent, the approach to sampling post-randomization will differ by treatment response. Subjects who develop GI-predominant adverse events that prompt their withdrawal from ARC003 or a protracted disruption of dosing with study product will be considered "cases" in this substudy. The second saliva sample will be collected from cases when the first PEESSV2.0 is completed. The final saliva sample for cases will be collected at the end of the protocol-defined 6-month follow-up period for subjects that withdraw from therapy.

"Controls" in this substudy will be defined as ARC003 participants receiving OIT (active and placebo) who do not develop intolerable GI symptoms. Following the baseline collection, asymptomatic subjects will provide saliva samples at the 6-week up-dosing visit and again at the end of the updosing period.

This substudy will principally involve: collection, shipment, and banking of saliva samples at specified time points; gene expression analysis of selected salivary biospecimens; and correlation with basic biometric data (eg, peripheral blood eosinophils, clinical symptom reports/PEESSv2.0 scores) obtained as necessary, and clinical outcome per the ARC003 protocol. Biochemical detection of eosinophil activation products or metabolites may also be possible from collected samples.

Subject participation will consist of signing an informed consent form (ICF) approved by the institutional review board (IRB), ethics committee (EC), research ethics board (REB), or like authority, and age-appropriate assent form, when indicated, as per local guidelines, and the provisions for biospecimen collection and handling (further detailed in **Section 4.3**).

Case Definition: ARC003 Events Triggering PEESS v2.0

The following passage is taken from **Section 7.4.3.2** of the ARC003 Protocol, Amendment 1 and serves to identify the case definition in this substudy; eg, the ARC003 subjects who develop the GI AESIs requiring further evaluation.

> *GI AEs, typically chronic/recurrent GI AEs, that result in a prolonged disruption of dosing will be considered AEs of special interest and will be assessed longitudinally according to the procedures described below. For the purpose of delineating these AEs of special interest, prolonged disruption of dosing is defined as withholding study product 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 (**Section 6.7** of the ARC003 protocol)*
> - *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 (**Section 6.7.3.2** of the ARC003 protocol);*
> - *Any subject who permanently discontinues dosing who had experienced GI AEs (**Section 4.3.2** of the ARC003 protocol).*
>
> *Subjects under the age of 18 years who fall into any of these 3 categories will be asked to fill out the PEESS v2.0 questionnaire (Franciosi et al., 2011), with the assistance of a parent or guardian, as appropriate, every month for 6 months; adults will be given the same version of the questionnaire. It should, however, be noted that the PEESS v2.0 was not designed to establish a diagnosis of EoE, and has not been validated for use in patients with GI symptoms of other etiologies. Furthermore, the discriminant validity of the questionnaire has not been reported in either longitudinal natural history or interventional studies. For these reasons, the use of the PEESS v2.0 to monitor the clinical course of GI symptoms must be considered exploratory. Nevertheless, the PEESS v2.0 has shown good content and construct validity (Franciosi et al., 2011; Martin et al., 2015)*

and so holds promise for being a valuable tool to follow the clinical course of EoE or an EoE-like immune-mediated GI syndrome. Thus, the PEESS v2.0, could reveal trends toward symptomatic improvement or worsening that might otherwise go undetected.

Exploratory Endpoints

All endpoints in this substudy are considered exploratory. The primary objective is to characterize RNA expression patterns in salivary specimens collected from peanut-allergic subjects who participated in a study of peanut OIT and developed intolerable GI adverse events that interfered with treatment (ie, resulted in reducing, holding, or discontinuing OIT dose levels). ARC003 subjects who do not develop limiting GI symptoms will also be studied as control specimens. Secondarily we will also examine the associations of the salivary RNA expression changes with selected clinical variables as listed in **Section 3.6** and **Section 3.7** and explore the within-subject correlation to RNA expression patterns observed in esophageal specimens, when available.

Bioinformatic analysis plan for primary and secondary objectives

The bioinformatic analysis plan for the primary and secondary objectives of this study include:

- Quality control of the genome-wide RNA sequencing data
- Expression filter and statistical filter
- Clustering analysis with known clinical outcomes
- Develop an algorithm (similar to Wen et al., 2013) to quantify the oral sample signature to correlate with the PEESS^{TM} v2.0
- Use a portion of the samples as a training set for machine learning, then carry out the support vector machines (SVMs) to predict the rest of the samples. SVM is a supervised learning model with associated learning algorithms that analyze data and recognize patterns.
- Principle Component Analysis (PCA) will be employed to globally categorize the samples, reduce the dimensionality for signature quantification and aid the graphical presentation of the data

Additional exploratory endpoints may include qualitative and/or quantitative comparisons to the patterns of biomolecular and biochemical expression seen in subjects with spontaneously occurring EoE or other esophageal pathologies (historical controls). These control specimens will be obtained under separate protocols at the investigative laboratory.

Criteria for Study Participation

Inclusion Criteria

Subjects who meet all of the following criteria are eligible for enrollment as study subjects:

- Participation in the ARC003 study

- Written informed consent from adult subjects
- Written informed consent from parent/guardian for minor subjects
- Written assent from minor subjects as appropriate (ie, above the age of 7 years)

Exclusion Criteria

1. Otherwise ineligible for ARC003

Subject Termination from the Substudy

After enrollment, subjects may withdraw consent from this substudy at any time. Subjects may also be withdrawn by the Investigator for reasons of safety or compliance.

Study Product

No study product will be administered in the substudy.

Study Procedures

The following procedures will be performed:

1. Enrollment and Permissions
   - Obtain subject/parental signatures on IRB-approved informed consent/assent form.
2. Subject Information
   - Confirm subject eligibility
3. Sample Collection, Handling and Analysis Procedures
   - Saliva is the principal biospecimen to be collected in this study with the aid of a commercially available kit designed expressly for salivary RNA research purposes. Specific details for saliva collection will be provided to sites in a manual of procedures.
   - Blood samples for CBC, already collected in ARC003, will also be included in analyses relating to the secondary objectives of this substudy.
   - Biospecimens may be temporarily stored at investigational sites to facilitate batch shipping and receiving. All biospecimens will be packaged and transported to the investigative laboratory in a manner compliant with all local, state, and federal laws and regulations, as per standard operating procedures of the shipping and receiving facilities.
   - Analyses will include one or more of the following:
     - Transcriptome analysis
     - EoE diagnostic panel comprising a 96-gene quantitative polymerase chain reaction array
     - Profiling of local cytokine expression

- Targeted analysis of expression of previously identified specific candidate genes
- Analysis of single nucleotide polymorphisms in previously identified specific candidate genes
- Inflammatory pathway analysis (Ingenuity, Toppfun or David)
- qPCR analysis
- Immunohistochemistry or other protein detection methods (eg ELISA, Western blot, etc.).
- Mass spectrometry
- Flow cytometry

Lead Investigative Laboratory

The lead investigative laboratory is the following:
Wen Lab – Cincinnati Children's Hospital Medical Center
S6.405 S Building
240 Albert Sabin Way,
Cincinnati, OH 45242
USA.

Permission to obtain samples of esophageal tissue from the residua (if any) of biopsy specimens obtained during the performance of routine clinical endoscopic biopsy will be requested for subjects who undergo this procedure.

4. Study Blinding Procedures

This substudy will be unblinded after ARC003 is unblinded. The precautions relating to maintenance of blinding are detailed in the ARC003 Masking Plan. In order to understand the clinical significance of the bioassays performed in this substudy, information about the clinical history (including history during participation in ARC003) and treatment assignment in ARC003 will be analyzed. However, ARC003 treatment assignments will not be provided to any individual directly involved in performance of laboratory assays until all assays are completed. Subject identification will be known only to the personnel at the investigational site obtaining informed consent, and potentially the site monitor(s) and auditors. Subject identification will be kept confidential.

5. Safety Monitoring

As the study entails no treatment, there can be no treatment-emergent or treatment-related adverse events (AEs) in this substudy. As outlined in **Section 1.3**, the principal risk associated with a genetic-based study is the potential for emotional reactions upon learning that the subject or a subject's family member does or does not carry or express a gene associated with a particular condition.

6. Statistical Considerations

   This substudy is a pilot characterization of biochemical and biomolecular markers in relation to GI side effects arising during peanut OIT in ARC003 subjects. The analyses to be conducted in this substudy are all considered exploratory in nature. As such, descriptive statistical techniques will be utilized to characterize demographic and basic clinical variables, with standard assessments for normality and adjustments as necessary. Measures of correlation and longitudinal repeated measures will be assessed with appropriate techniques (eg regression modeling) as necessary. Statistical testing for differences between treatment groups or time points may be assessed, but specific hypotheses are not pre-specified.

7. Study Endpoint Assessment

   All endpoints in this study are considered exploratory and are defined in **Section 3.8**.

8. Subject and Demographic Data

   Baseline Characteristics, Demographics, and Safety Data

   Baseline and demographic characteristics may be reported for each subject enrolled in the present study as they were obtained in ARC003. Demographic data could include age, race, sex, body weight and height. Other analyses involving safety data may also be performed.

   Use of Medications

   There will be no medications used in this substudy. Data from concomitant medication use in ARC003 related to AEs may be analyzed as part of this substudy.

9. Sample Size Calculations

   This is an exploratory and hypothesis-generating study involving minimal risk to subjects. No specific sample size calculations have been performed.

Identification and Access to Source Data

Data Management

Information regarding the subject's history, laboratory tests, nutritional intake, evaluation of allergic response and follow-up status will be stored and processed through the ARC003 clinical trial database. All participating laboratories will collect data in a manner that allows independent verification of the results and their communication to the Sponsor. All participating laboratories will maintain study records for at least 2 years after acceptance of a licensure application for AR101. Quality control procedures and a feedback system between Aimmune and the investigational laboratory site(s) may be instituted to ensure the accuracy and completeness of the data collected and transmitted.

Access to Data

The investigational sites shall periodically permit authorized representatives of the Study sponsor, and/or regulatory health authorities to examine clinical records and other source documents for the purpose of safety monitoring, quality assurance reviews, audits and evaluation of the study progress throughout the entire study period. The investigator is required by law and applicable guideline (21 CFR 312.62, EU Clinical Trials Directive 2001/20/EC and ICH E6) to keep accurate case records for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing application in an ICH region. These documents should be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with the sponsor.

Quality Control and Quality Assurance

Statement of Compliance

This study will be conducted using good clinical practice (GCP), as delineated in the United States Code of Federal Regulations (CFR) – 21 CFR Parts 50, 54, 56 and 312 and in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) "Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance", and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate IRB/EC and other applicable health authorities. Any amendments to the protocol must also be approved by Aimmune Therapeutics, IRB/EC and other applicable health authorities before they are implemented. Any amendments to the consent materials must also be approved by Aimmune Therapeutics and IRB/EC before they are implemented.

Changes to assay details and laboratory information will not require a protocol amendment, but will be reflected in amendments to consent materials and other accessory documents as appropriate.

The participating laboratory will cooperate with the Sponsor in complying with additional requests from the appropriate IRB/EC and the applicable regulatory health authority of the countries in which ARC003 is conducted.

Informed Consent/Assent

The informed consent form is a means of providing information about the study to a prospective subject's parent/guardian and allows for an informed decision about participation in the study. Because the study population will include children, parents or legal guardians will be asked to read, sign and date a consent form before a child enters the study, takes study product, or undergoes any study-specific procedures. Children will sign an assent as appropriate. Consent materials for parents/guardians who do not speak or read English will be translated into the appropriate language. The informed consent form will be revised whenever the protocol is amended. A copy of the informed consent will be given to a prospective parent/guardian for review. Appropriately trained study personnel, in the presence of a witness, will review the consent and answer questions. The prospective parent/guardian will be told that being in the

study is voluntary, that he or she is under no obligation to enter the study, and that he or she may withdraw his/her child from the study at any time, for any reason.

Privacy and Confidentiality

A subject's privacy and confidentiality will be respected throughout the study. Subject data will be anonymized by use of subject identification numbers assigned in ARC003. These numbers will be used to collect, store and report subject information.

Resource Sharing

All data derived from this study will be sent to the investigational laboratory for storage and analysis and will also be provided to the Sponsor. Subject data will be coded as described above to maintain subject confidentiality. The Sponsor and laboratory will review all data communications (including but not limited to abstracts, presentations, and manuscripts) prior to external submission. All data sets will be archived by the laboratory and may be made externally available after approval by the Sponsor.